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Original Article

Differential relations between fronto-limbic metabolism and executive function in patients with remitted bipolar I and bipolar II disorder

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Objectives: The aim of this study was to investigate the relationship between resting brain glucose metabolism and cognitive profiles in patients with remitted bipolar I disorder (BD-I) and bipolar II disorder (BD-II). We hypothesized that BD-I patients (compared to BD-II patients) would perform worse on tests of cognitive function because of abnormal metabolism in the prefrontal cortex and other mood-related brain areas.

Methods: Thirty-four patients with remitted bipolar disorder (BD) (BD-I = 17, BD-II = 17) under treatment and 17 well-matched healthy controls received both fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and neuropsychological tests of attention, memory, and executive function.

Results: Clinical features in patients with BD-I and BD-II were comparable. Executive function, as indicated by performance on the Wisconsin Card Sorting Test, was significantly worse (i.e., higher percentage of errors, lower percentage of conceptual level responses, and fewer categories completed) in BD-I patients than in BD-II patients and healthy subjects. No difference in attention and memory tests was found among these three groups. Brain PET analysis showed that BD-I patients (compared to BD-II patients) had significantly lower glucose uptake in the bilateral anterior cingulum, insula, striatum, and part of the prefrontal cortex, and higher glucose uptake in the left parahippocampus. Further analyses revealed significant correlations between poor executive function and abnormal glucose uptake in other brain areas in BD-I patients.

Conclusions: There are neurobiological differences between subtypes of BD. BD-I is associated with more impaired fronto-limbic circuitry, which might account for reduced executive function in BD-I patients during remission.

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Growing evidence has shown that cognitive dysfunction persists in patients with bipolar disorder (BD), regardless of mood state (1–6) or medication effects (7, 8). Persistent deficits in attention (1, 3, 8–10), memory (1, 3, 9–11), and executive function (1, 7, 10–13) during euthymic or relatively stable periods have been reported. These cognitive deficits, particularly in executive function or working memory, are regarded as trait markers of BD and have negative impacts on quality of life and psychosocial functioning (1–3, 14).

Because they persist even in remission, cognitive deficits may be the core deficits of BD (4) and be caused by dysfunction in certain brain areas [e.g.,

the prefrontal cortex (PFC)], as revealed by several functional neuroimaging studies. Many ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) studies have reported abnormalities of brain glucose metabolism in BD (15–20). A relationship between neurocognitive deficits and central glucose metabolism in BD has also been reported (21, 22). It has been suggested that metabolic abnormalities in some prefrontal areas [e.g., the dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex (mPFC)] and anterior limbic or paralimbic structures (e.g., the striatum, hippocampus, parahippocampus, fusiform, and temporal cortex) not only explain the severity of depression in BD (16, 18–20), but also cognitive deficits in euthymic BD (23). For example, in BD patients during remission, Brooks et al. (23) demonstrated a correlation between impaired working memory, resting prefrontal hypometabolism (DLPFC), and paralimbic hypermetabolism (hippocampus, parahippocampus, amygdala, and temporal cortex). These findings suggest that BD patients have abnormal neuronal activities, mostly in the fronto-limbic circuit, even in the resting state, and that their cognitive deficits may be related to these abnormal activities. Likewise, functional magnetic resonance imaging (fMRI) studies, which assessed relative neuronal activation in response to cognitive tasks, showed hypofrontality and failure to engage the fronto-executive regions of the brain (24), or fronto-limbic dysfunction (25, 26) in euthymic BD. Euthymic BD patients exhibited decreased activity predominantly in the DLPFC, mPFC, anterior cingulate cortex (ACC), and thalamus during working memory tasks (25, 27–30). In addition, activities in the ventral limbic (e.g., caudate and insula) and temporal cortical areas were increased during emotional Go/No-Go tasks in euthymic BD (26). Taken together, these findings suggest that trait-related impaired brain functioning in the above-mentioned mood-related structures may underlie cognitive deficits (e.g., executive dysfunction or impaired working memory) in euthymic BD.

Subtypes of BD, including BD type I (BD-I) and type II (BD-II) according to the DSM-IV diagnostic system, exhibit different cognitive profiles. Patients with BD-I (compared to patients with BD-II) performed worse on neurological tests (31–33), suggesting possible neurobiological differences between these subtypes. In addition, resting cerebral glucose metabolism (e.g., in various parts of the frontal cortex, temporal cortex, thalamus, striatum, and insula) was found to differ between BD-I and BD-II in the study by Ketter et al. (34). However, in that study (34), all the recruited subjects had treatment-resistant BD, and most had rapid-cycling and non-remitted BD. Investigating brain glucose metabolism in patients during symptomatic remission is important for probing core neurobiological deficits in BD as patterns of glucose metabolism and cognitive profiles depend on mood states (3, 15, 34). However, ^{18}F-FDG PET cannot determine whether differences in neuronal activation during cognitive tasks are specific to the tasks and fail to occur at rest. Moreover, the observed differences at rest may represent a more generalized finding for the disorder. Therefore, in the present ^{18}F-FDG PET study, we aimed to investigate the relationship between resting brain glucose metabolism and cognitive profile by comparing symptomatically remitted BD-I patients versus symptomatically remitted BD-II patients and healthy groups. We hypothesized that BD-I patients perform worse than BD-II patients in cognitive function tests, and that abnormal resting cerebral glucose metabolism in the PFC (DLPFC and mPFC), ACC, striatum, insula, thalamus, parahippocampus, and temporal cortex could account for this relatively poorer performance.

Material and methods

Study subjects

A total of 66 adults with BD (BD-I = 32, BD-II = 34) who were followed as outpatients at the Taipei Veterans General Hospital were recruited. The diagnoses were established by structural history-taking and on the basis of the Mini-International Neuropsychiatric Interview (MINI) (i.e., on the basis of Diagnostic and Statistical Manual Fourth Edition criteria). The criteria for inclusion were: age 21–65 years; no history of alcohol or substance abuse/dependence during the previous 12 months; no major physical or neurological illness; and no comorbidity with schizophrenia, obsessive–compulsive spectrum disorders, or post-traumatic stress disorder. Open-label valproic acid, lamotrigine, quetiapine, or a combination of these, was administered based on clinical presentation and the clinician's judgment. To exclude influences from active mood symptoms, ^{18}F-FDG PET studies and neuropsychological tests, including Attentional Performance tests, Word List Recall, Face memory tasks, and the Wisconsin Card Sorting Test (WCST), were conducted only in patients in remission. Remission was defined as a score of ≤9 on the 17-item Hamilton Depression Rating Scale (HDRS-17) and ≤7 on the Young Mania Rating Scale for at least two weeks (35, 36). Although there is no

current international consensus criterion for the duration of BD remission (37), we recruited only patients who had been euthymic for more than two weeks, to ensure the stability of the remission. After MINI screening, a group of age-, education-, and handedness-matched healthy controls (n = 17; 12 female subjects) was recruited to the study for the neurocognitive and ^{18}F-FDG PET comparison. Those with a family history of an Axis I disorder, including schizophrenia, major depression, or BD in first-degree relatives, were excluded. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of Taipei Veterans General Hospital. The study was described comprehensively to all subjects prior to their enrollment, and all participants provided written informed consent.

Neurocognitive assessment

Neurocognitive assessments and PET scans were done at different times but mostly on the same day, or at most three days apart, to avoid mood changes. Attention functions were measured by Tests for Attentional Performance (38). We chose an acoustic task for evaluating auditory attention and a Go/No-Go task for assessing visual attention. Reaction time (median) and false alarms in the acoustic and Go/No-Go tasks were recorded for further analysis. Faster reaction time and fewer false alarms indicated better attentional performance. Verbal memory and visual memory were measured using a Word List Test and Face Memory Test, respectively (39). Immediate recall (i.e., score on the first word list task) and delayed recall (score on the second word list task) were used as outcome measures for verbal memory, while immediate recall (i.e., score on an immediate face recognition task) and delayed recall (score on a delayed face recognition task) were recorded for visual memory. High scores indicated efficient learning and recall. The WCST was used to evaluate executive function (40). Three WCST indices were used for analysis: (i) percent errors, (ii) percent conceptual level responses, and (iii) categories completed. Fewer errors and more conceptual responses or categories completed indicated better executive function. Other procedural details of these neurocognitive tests have been described previously (41).

PET imaging acquisition and analysis

PET images were acquired during the resting state with eyes closed. Patients fasted for at least four hours before the PET examination. PET scans of glucose utilization were acquired on a 64-slice PET/computed tomography (CT) scanner (Discovery VCT; GE Healthcare, Waukesha, WI, USA) operating in a three-dimensional (3-D) brain mode. PET images were acquired 45 min after an intravenous injection of FDG (370 MBq). The brain acquisition time was 15 min. The PET camera consisted of 24 bismuth germanate detector rings. The transaxial resolution full-width at half-maximum (FWHM) was 5.12 mm (1 cm off-center) and the axial resolution was 5.18 mm. The system produced 47 consecutive slices over an axial length of 15.7 cm, with a slice thickness of 3.75 mm and a transaxial field of view of 70 cm. PET images were reconstructed in a 128×128 matrix and using CT for attenuation correction and an ordered-subset expectation maximization (OS-EM) iterative reconstruction algorithm (six iterations and 14 subsets). The axial images were then realigned to yield sagittal and coronal images (42). The counts in each image were converted to radioactivity concentration using a calibration factor. This factor was calculated from a cylinder phantom scan of ^{18}F-FDG and a well-counter measurement of an aliquot of the phantom activity. All images (in radioactivity concentration) were then normalized by injected dose and body weight to get standardized uptake value images (43). Brain uptake of ^{18}FDG is suggestive of, but not equal to, brain glucose metabolism.

Statistics

PET data were analyzed using Statistical Parametric Mapping version 2 (SPM2, Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, UK) implemented in Matlab 7.0 (The Mathworks Inc., Sherborn, MA, USA). First, an ^{18}F-FDG template was created from all subjects, including all BD patients and healthy controls, according to previously described procedures of spatial normalization (44, 45). Then, each subject's images were normalized to the ^{18}F-FDG template and transformed into the standardized Montreal Neurological Institute space, sampled at a $2 \times 2 \times 2$ mm voxel size. The transformed images were further smoothed with a 3-D Gaussian kernel (FWHM = 12 mm) to compensate for inter-subject differences and to suppress high-frequency noise in the images (46). The overall grand mean from PET scans was centered and normalized to 100, and global variance across scans was removed by analysis of covariance (ANCOVA) (47). To assess potential group differences in normalized brain glucose uptake, an ANCOVA using age,

gender (48), and global gray matter values as covariates of no interest was used for between-group comparisons (BD-I or BD-II versus healthy controls; BD-I versus BD-II; BD-I versus BD-II and healthy controls). Since *a priori* knowledge of the brain network involved in cognitive functioning in euthymic BD includes the DLPFC, mPFC, ACC, striatum, insula, thalamus, parahippocampus, and temporal cortex (i.e., *a priori* regions), the significance thresholds were elevated to those needed for cluster-level analysis (49–51). The significance thresholds were set at $p < 0.05$ uncorrected at the voxel level, followed by a cluster-level analysis with an uncorrected $p < 0.05$. Due to the problem of multiple comparisons, those clusters exceeding the threshold of uncorrected $p < 0.05$ were further examined by small-volume correction (SVC) with an anatomically defined regional mask in the relevant gray matter area (52). The clusters exceeding the threshold of SVC $p < 0.05$ were also considered significant. Since the regions of interest (ROIs) are predefined, the use of the *corrected* p-values is unnecessary and inappropriately conservative (53). We also reported those ROIs with clusters of voxels exceeding the $p < 0.001$ threshold and which survived SVC correction for multiple comparison of results. In addition, voxel-based partial correlations were performed to investigate the association between ^{18}F-FDG uptake and cognitive measures such as percent conceptual level responses, which were found to differ significantly between groups, after adjusting for age, gender, and total gray matter counts. A cluster-level $p < 0.05$ (SVC-corrected) was considered statistically significant (52, 54). The statistical threshold for correlations between cerebral glucose metabolism and other cognitive functions (i.e., attention and memory) was set at a cluster-level familywise error-corrected $p < 0.05$. To further investigate associations between cognitive function and glucose metabolism in specific brain areas, the ratio of glucose metabolism in each brain region to that in the whole brain was used as an index in ROI analysis, which was carried out with the aid of PMOD software (PMOD Technologies Ltd., Zurich, Switzerland). Scaling of PET data to the global mean value of the whole brain was carried out to reduce inter-subject variability in global brain PET measures (55). The Automated Anatomical Labeling template (56) was used to obtain relative metabolic values in the predefined ROI areas.

Statistical analysis of demographic and clinical data was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) (or Student's *t*-test) and the Chi-square test were applied to compare the continuous and categorical variables among groups, respectively. *Post-hoc* least significant difference analysis was performed to determine which of these groups accounted for significant between-group differences. As age, duration of illness, and total number of past episodes might influence cognitive performance, they were used as covariates in univariate ANCOVA to evaluate differences between the BD groups in variables found to have statistical significance ($p < 0.05$) in the ANOVA. Pearson's correlation was performed in order to determine correlations between the ratio of glucose metabolism in each brain region and neurocognitive scores for all patients and healthy subjects. A $p < 0.05$ was deemed to be statistically significant.

Results

Demographic and clinical variables

Of the 66 right-handed patients recruited, 34 patients (BD-I = 17, BD-II = 17) with remitted BD after treatment were included, and 32 patients (BD-I = 15, BD-II = 17) were excluded because they remained depressed or manic. Seventeen right-handed healthy controls were enrolled for comparison. The demographic data of all participants are listed in Table 1. Eight patients had comorbid panic disorder (BD-I = 3, BD-II = 5), four had generalized anxiety disorder (BD-I = 3, BD-II = 1), and two had social phobia (BD-I = 0, BD-II = 2). Except for fewer past depressive episodes ($p = 0.042$) in BD-I patients, there were no significant between-group differences in mood ratings or in other clinical variables, such as age, gender, education level, age at onset, illness duration, number of manic/hypomanic episodes, and average dose of medication (Table 1).

Cognitive profiles of patients with remitted BD and healthy subjects

There were no significant among-group differences in attentional performance (median reaction time and rate of false alarm responses to acoustic attention and visual attention tasks) and memory (scores on verbal recall and facial recognition tests) (Table 2). However, the BD-I patients scored significantly worse than the other two groups on all measures of executive function, including percent errors, percent conceptual levels, and categories completed (all with $p < 0.01$). We also found that patients with remitted BD-II had higher percent errors and lower percent conceptual level responses than healthy subjects, but the difference was without statistical significance. This might be

Table 1. Demographic and clinical characteristics of patients in the bipolar I disorder (BD-I) and bipolar II disorder (BD-II) groups, and of the subjects in the healthy control group

	BD-I (n = 17)	BD-II (n = 17)	Healthy controls (n = 17)	*F*/*t*-value	p-value
Gender, n (male:female)[a]	7:10	5:12	5:12	0.706	0.703
	Mean (SD)	**Mean (SD)**	**Mean (SD)**		
Age, years[b]	43.9 (11.9)	41.6 (13.0)	41.3 (10.5)	0.256	0.775
Range: minimum–maximum	23–61	21–64	24–62		
Education level, years[b]	13.4 (2.5)	14.9 (2.0)	14.2 (2.2)	2.119	0.131
Age of onset, years[c]	31.4 (11.1)	29.7 (10.9)	–	0.438	0.664
Illness duration, years[c]	13.5 (11.9)	11.9 (7.2)	–	0.489	0.628
Number of past manic/hypomanic episodes[c]	3.5 (3.1)	3.6 (2.9)	–	–0.057	0.955
Number of past depressive episodes[c]	3.4 (2.6)	5.5 (3.2)	–	–2.116	0.042[d]
HDRS-17[c]	3.1 (2.7)	3.6 (3.0)	–	–1.243	0.223
YMRS[c]	2.8 (3.5)	1.5 (2.3)	–	1.322	0.195
Medications: n, mean [range]					
Valproic acid, mg/day	13,790 [500–1000]	11,747 [500–1000]	–	–	–
Lamotrigine, mg/day	10,128 [100–300]	13,143 [100–200]	–	–	–
Quetiapine, mg/day	9,283 [100–600]	9,264 [100–300]	–	–	–

HDRS-17 = 17-item Hamilton Depression Rating Scale; SD = standard deviation; YMRS = Young Mania Rating Scale.
[a]Pearson chi-square tests.
[b]Analysis of variance, $F(df = 2,48)$.
[c]Student's *t*-test.
[d]$p < 0.05$.

Table 2. Cognitive profiles of patients in the bipolar I disorder (BD-I) and bipolar II disorder (BD-II) groups, and of the subjects in the healthy control group

	BD-I (n = 17)	BD-II (n = 17)	Healthy controls (n = 17)				
	Mean (SD)	Mean (SD)	Mean (SD)	*F*-value[a]	p-value	*Post-hoc* (LSD)	ANCOVA[b] *F*(1,29)
Acoustic attention							
Median reaction time	588.8 (153.8)	602.3 (73.5)	615.1 (74.6)	0.255	0.776	–	–
False alarm	0.8 (1.2)	0.2 (0.4)	0.4 (0.7)	2.781	0.072	–	–
Visual attention							
Median reaction time	475.7 (71.8)	464.2 (58.8)	458.2 (69.6)	0.301	0.741	–	–
False alarm	1.1 (1.2)	1.2 (1.0)	0.8 (1.4)	0.494	0.613	–	–
Verbal memory							
Immediate: Word lists I first recalls	5.9 (1.9)	6.9 (1.7)	6.4 (1.7)	1.182	0.315	–	–
Delayed: Word lists II recalls	8.2 (2.1)	9.5 (2.4)	8.8 (1.5)	1.732	0.188	–	–
Delayed facial memory							
Immediate: Face recognition I	37.3 (3.3)	38.2 (4.5)	36.4 (3.5)	1.047	0.359	–	–
Face recognition II	35.1 (3.3)	35.2 (4.2)	36.5 (3.5)	0.834	0.441	–	–
Executive function: WCST							
Percent errors	41.9 (22.4)	28.5 (15.2)	20.6 (7.2)	7.559	0.001[c]	BD-I > Healthy[d] BD-I > BD-II[d]	0.011[d]
Percent conceptual level responses	46.9 (28.9)	64.3 (20.2)	75.8 (10.0)	8.052	0.001[c]	BD-I < Healthy[d] BD-I < BD-II[d]	0.012[d]
Categories completed	3.5 (2.5)	4.6 (2.0)	5.8 (0.8)	6.201	0.004[c]	BD-I < Healthy[d]	0.045[d]

LSD = least significant difference; SD = standard deviation; WCST = Wisconsin Card Sorting Test.
[a]Analysis of variance (ANOVA) test, $F(df = 2,48)$.
[b]Analysis of covariance (BD-I versus BD-II); covariates: age, duration of illness, and total number of past episodes.
[c]$p < 0.01$.
[d]$p < 0.05$.

due to the relatively small sample size in the present study. The subsequent ANCOVA results showed that age and total number of past episodes, but not illness duration, had a significant negative influence on executive functions. Moreover, the differences in executive function subscores between the two BD groups were also significant (Table 2). In total, these findings suggest that patients with remitted

BD-I have greater executive function impairment than patients with BD-II.

Correlations between brain glucose uptakes and executive function performance

After controlling for sex and age, partial correlation analyses showed that higher executive function (using percent conceptual level responses from the WCST as a yardstick) was correlated with higher glucose uptakes in the bilateral DLPFC, mPFC, ACC, striatum (caudate and putamen), thalamus, and bilateral operculum-insula in patients with remitted BD and healthy subjects (Fig. 1 and Table 3). By contrast, lower executive function was significantly correlated with higher glucose uptakes in the parahippocampus (Fig. 1 and Table 3). Further ROI analysis involving the ratio of glucose uptake in each specific brain area to that of the whole brain revealed that better executive function (i.e., higher percent conceptual level responses) was significantly correlated with higher glucose uptake in the ACC, PFC, insula, caudate, and thalamus (Fig. 2 and Table 4).

Regional brain glucose uptake in patients with remitted illness and healthy subjects

BD-I patients and BD-II patients showed similar patterns of fronto-thalamic-limbic dysregulation (See *Supplementary Fig. 1*). Compared to the healthy control group, both groups of patients showed significantly lower glucose uptake in the bilateral prefrontal areas (DLPFC and mPFC), cingulate cortex, and thalamus, as well as the bilateral inferior frontal gyri extending to the anterior insula and temporal poles bilaterally.

However, BD-I patients (compared to BD-II patients) had significantly lower glucose uptake in the bilateral insula, striatum, ACC, and right DLPFC, and significantly higher glucose uptake in the left parahippocampus and left middle temporal gyrus (Fig. 3 and Table 3). Moreover, taken together with the findings of worse performance on executive function tests in remitted BD-I patients versus BD-II patients and healthy subjects (Table 2: see *Executive function: WCST*), these findings suggest that the loss of executive function ability in BD-I patients could be attributable to frontal-limbic dysfunction (57, 58).

Discussion

To the best of our knowledge, this is the first study relating poor cognitive function in subtypes of BD patients during remission to glucose uptake (suggestive of glucose metabolism) in specific regions of the cerebrum. We found that impaired executive function, as shown by WCST measurements of higher percent errors and lower percent conceptual level responses, persisted in patients with BD-I, despite remission. This result indicated that cognitive profiles differed between subtypes of BD, with BD-I patients performing worse than BD-II patients on tests of executive function. Although the pattern of fronto-thalamic-limbic dysregulation was similar in both subtypes of BD patients, BD-I patients had even greater fronto-limbic dysfunction, with more severe hypometabolism in the DLPFC, ACC, insula, and striatum, and more intense hypermetabolism in limbic structures such as the left parahippocampus. The differential correlations between regional glucose uptakes and executive function performance across the groups implied that the ACC and caudate (but not the PFC) play a role in executive functioning in BD-I, whereas the PFC may be more critical in BD-II and healthy controls (Fig. 2). The reduced performance in BD-I subjects by using abnormal neural substrates to perform the task further suggests that abnormal glucose metabolism might account for the persistence of executive dysfunction in patients with remitted BD-I. These results support our

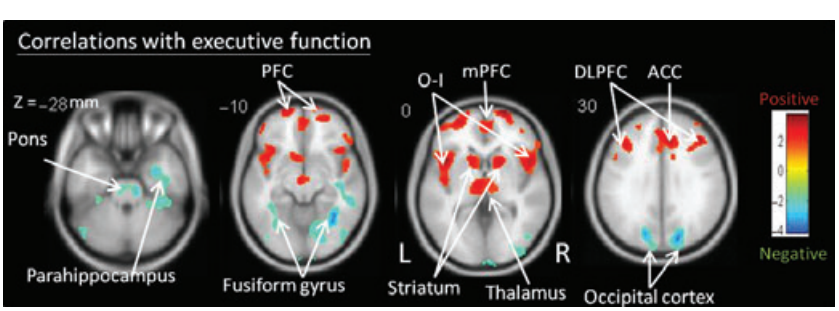

Fig. 1. Correlations between cerebral glucose metabolism and executive function in patients with remitted bipolar disorder and healthy subjects. ACC = anterior cingulate cortex; DLPFC = dorsolateral PFC; L = left; mPFC = medial PFC; O-I = operculum-insula; PFC = prefrontal cortex; R = right.

Table 3. Correlation between glucose uptake and executive function scores, and comparison of glucose metabolism between subtypes of bipolar disorder patients

Glucose metabolism	BA	Cluster size	MNI coordinates x	y	z	*t*	*Z*	$p_{uncorrected}$ [a]	$p_{uncorrected}$ [b]
Positive correlation with % CLR									
R DLPFC	46	6661	42	32	26	3.86	3.57	0.000[c]	0.000
R ACC	32		10	34	30	3.80	3.53		0.000
L DLPFC	10		−30	52	8	3.11	2.95		–
L ACC	32		−2	36	18	3.08	2.92		–
R Medial frontal gyrus	10		2	52	0	2.71	2.60		–
L Medial frontal gyrus	9		−2	38	32	2.50	2.41		–
L Anterior O-I	13	2575	−44	16	0	3.49	3.27	0.001	0.001
R Striatum (caudate nucleus/putamen)		2564	16	12	2	3.17	3.02	0.001	–
L Striatum (caudate nucleus/putamen)			−14	14	0	3.02	2.87		–
L Thalamus			−2	−10	−18	2.94	2.80		–
R Thalamus			6	−10	2	2.19	2.13		–
R Anterior O-I	47	1266	52	14	0	3.15	3.00	0.015	–
R Frontal pole	10		22	68	2	3.62	3.38		0.000
L Frontal pole	10		−20	64	12	3.30	3.09		0.000
Negative correlation with % CLR									
R Parahippocampal gyrus	34	7116	32	−2	−28	2.81	2.69	0.000[c]	0.001
L Parahippocampal gyrus	36	1050	−34	−28	−24	2.01	1.96	0.024	–
BD-I < BD-II									
R DLPFC	8	620	30	12	44	3.84	3.54	0.032	0.000
ACC	32	654	−14	16	48	3.77	3.49	0.029	0.000
R Anterior O-I	47	624	52	12	2	2.62	2.51	0.031	–
R Striatum (caudate nucleus/putamen)			16	15	0	2.10	2.05		–
L Anterior O-I	13	625	−38	6	2	3.72	3.44	0.031	0.000
L Striatum (caudate nucleus/putamen)			−13	10	6	2.07	2.01		–
BD-I > BD-II									
L Middle temporal gyrus	21	650	−46	−12	−16	3.51	3.28	0.030	0.001
L Parahippocampus	36		−32	−26	−18	2.68	2.56		0.001

All reported p-values passed small volume correction (SVC)-corrected $p < 0.05$. ACC = anterior cingulate cortex; BA = Brodmann area; CLR = conceptual level responses; DLPFC = dorsolateral prefrontal cortex; L = left; MNI = Montreal Neurological Institute; O-I = operculum-insula; R = right.
[a]Cluster level < 0.05.
[b]Voxel level < 0.001.
[c]Also passed cluster-level familywise error-corrected $p < 0.001$.

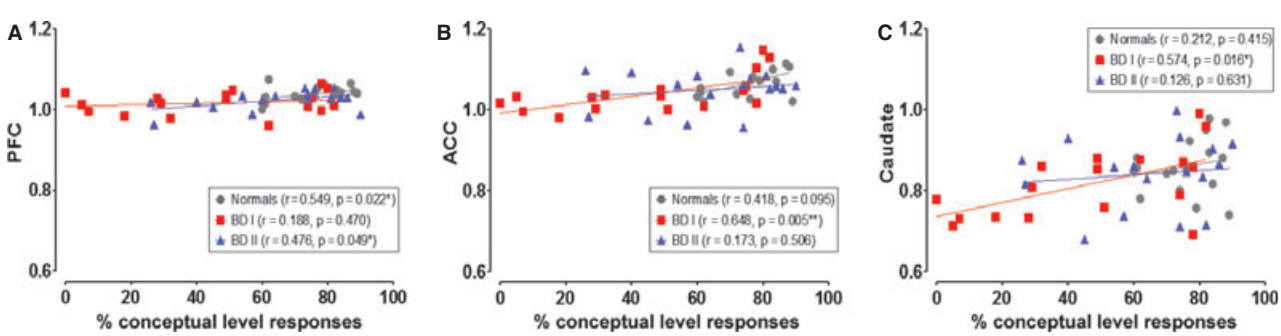

Fig. 2. Plot of the ratio of regional glucose uptakes versus executive function. Better conceptual level response is correlated with higher glucose metabolism in the prefrontal cortex (PFC) (**A**), anterior cingulate cortex (ACC) (**B**), and caudate (**C**). BD-I = bipolar I disorder; BD-II = bipolar II disorder.

hypothesis that there are neurobiological differences between subtypes of BD.

Our results on cognitive function in remitted BD patients were consistent with those of previous studies. A large body of evidence has shown that neurocognitive deficits persist in euthymic or remitted BD patients (1, 3–9, 11–13). Several studies that directly compared neurocognitive functions between subtypes of BD found greater cognitive impairment in remitted BD-I patients than in

Table 4. Correlation between regional glucose uptake and executive function

Anatomical regions	Correlation (*r*)	p-value
ACC	0.481	<0.001
Left	0.472	<0.001
Right	0.471	<0.001
PFC	0.416	0.002
Left	0.395	0.004
Right	0.411	0.003
Insula	0.327	0.019
Left	0.345	0.013
Right	0.279	0.047
Caudate	0.402	0.003
Left	0.399	0.004
Right	0.401	0.004
Thalamus	0.348	0.012
Left	0.324	0.020
Right	0.366	0.008

ACC = anterior cingulate cortex; PFC = prefrontal cortex.

remitted BD-II patients (31, 33). The possible reasons for the inconsistency in the findings of impaired attention, memory, or executive function across studies could be different batteries of neurocognitive tasks or other possible confounding variables such as mood status or past history of alcohol dependence (10). In the present study, all patients had remitted BD and no history of alcoholism. Only executive function was impaired in BD-I patients during remission, supporting the notion that impaired executive function, but not attention or memory, might be a trait marker and endophenotype in patients with BD-I (7, 59, 60).

Of the two PET studies in BD patients relating brain glucose metabolism to cognitive tasks (21, 22), one assessed neurocognitive function in depressed patients (21) and one assessed neurocognitive function in manic patients (22). In the present study, poor executive function in BD patients during remission was significantly associated with hypometabolism of the PFC, ACC, striatum, and thalamus, and with hypermetabolism of the limbic structures (left parahippocampus and fusiform gyrus). Previous fMRI studies in remitted BD patients (29, 30) found poorer performance in working memory tasks by patients than by healthy controls, demonstrating abnormal activation of several brain areas such as the PFC and thalamus. Malhi et al. (30) also found that an emotion-evoking fMRI task abnormally activated the PFC and thalamus of BD-I patients but not of healthy subjects. Likewise, previous ^{18}F-FDG PET studies have shown widespread hypometabolism in the PFC, and hypermetabolism in the amygdala, parahippocampus, and cerebellum of euthymic BD patients. This abnormal metabolic pattern explains the impaired performance of patients on working memory tasks (61). Our results support the hypothesis that frontal-thalamic-limbic circuits play a role in mood disorders (57, 58) and that mood disorders are involved in trait-related cognitive impairment (e.g., executive dysfunction as demonstrated in this study) in remitted BD patients. Although no differences in attention and memory performance between BD subtypes were found in the present study, a correlation of cerebral glucose metabolism with attention and memory was found, which suggests that some brain areas are multifunctional. For example, the DLPFC and insula control not only executive function, but also attention and memory (See *Supplementary Fig. 2*). Multifunctionality also implies that hypofunctioning in critical brain areas could lead to deficits in several cognitive domains at the same time. On the other hand, a review of the evidence shows that in healthy humans, the PFC and anterior cingulum are activated, and limbic structures, particularly the hippocampus, are deactivated in response to stress (62). The abnormal hypofunction of the PFC and anterior cingulum, and hyperfunction of the limbic structures also explain the vulnerability of BD patients to stress.

A small portion of PET research has focused on differentiating subtypes of BD patients, and no PET research has directly compared subtypes of BD during remission (63). In one study comparing BD-I to BD-II patients (34), the pattern of glucose metabolism varied with BD subtype and mood status. However, Ketter et al. (34) found higher

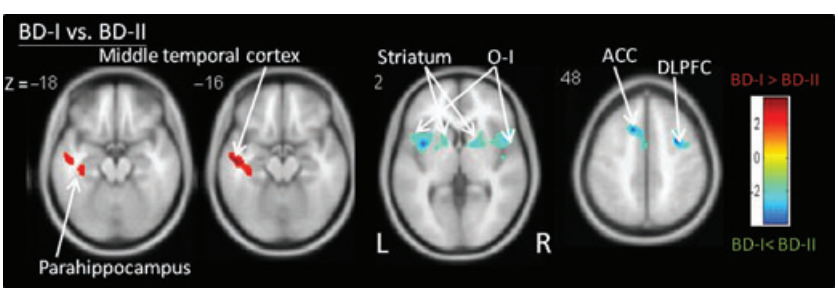

Fig. 3. A comparison of cerebral glucose metabolism between bipolar I disorder (BD-I) and bipolar II disorder (BD-II) patients. ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; L = left; O-I = operculum-insula; R = right.

than normal glucose metabolism in the right medial frontal gyrus and anterior cingulum in BD-I patients (n = 14; euthymic = 3) than in BD-II patients (n = 29; euthymic = 7). By contrast, we found even lower metabolism in the prefrontal areas, anterior cingulum, and insula in BD-I patients. This discrepancy with the Ketter et al. study might be due to: (i) the small fraction of their patients who were euthymic (n = 10; BD-I = 3, BD-II = 7), (ii) the treatment resistance of all patients, and (iii) the rapid recycling in almost all of the patients (n = 35). In addition, it has been shown that the metabolism of the anterior cingulum in BD patients seems to increase during mania (16, 64), and the metabolism of both the anterior cingulum and PFC seems to decrease during depression (15, 18). Taken together, these findings suggest that many clinical variables can influence ^{18}F-FDG PET results and that brain activity remains abnormal in remitted BD patients. Our results also suggest that brain areas that control emotion, such as the PFC, ACC, and insula, are less active in BD-I than in BD-II.

Our findings indicated that the PFC, anterior cingulum, and limbic structures such as the parahippocampus play important roles in BD-I. The DLPFC and mPFC are critical brain areas in mood regulation (58, 65–67). The smaller gray matter volume of the left DLPFC is associated with antidepressant resistance in depression (41). The DLPFC is also responsible for cognitive functions such as attention maintenance, memory, and decision making (68–70). The altered metabolism in the ACC of BD patients has been associated with poor attentional performance (21, 58). The thalamus processes and relays sensory information selectively to various parts of the cerebral cortex, where it plays an important role in working memory (71). With connection to the PFC, cingulate cortex, and midbrain, the limbic system (i.e., amygdala, hippocampus, parahippocampus, and some parts of the neocortex) is thought to play a critical role in the processing of emotion (72). Increased limbic activity has been associated with depression and anxiety (58, 73) and with certain cognitive functions such as face and scene recognition and perception (74). Our data suggest that fronto-limbic dysfunction is worse in BD-I patients, which might explain their greater executive function deficits. This correlation indicates that assessment of the severity of fronto-limbic dysfunction has a potential role in differentiating BD-I from BD-II patients.

The interpretation of our findings should be tempered by four limitations of this study. First, all of the patients were receiving medication for BD. However, it was necessary to bring patients to symptomatic remission, to control affective influences on cognition or central glucose metabolism. Notably, the drugs and doses used to treat patients in both BD groups (BD-I and BD-II) were similar. In addition, previous studies have shown no significant worsening of neurocognitive functions by mood stabilizers and atypical antipsychotic agents (1, 75, 76). Moreover, Mah et al. (20) reported that BD patients on lithium and those on valproic acid had a similar abnormal pattern of metabolism. The second limitation is based on the assumption that attention and memory function are exactly the same in patients with remitted BD-I and healthy people, although our results showed no between-group difference in these. Such results might stem from the relatively small sample size of each group. Third, an HDRS-17 score $\leq$9 instead of $\leq$7 (which has been recommended by an expert panel) was adopted as a criterion of remission. However, most of our BD patients (16 with BD-I and 14 with BD-II) met the HDRS-17 $\leq$ 7 criterion. In addition, it was still hard to define remission, as all of the other recruited BD patients in the present study reported a much improved emotional status or a return to baseline emotional state. Fourth, the cognitive tasks were not performed during the acquisition of PET scans. Therefore, the findings of the correlations are only suggestive of a relationship between hypometabolism and reduced cognitive function. However, several studies have shown that resting cerebral glucose metabolic rate correlates well with cognitive performance, even if assessed non-concurrently (21–23).

Conclusions

To the best of our knowledge, this is the first study relating poor executive function to glucose hypometabolism in specific brain regions in patients with remitted BD-I and BD-II, and our findings support the hypothesis of a neurobiological difference between subtypes of BD. BD-I (even remitted BD-I) is associated with significant worsening of executive function. More impairment of fronto-limbic regulation, more severe glucose hypometabolism in the PFC, ACC, and insula, and more severe glucose hypermetabolism in the limbic structures of the brain may explain the loss of executive function.

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Disclosures

The authors of this paper declare that they have no actual or potential conflicts of interest in connection with this manuscript.

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Supporting information

Additional Supporting information may be found in the online version of this article:

Figure S1. Similar fronto-thalamic-limbic pattern of glucose metabolism dysregulation in patients with remitted bipolar I disorder (BD-I) and bipolar II disorder (BD-II) versus healthy controls (HC).

Figure S2. Correlation between cerebral glucose metabolism and attention and memory in patients with remitted bipolar disorder (BD) and healthy subjects.