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A Reduced Gray Matter Volume in Patients with Bipolar II Disorder in a Japanese Sample: A Comparison with Schizophrenia

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Abstract

Objective: Neuroimaging studies of bipolar disorders have provided an insight into the pathophysiology, and have raised an issue of a shared change with schizophrenia and the normalizing effect of lithium on the alteration. Despite the classification of the bipolar disorders into the bipolar I disorder (BP-I) and bipolar II disorder (BP-II), the patients with BP-II have only been involved in a limited number of the neuroimaging studies. There is minimal information about the direct comparison between BP-II and schizophrenia.

Methods: All patients were diagnosed using DSM-5 criteria. A cross-sectional study was carried out to compare the regional brain volumes among the patients with BP-II taking lithium (BP-II-On, n=17) and not taking it (BP-II-Off, n=22), the patients with schizophrenia (n=35) and healthy controls (n=36). The MRI data were processed using Statistical Parametric Mapping 8 and the divided brain areas were defined by an automated anatomical labeling.

Results: A significant reduction in the gray matter volume of the frontal, temporal and limbic lobes was similarly observed in BP-II-off and schizophrenia patients when compared to the controls. The brain volume of BP-II-On had significantly decreased in the temporal lobe, but not in either the frontal or limbic lobe. The less pronounced reduction of BP-II-On was also observed in the sub-regions of the prefrontal and limbic cortices, such as the anterior cingulate cortex.

Conclusion: The present study suggests that there was a similarity in the distribution pattern of the decreased gray matter volume in the brain between BP-II and schizophrenia, placing an emphasis on the lithium effect that putatively normalized the abnormality in the anterior frontal and limbic brain areas of BP-II. However, further studies are required to replicate the results in a larger cohort and to confirm the lithium effect in a longitudinal study.

Keywords: Bipolar II disorder; Schizophrenia; Gray matter: SPM8; An atlas-based method; Lithium; Prefrontal cortex; Anterior cingulate cortex

Introduction

The pathophysiology of psychiatric disorders may underlie an abnormality in the brain structure constituting the functional neural circuitry [1,2]. Studies employing the neuroimaging technique have revealed a significant change in bipolar disorders [2-8] as well as schizophrenia [9,10], showing a potential overlap of the structural abnormalities in the front-temporal cortices and cingulate cortex [11-13]. In addition to the neuroimaging study, evidence of co-aggregation of bipolar disorders and schizophrenia in families [14,15] and sharing of the susceptibility genes [16,17] have stimulated an argument about the continuity between the two psychiatric disorders [18-20].

The bipolar II disorder (BP-II) characterized by depressive and hypomanic episodes were initially distinguished by Dunner et al. [21] from the bipolar I disorder (BP-I) or unipolar depression. The BP-II was then officially recognized as a distinctive mental disorder from the BP-I in DSM-IV. The high diagnostic stability of each bipolar disorder was supported by long-term follow-up studies [22,23]. BP-II was more common than BP-I in relatives of probands with BP-II, and vice versa [24]. BP-II was more prominent than BP-I in several clinical features, such as the number of mood episodes, chronic course of illness, seasonality and suicide attempts [25]. Thus, accumulating evidence has supported the division of the bipolar disorders.

In spite of the diagnostic classification of the bipolar disorders, most of the volumetric neuroimaging studies examined only the BP-I patients or patients with indiscriminately combined BP-I and BP-II [3,4,11-13,26,27]. A limited number of studies focused on the BP-II patients reported a reduction in the brain areas such as the frontal, temporal and limbic lobes, indicating that abnormalities in patients with BP-II were less widespread and more focal than those in patients with BP-I [28-32].

The present study carried out a cross-sectional neuroimaging investigation to make a direct comparison among the BP-II, schizophrenia and healthy controls. However, exposure to a psychotropic drug is a potentially effective factor on changes in the volumes of the brain areas. Many studies suggested the normalizing effect of lithium on the decreased volumes of the limbic brain area such as the hippocampus, amygdala and cingulate cortex [33,34]. As the present study examined the patients receiving the naturalistic clinical treatment with medications, the patients with BP-II were separated into two groups, i.e., the BP-II patients taking lithium or not.

An atlas-based method for *in vivo* volumetric studies using MRI data has been used to calculate the absolute volumes of the pre-defined

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brain areas of an individual subject [35]. Using the automated method, we evaluated the similarity and difference between the BP-II and schizophrenia in the regional brain volumes with an interest in the effect of lithium on the BP-II patients.

Materials and Methods

Participants

The demographic and clinical characteristics of the participants of this study are listed in Table 1. The subjects ranged in age from 20 to 56 years old, and included patients with BP-II (n=39), patients with schizophrenia (n=35) and the healthy controls (n=36). The BP-II patients were divided into two groups, namely, the patients with BP II who were currently treated with lithium for more than four weeks (BP-II-On; n=17) and the patients with BP II who had never taken lithium (n=14) or did not receive lithium for more than four weeks prior to the MRI study (n=8) (BP-II-Off; n=22). All patients were recruited from inpatients or outpatients of the Tokyo Medical and Dental University Medical Hospital, and were diagnosed using DSM-5 criteria [36]. At the time of the MRI scanning session, patients with BP-II were evaluated by the Hamilton Rating Scale for Depression-17 items (HAMD) and the Young Mania Rating Scale (YMRS), while patients with schizophrenia were assessed by the Positive and Negative Syndrome Scale (PANSS) [37]. The control group comprised of healthy comparison subjects matched to the patients in terms of age and gender distribution that were screened for a current or lifetime history of DSM-IV-TR Axis I using the SCID-I/NP [38]. None of the patients or controls had any history of neurological injury or disease, severe physical diseases, or substance abuse that could affect their brain function and they were physically healthy at the time of the scanning.

This study was approved by the Ethics Committee of the Tokyo Medical and Dental University Medical Hospital and written informed consent was obtained from all the subjects.

MRI data acquisition

All subjects underwent an MRI study using a 3.0-tesla General Electric Signa (General Electric, Milwaukee, WI, USA). A T1-weighted 3 dimensional fast spoiled-gradient recalled (3D-FSPGR) sequence that yielded 160-192 contiguous slices of 1.0 mm thickness in the sagittal plane (repetition time [TR]=7.288 ms; echo time [TE]=2.752 ms; flip angle=20°; field of view [FOV]=240 mm; number of excitations=1; pixel matrix=288 × 256) was used for the volume analysis.

MRI data processing

The analysis of the MRI data was carried out by a previously described procedure [39]. The MRI data were processed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm) in which we applied the VBM8 toolbox which is an extension of the unified segmentation model consisting of a spatial normalization, bias field correction, and tissue segmentation [40]. Registration to the stereotactic space of the Montreal Neurological Institute (MNI) consisted of a linear affine transformation and nonlinear deformation using high-dimensional Diffeomorphic Anatomical Registration through Exponential Lie Algebra (DARTEL) normalization [41]. Six parameters of the segmentation process, i.e., 'Bias regularization', 'Bias FWHM', 'Warping regularization', 'Sampling distance', 'Use-SANLM de-noising filter' and 'MRF weighting' were carried out with the default settings of VBM8, whereas the 'Modulated normalized' in the 'Writing options' was set to 'affine+non-linear (SPM8 default)' to obtain the absolute volume.

The GM volume of the region of interest was evaluated using the WFU PickAtlas ver. 2.5.5 [35] in SPM8. The subdivided brain areas in the cortical and limbic lobes were defined by the Automated Anatomical Labelling (http://neuro.imm.dtu.dk/wiki/Automated_Anatomical_Labeling). The evaluated volume was expressed as the

	Healthy Controls (n=36)	Bipolar II Disorder		Schizophrenia (n=35)	Values of Statistics
		Off-drug of Lithium (n=22)	On-drug of Lithium (n=17)		
Gender (F/M)	17/19	14/8	7/10	19/16	χ^2=2.392, d.f.=3, p=0.495
Age (years)	35.1 ± 9.68	39.5 ± 9.97	37.6 ± 11.7	35.1 ± 8.90	F=1.231, d.f.=3, p=0.302
Education year (years)	15.9 ± 1.89	14.4 ± 1.97	14.2 ± 2.11	13.8 ± 2.43***	F=6.389, d.f.=3, p=0.001
Handedness (r/l)	34/2	22/0	14/3	32/3	χ^2=4.684, d.f.=3, p=0.196
Age of onset of disorders (years)	nd	25.6 ± 10.6	28.6 ± 10.1	22.9 ± 6.3	F=2.589, d.f.=2, p=0.082
Hamilton Depression Rating Scale score (17 items)	nd	11.9 ± 5.01	14.0 ± 9.0	nd	t=0.918, d.f.=37, p=0.364
Young Mania Rating Scale score	nd	2.4 ± 3.9	4.2 ± 4.2	nd	t=1.409, d.f.=37, p=0.167
Positive and negative syndrome scale					
Positive	nd	nd	nd	14.2 ± 7.2	
Negative	nd	nd	nd	19.0 ± 7.8	
General	nd	nd	nd	32.4 ± 10.4	
Lithium use	0	0	17 (100)	0	
Dosage (mg/day)	0	0	705 ± 253	0	
Serum concentration (mEq/L)	0	0	0.64 ± 0.18	0	
Antipsychotics use	0	14 (63.06)	14 (82.4)	35 (100)	χ^2=14.250, d.f.=2, p=0.001
CP-equivalent dosage (mg/day)	0	367 ± 98.2	258 ± 69.0	867 ± 1071	
Anticonvulsanats use	0	19 (86.3)	7 (41.2)	5 (14.2)	χ^2=28.835, d.f.=2, p<0.001
Antidepressants use	0	10 (45.5)	5 (29.4)	3 (8.6)	χ^2=10.294, d.f.=2, p=0.006
Benzodiazepines use	0	22 (100)	17 (100)	24 (68.6)	χ^2=14.397, d.f.=2, p=0.001

Continuous variables are expressed as mean ± SD and categorical data are expressed by the number of patients (%). For continuous variables, the comparison between two groups was carried out by the two-tailed Student t test and the comparison among more than three groups was done by the one-way ANOVA with the Scheff post hoc multiple comparisons. The comparison of proportions was analyzed by the Chi square tests. If the expected cell frequencies were <5, we used Fisher's exact test for the analysis. CP: Chloropromazine; nd: not determined

Table 1: Demographic, psychological and clinical characterizations of the participants.

fraction (%) of the total intracranial volume, i.e., the sum of the total volumes of the gray matter (GM), white matter (WM) and CSF space.

Statistical Analysis

We compared the demographic, psychological and clinical characteristics of the participants. The continuous variables are expressed as the mean ± SD and the categorical data are expressed as numbers. The two-tailed Student *t* test was used for the continuous variables. The comparison of the proportions was analyzed by the Chi square tests. In addition, a comparison among more than two groups was carried out using one-way ANOVA followed by the post hoc Scheffe's test. For adjustment of the multiple analysis of the ANOVA within three intracranial components (Table 2), within eight brain areas (Table 3) and within 20 sub-divided region in the frontal and limbic lobes (Table 4), the statistical significance level was set at a *p* value of <0.05 by the Bonferroni correction. All the statistical analyses were carried out using the Statistical Package for the Social Sciences, version 21.0 (SPSS, Inc., Chicago, IL, USA).

Results

There were no differences in age, sex or handedness among the groups of patients and healthy controls, while the number of education years of the schizophrenia group was significantly shorter than that of the control. There were no differences in the age of onset of the disorders among the three groups of patients. The score of the 17-item HAMD or the YMRS did not differ between the two BP-II groups in the MRI study.

The comparisons of the absolute total intracranial volume and the fractions of the GM, WM and CSF space among the groups are shown in Table 2. The one-way ANOVA analysis revealed a statistically significant decrease in the GM (F=5.922, d.f.=3, 106, p<0.05 after adjustment) and the CSF (F=14.940, d.f.=3, 106, p<0.05 after adjustment). Compared to the healthy controls, a statistically significant decrease was observed in the ratio of the GM of the BP-II-Off and the schizophrenia, but not of the BP-II-On. The ratio of CSF space of each group of patients significantly differed from that of the healthy controls.

Table 3 shows the results of the GM for the whole brain divided into eight areas. The ANOVA analysis revealed a statistically significant change in the ratio of the frontal lobe (F=8.113, d.f.=3, 106, p<0.05 after adjustment), temporal lobe (F=8.605, d.f.=3, 106, p<0.05 after adjustment) and limbic lobe (F=5.559, d.f.=3, 106, p<0.05 after adjustment). In the BP-II-Off and schizophrenia groups, the GM ratio had statistically and significantly decreased in the frontal, temporal and limbic lobes, compared to that of the controls. The ratio of the BP-II-On was significantly reduced in the temporal lobe, but not in the frontal lobe or the limbic lobe, in comparison to that of the controls (Figure 1).

The results of the subdivided brain regions of the frontal and limbic lobes are shown in Table 4. There was a statistically significant change (p<0.05 after adjustment) in the five regions of the frontal lobe, i.e., superior frontal gyrus (medial) (F=5.365, d.f.=3, 106), superior frontal gyrus (medial orbital) (F=6.513, d.f.=3, 106), middle frontal gyrus (F=6.310, d.f.=3, 106), inferior frontal gyrus (trianglular part) (F=8.849, d.f.=3, 106) and inferior frontal gyrus (opercular part) (F=6.313, d.f.=3, 106) and one region of the limbic lobe, i.e., the anterior cingulate and paracingulate gyri (F=9.354, d.f.=3, 106). In all of the regions, the GM ratio of the BP-II-Off as well as the schizophrenia differed from that of the controls, while there was no change between the BP-II-On group and the controls regarding the GM ratio.

	Healthy Controls (n=36)	Bipolar II Disorder		Schizophrenia (n=35)	F value of ANOVA
		Off-drug of Lithium (n=22)	On-drug of Lithium (n=17)		
Total intracranial volume (ml)	1441 ± 141 (1393~1489)	1396 ± 149 (1329~1461)	1416 ± 130 (1349~1483)	1419 ± 141 (1371~1468)	0.499
Gray matter (%)	44.00 ± 2.09 (43.29~44.70)	41.49 ± 3.12 ** 40.10~42.87)	42.45 ± 2.50 (41.16~43.74)	42.29 ± 2.01 * (41.60~42.98)	5.922#
White matter (%)	40.36 ± 2.02 (39.672~41.04)	40.40 ± 2.85 (39.15~41.67)	40.00 ± 1.31 (39.33~40.67)	40.28 ± 1.55 (39.74~40.81)	0.159
CSF space (%)	15.65 ± 1.38 (15.18~16.11)	18.10 ± 1.33 *** (17.519~18.69)	17.55 ± 1.89 ** (16.58~18.52)	17.43 ± 1.59 *** (16.89~17.98)	14.940 #

Data are expressed as mean ± SD. The volume of each component, i.e., gray matter, white matter and CSF space, is expressed as a fraction (%) of the total intracranial volume. The comparison among the groups and the estimation of the 95% confidence interval (CI) were analyzed by the one-way ANOVA. # The statistical significance level was set at a p value of <0.0167 adjusted by the Bonferroni correction for the multiple comparison within the three components. After the ANOVA, a multiple comparison among the four groups in each brain component was carried out by Schffe's test. * p<0.05 vs. healthy controls, ** p<0.01 vs. healthy controls, *** p<0.001 vs. healthy controls

Table 2: Comparison of the total intracranial volume and the components among the four groups.

Brain Areas	Healthy Controls (n=36) (95% CI)	Bipolar II Disorder		Schizophrenia (n=35) (95% CI)	F value (ANCOVA)
		Off-drug of Lithium (n=22) (95% CI)	On-drug of Lithium (n=17) (95% CI)		
Frontal lobe	11.15 ± 0.77 (10.89~11.29)	10.16 ± 0.85 ** (10.07~10.59)	10.51 ± 0.88 (10.28~10.87)	10.47 ± 0.78 *** (10.19~10.61)	8.113 #
Temporal lobe	7.07 ± 0.42 (6.93~7.16)	6.69 ± 0.36 ** (6.60~6.91)	6.63 ± 0.46 ** (6.48~6.83)	6.64 ± 0.40 *** (6.49~6.73)	8.605 #
Parietal lobe	5.47 ± 0.45 (5.31~5.57)	5.22 ± 0.53 (5.12~5.47)	5.24 ± 0.51 (5.08~5.46)	5.29 ± 0.40 (5.13~5.40)	1.794
Occipital lobe	3.98 ± 0.31 (3.87~4.08)	3.82 ± 0.40 (3.72~3.98)	3.91 ± 0.26 (3.79~4.08)	3.83 ± 0.31 (3.70~3.91)	1.768
Limbic lobe	4.27 ± 0.22 (4.18~4.32)	4.07 ± 0.29 * (4.02~4.20)	4.18 ± 0.26 (4.10~4.30)	4.07 ± 0.21 ** (3.98~4.12)	5.558 #
Sub-lobal area	3.76 ± 0.29 (3.66~3.84)	3.51 ± 0.34 (3.42~3.67)	3.68 ± 0.32 (3.56~3.83)	3.68 ± 0.27 (3.57~3.76)	3.304
Cerebellum	5.49 ± 0.43 (5.35~5.69)	5.35 ± 0.64 (5.15~5.57)	5.59 ± 0.43 (5.37~5.84)	5.62 ± 0.46 (5.43~5.76)	1.508
Brainstem	0.407 ± 0.060 (0.388~0.425)	0.379 ± 0.053 (0.355~0.402)	0.372 ± 0.044 (0.345~0.398)	0.382 ± 0.054 (0.363~0.400)	2.268

Data are expressed as mean ± SD. The volume of each brain area is expressed as a fraction (%) of the total intracranial volume. The comparison among the groups and the estimation of the 95% confidence interval (CI) were analyzed by the one-way ANOVA. # The statistical significance level was set at a p value of <0.00625 adjusted by the Bonferroni correction for the multiple comparison within the eight brain areas. After the ANOVA analysis, a multiple comparison among the four groups in each brain area was carried out by Schffe's test. * p<0.05 vs. healthy control, ** p<0.01 vs healthy controls, *** p<0.001 vs. healthy controls

Table 3: Comparison of eight brain areas in the entire brain among the four groups.

Discussion

The BP-II patients in the present study were divided into the two sub-groups, i.e., BP-II-Off and BP-II-On, according to their treatment condition with lithium. The volumetric reduction in the whole gray matter was significant in the BP-II-Off and schizophrenia patients, but not in the BP-II-On group. The gray matter volume of the BP-II-Off was also significantly decreased in the discrete areas of the whole brain, i.e., frontal, temporal and limbic lobes, which was similar to the change in the schizophrenic patients. A number of studies using voxel-based-morphometry (VBM) on the BP-II patients also revealed reduced volumes in the brain regions of the prefrontal, limbic and temporal cortices [28,29,31,32,42]. In schizophrenics at the chronic state, a consistent finding of the VBM studies was also the deficits in the regions of the frontal and temporal lobes [9,10,43,44]. In addition, the direct comparison between BP-II and schizophrenia in the present study suggested that there was a similarity between the two psychiatric disorders in the distribution of the brain areas involved in the deficits of the gray matter volume.

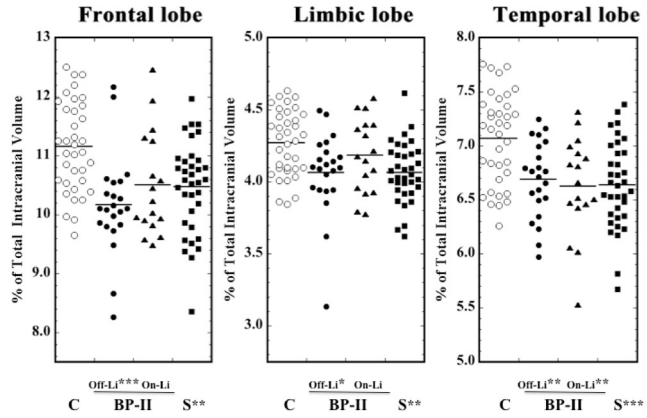

Figure 1: The scatter plots of the fraction of the gray matter volume in the frontal, limbic and temporal lobes.
Data are expressed as a fraction (%) of the total intracranial volume of each individual. The comparison among the four groups was analyzed by a one-way ANOVA, and the statistical significant level was set at a p value of <0.00625 adjusted by the Bonferroni correction for the multiple comparisons within the eight brain areas. After the analysis, a post hoc analysis using the Scheffe's test was carried out. The horizontal bar indicates the mean of each group. ○ ; healthy controls (C), ● ; patients with bipolar II disorder (BP-II) who were not taking lithium (Off-Li), ▲; patients with BP-II who were taking lithium (On-Li), ■; patients with schizophrenia (S), * p<0.05 vs. healthy controls, ** p<0.01 vs. healthy controls, *** p<0.001 vs. healthy controls.

In the brain of the BP-II-On, the changes in the whole gray matter volume and the frontal-limbic lobes were less prominent, whereas the brain volume was significantly decreased in the temporal lobe. The pattern of the less significant reduction of the BP-II-On and the pronounced decrease in both the BP-II-Off and the schizophrenic patients was also observed in five prefrontal gyri of 14 sub regions of the frontal lobe and in one area of six sub regions of the limbic lobe, i.e., the anterior cingulate cortex. Circumstantial evidence suggests that lithium use could be associated with the increased or normalized volume of gray matter in patients with a bipolar disorder [33,34]. The anterior cingulate cortex could be one of the possible brain regions where lithium could normalize the reduced brain volume of the bipolar patients. However, more attention to the effect of lithium on bipolar disorders has been paid to other areas such as the hippocampus and amygdala, while the studies were carried out mainly on BP-I [34,45,46]. The volumetric studies of BP-II did not find any change in either the hippocampus or amygdala or any effect of lithium [28-32,42]. The present study also demonstrated that there were no changes in the

Brain Areas	Healthy Controls (n=36) (95% CI)	Bipolar II Disorder		Schizophrenia (n=35) (95% CI)	F value (ANOVA)
		Off-drug of Lithium (n=22)	On-drug of Lithium (n=17)		
Superior fronal gyrus, dorsolateral	1.244 ± 0.128 (1.201~1.287)	1.122 ± 0.0.134 (1.062~1.181)	1.175 ± 0.128 (1.109~1.240)	1.197 ± 0.127 1.154~1.241)	4.296
Superior fronal gyrus, medial	0.879 ± 0.086 (0.850~0.908)	0.796 ± 0.086 ** (0.758~0.834)	0.836 ± 0.100 (0.784~0.887)	0.810 ± 0.086 * (0.781~0.840)	5.365 #
Superior fronal gyrus, medial orbital	0.354± 0.042 (0.340~0.368)	0.316 ± 0.037 ** (0.299~0.332)	0.325 ± 0.032 (0.308~0.341)	0.325 ± 0.034 * (0.313~0.336)	6.513 #
Superior fronal gyrus, orbital part	0.448 ± 0.034 (0.436~0.459)	0.433 ± 0.024 (0.422~0.444)	0.431± 0.028 (0.417~0.445)	0.433 ± 0.033 (0.421~0.444)	1.992
Middle frontal gyrus	1.850 ± 0.185 (1.787~1.912)	1.671 ± 0.176 ** (1.593~1.749)	1.724 ± 0.183 (1.630~1.818)	1.692 ± 0.180 ** (1.631~1.754)	6.310 #
Middle frontal gyrus, orbital part	0.457 ± 0.043 (0.443~0.472)	0.425± 0.03533 (0.409~0.441)	0.444 ± 0.033 (0.427~0.460)	0.429 ± 0.037 (0.416~0.441)	4.630
Inferior frontal gyrus, triangular part	1.99 ± 0.16 (1.93~2.03)	1.77 ± 0.18 *** (1.749~1.87)	1.85 ± 0.20 (1.79~1.94)	1.81 ± 0.19 ** (1.75 ± 1.868)	8.849 #
Inferior frontal gyrus, opercular part	2.92 ± 0.25 (2.83~3.00)	2.66 ± 0.23 ** (2.56~2.76)	2.76 ± 0.25 (2.63~2.89)	2.76 ± 0.24 * (2.68~2.84)	6.313 #
Inferior frontal gyrus, orbital part	2.92 ± 0.25 (2.83~3.00)	2.66 ± 0.23 (2.56~2.76)	2.76 ± 0.25 (2.63~2.89)	2.76 ± 0.24 (2.68~2.84)	4.869
Precentral gyrus	1.04 ± 0.11 (1.00~1.07)	0.95 ± 0.14 (0.92~1.01)	0.98 ± 0.14 (0.94~1.04)	0.98 ± 0.10 (0.94~1.01)	3.202
Supplementary motor area	0.834 ± 0.097 (0.799 ~0.860)	0.767 ± 0.12 (0.739~0.818)	0.796 ± 0.10 (0.756~0.845)	0.801 ± 0.084 (0.765~0.827)	2.188
Paracentral lobule	0.314 ± 0.050 (0.295~0.329)	0.312 ± 0.057 (0.294~0.338)	0.318 ± 0.056 (0.294~0.344)	0.317 ± 0.049 (0.298~0.333)	0.059
Olfactory cortex	0.154 ± 0.015 (0.148~0.157)	0.141 ± 0.015 (0.138~0.149)	0.142 ± 0.011 (0.136~0.149)	0.145 ± 0.016 (0.139~0.148)	4.382
Gyrus rectus	0.355 ± 0.035 (0.342~0.363)	0.336 ± 0.031 (0.329~0.356)	0.337 ± 0.040 (0.325~0.355)	0.338 ± 0.040 (0.325~0.346)	0.130
Anterior cingulate and paracingulate gyri	0.772 ± 0.074 (0.747~0.787)	0.691 ± 0.073 ** (0.676~0.729)	0.736 ± 0.084 (0.711~0.770)	0.693 ± 0.059 *** (0.668~0.709)	9.354 #
Middle cingulate and paracingulate gyri	1.13 ± 0.096 (0.747~0.787)	1.05 ± 0.11 (0.676~0.729)	1.09 ± 0.13 (0.711~0.7709)	1.07± 0.091 (0.668~0.709)	3.745
Posterior cingulate gyrus	0.148 ± 0.021 (0.140~0.1537)	0.138 ± 0.024 (0.133~0.150)	0.140 ± 0.011 (0.1313~0.150)	0.146± 0.025 (0.138~0.151)	1.119
Amygdala	0.134 ± 0.12 (0.129~0.138)	0.128 ± 0.018 (0.122~0.134)	0.135 ± 0.010 (0.129~0.142)	0.132 ± 0.014 (0.127~0.137)	1.123
Hippocampus	0.538 ± 0.029 (0.524~0.552)	0.544 ± 0.044 (0.527~0.562)	0.547 ± 0.029 (0.527~0.567)	0.531 ± 0.053 (0.517~0.545)	0.709
Parahippocampus gyrus	0.547 ± 0.035 (0.747~0.797)	0.550± 0.049 (0.658~0.723)	0.557 ± 0.035 (0.693~0.779)	0.534 ± 0.036 (0.673~0.713)	0.059

Data are expressed as mean ± SD. The volume of each brain area is expressed as a fraction (%) of the total intracranial volume. The comparison among the groups and the estimation of the 95% confidence interval (CI) was analyzed by the one-way ANOVA. # The statistical significance level was set at a p value of <0.0025 adjusted by the Bonferroni correction for the multiple comparison within the 20 brain areas. After the ANOVA analysis, a multiple comparison among the four groups in each brain area was carried out by Schffe's test. The subdivided brain areas in the frontal and limbic lobes were defined by the Automated Anatomical Labelling. * p<0.05 vs. healthy controls, ** p<0.01 vs. healthy controls, *** p<0.001 vs. healthy controls

Table 4: Comparison of the subdivided brain areas in the frontal and limbic lobes among the four groups.

brain volumes of the two limbic areas in any BP-II patient groups. Thus, it appears that the normalizing effect of lithium might work on the selective brain areas of the BP-II patients such as the prefrontal and cingulate gyri.

The present study has a number of limitations to be carefully considered. As the study was a cross-sectional one, the alteration observed in the study included both a premorbid change as well as a progressive one after the onset of the disorder. The number of patients was relatively small, taking the heterogeneity of the psychiatric disorders into account [47]. Although the present study was controlled for important demographic and clinical variables, i.e., age, sex and age at onset, all the patients with schizophrenia and about 70% of the BP-II were treated with antipsychotic drugs. It may not be negligible that other medications such as antiepileptic drugs, antidepressants and benzodiazepines might confound the volumetric assessments. In addition, we could not control other factors, such as social and environmental, which might have an unknown effect on the brain structure, particularly during the longitudinal clinical course. Finally, the atlas-based method used in the procedure of the MRI data analysis may fail to detect an isolated, spotty and significant change in the predefined brain area. Hence, the current findings need to be replicated in independent cohorts consisting of a large number of subjects in order to generalize them.

In conclusion, the present study suggested a similarity in the distribution of the decreased brain volume between the BP-II patients and the schizophrenics, and the possibility of the normalizing effect of lithium in selective brain areas. However, further studies are required to replicate the similarity in an independent cohort and to confirm the lithium effect in a longitudinal study.

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