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ORIGINAL ARTICLE

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Increased hippocampal, thalamus and amygdala volume in long-term lithium-treated bipolar I disorder patients compared with unmedicated patients and healthy subjects

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Objective: Magnetic resonance imaging (MRI) studies in bipolar I disorder (BD-I) suggest that lithium is associated with increased volumes of cortico-limbic structures. However, more rigorous control of confounding factors is needed to obtain further support for this hypothesis. The aim of the present study was to assess differences in brain volumes among long-term lithium-treated BD-I patients, unmedicated BD-I patients, and healthy controls.

Methods: This was a cross-sectional study with 32 euthymic BD-I patients (16 on lithium monotherapy for a mean of 180 months, and 16 receiving no medication for at least the 2 months prior to the study) and 20 healthy controls. Patients were euthymic (Hamilton Depression Rating Scale [HDRS] <6 and Young Mania Rating Scale [YMRS] <7) and had not taken psychotropic medications other than lithium for at least 6 months. Brain images were acquired on a 1.5 Tesla MRI (Phillips, Amsterdam, The Netherlands) and segmented to generate volumetric measures of cortical and subcortical brain areas, ventricles and global brain.

Results: Significant differences were found in the volumes of the left amygdala (P=.0003), right amygdala (P=.030), left hippocampus (P=.022), left thalamus (P=.022), and right thalamus (P=.019) in long-term lithium-treated BD-I patients, compared to unmedicated patients and controls, after multivariable adjustment. No differences were observed in global brain volume or in ventricular size among the three groups. Likewise, there was no correlation between serum lithium levels and the increase in size in the described brain areas.

Conclusions: The structural differences found among the three groups, and specifically those between long-term lithium-treated and unmedicated BD-I patients, indicate increased limbic structure volumes in lithium-treated patients.

KEYWORDS
bipolar disorder, brain volume, lithium, neuroimaging

1 | INTRODUCTION

Neuroimaging studies have contributed significantly to our understanding of biological alterations in bipolar disorder (BD),[1,2] but further research is still needed to definitively elucidate the effects that psychotropic medications have on brain structure and activation in bipolar patients. Even some of the first-line agents for the treatment of BD, such as lithium, have an unknown effect on brain structures. Often the continuation of medications for BD to achieve relapse prevention or mood stabilization is based on clinical judgment. However,

limited data are available about the neurobiological reasons why they should be continued or discontinued in euthymic patients, and about their neuroanatomical effects on the neural circuits of emotion regulation.[3–5]

A number of studies and meta-analyses have reported cerebral structural alterations in patients with BD. Compared to healthy subjects, BD-I patients on average have diminished hippocampal gray matter[6] and, as demonstrated by a recent meta-analysis, increased volume of the lateral ventricles, mainly the right ventricle.[6–9] Additionally, decreased amygdala volume has been reported in adults,[10] children and adolescents with BD-I when compared to healthy control subjects.[11]

Moreover, there is evidence of amygdala abnormalities prior to bipolar disorder onset in ultra-high risk patients compared with a healthy control group.[12] It has also been found that there is a direct relationship between the incidence of manic episodes and frontal cortical volume decrease (dorsolateral prefrontal and inferior frontal cortex) in BD patients.[13] Nevertheless, other studies have reported either no difference [14] or even increased amygdala volume in BD patients compared with control subjects [15] and schizophrenic patients,[16] which shows that changes in amygdala volumes are not a universal finding.

Psychotropic drugs commonly used to treat BD-I, including lithium, have been reported to revert or attenuate these neuroanatomical abnormalities associated with the disorder.[8] An apparent neuroprotective effect of lithium is associated with increased volumes of some neuroanatomical structures within the cortico-limbic neural circuit.[17] Baykara et al. found, as a secondary outcome, that right hippocampal volume was increased in lithium-treated young patients with BD compared to the unmedicated group.[18] Although the mechanism of action of the effects of lithium on brain structures is not fully understood, studies in both humans and animals have provided evidence for its neurotrophic action.[19] In adult rodents, lithium produces a significant 25% increase in new cells in the dentate gyrus, suggesting that lithium enhances hippocampal neurogenesis.[20] However, no association has been found between changes in hippocampal anatomy and lithium dosage.[21]

The effect of medication on these brain structures is not yet clear and the studies conducted to date have some limitations concerning their samples, particularly the exclusion criteria for participation.[9] Experimental groups very often comprise patients who are taking combinations of psychotropic medications, with different subtypes of BD in the same sample, high psychiatric comorbidity, and unknown personal history of traumatic brain injury, substance dependence and electroconvulsive therapy; and some of the studies have no control group.[22–24] It has been strongly recommended that future studies recruit both unmedicated and medicated individuals for cross-sectional comparison studies. The unmedicated subjects included should not be going through a "wash-out" period, in which the medication is stopped for a short period prior to magnetic resonance imaging (MRI) acquisition, mainly on the grounds that many neurobiological and structural changes that may be induced by psychotropic medications might persist after pharmacological treatment discontinuation [4] or because discontinuation itself may cause brain changes.

The aim of this study was to assess the effect of long-term lithium treatment on both global brain volume and limbic brain structures, by comparing euthymic BD-I patients on long-term lithium monotherapy to unmedicated euthymic BD-I patients and to demographically matched healthy control subjects, in a population, namely Hispanic bipolar patients, largely unrepresented in previous research.

2 | METHODS

2.1 | Subjects

The study participants were 32 patients diagnosed with BD-I according to DSM-IV-TR criteria and 20 healthy controls. Participant inclusion criteria included being right-handed (Edinburgh Handedness Test), being between 18 and 60 years old, and having 5–16 years of education.

BD-I patients were recruited from the Mood Disorders Program of the university hospital Hospital Universitario San Vicente Fundación. The BD-I patients on long-term lithium monotherapy had stayed solely on lithium for at least 2 years, and the unmedicated BD-I subjects had decided to voluntarily abandon their medication and had been under no pharmacological treatment for at least 2 months prior to the study. The control group was comprised of individuals with no history of psychiatric illness or neurological treatment.

Exclusion criteria included a history of structural or degenerative neurological injuries, epilepsy, a psychiatric diagnosis other than mild BD-I, the use of benzodiazepines in the previous 6 months, a personal history of electroconvulsive therapy, the use of heart pacemakers or metal prostheses, pregnancy and treatment with psychotropic drugs other than lithium in the previous 6 months.

Bipolar I disorder was diagnosed using DSM-IV criteria based on the Diagnostic Interview for Genetic Studies (DIGS).[25] The presence of euthymia at the time of the MRI scanning was determined on the basis of a Young Mania Rating Scale (YMRS) score <6 [26] and a Hamilton Depression Rating Scale (HDRS) score <7,[27] according to international consensus. Serum lithium levels were evaluated once, in all lithium-treated patients, shortly before the MRI scans. The patients with serum lithium levels below the cut point (<0.6 mEq/l) were also included in the study (three patients). These data were taken into account when analyzing the correlation between serum lithium levels and structural changes. Lithium-treated patients received a clinical assessment to adjust their doses and continued to receive periodic follow-up evaluation.

All patients signed an informed consent form where the objectives, procedures and risks of their participation in the study were explained in detail. The Research Ethics Committees of the University of Antioquia and of the High Technology Medical Institute (CEI IATM; Instituto de Alta Tecnología Médica) approved the study.

2.2 | Acquisition and processing of MRI

A T1 volumetric sequence (TR/TE=9/4.1 ms; flip angle=8; voxel size 1×1×1 mm) was acquired on a Phillips Achieva 1.5T system powered by advanced Nova Dual gradients (Phillips, Amsterdam, the Netherlands). Participants were required to lie still for 1 h.

TABLE 1 Socio-demographic and clinical characteristics of the study groups

Variables	BD-I patient groups		Healthy control subjects (n=20)	*P*- value
	Lithium-treated BD-I patients (n=16)	Unmedicated BD-I patients (n=16)		
Age (years)	40.87 ± 7.10	41.81 ± 9.70	39.55 ± 10.25	0.761
Sex ratio (M/F)	6/10	8/8	6/14	0.470
Education (years)	14 (5)	11 (5)	13 (8)	0.665
Age at first episode (years)	23.63 ± 6.4	24.5 ± 5.4	NA	0.678
Illness duration (years)	17.25 ± 6.61	17.44 ± 8.52	NA	0.945
Number of manic and depressive episodes	4 (2)	2 (1)	NA	0.010
Serum lithium levels (mEq/l)	0.76 (0.44)	NA	NA	NA
Treatment duration (months)	130 (184)	NA	NA	NA

Values are presented as median, n/n, or mean ± standard deviation. NA, not applicable; M, male; F, female; BD-I, bipolar disorder type I.

Volumetric segmentation was performed with the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). This processing includes motion correction and averaging, removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter–white matter boundary and automated topology correction.[28] Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation, registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across subjects, parcellation of the cerebral cortex into units with respect to gyral and sulcal structure, and creation of a variety of surface-based data including maps of curvature and sulcal depth.[29] All volumes were normalized for the subject's head size.

2.3 | Statistical analysis

The descriptive analysis of the study participants was based on measures of central tendency and dispersion for quantitative and continuous variables, and on frequency and percentages for qualitative and categorical variables. The Shapiro–Wilk test was used to determine if continuous variables were normally distributed and to establish the normality of the data. The homogeneity of the variances of whole-brain normalized volumes was assessed with Bartlett's chi-square test, and the differences between the three groups (lithium-treated patients, unmedicated patients and healthy controls) were statistically analyzed with analysis of covariance (ANCOVA) adjusted by age. After Scheffe's post hoc analysis of contrasts among pairs of adjusted means had been carried out, comparisons between groups (lithium-treated patients vs unmedicated patients, and lithium-treated patients vs healthy controls) were performed using multivariable linear regression.

The comparison of brain normalized volumes between long-term lithium-treated patients and healthy control subjects was adjusted for age, gender and years of education. In a similar fashion, the comparison between lithium-treated and unmedicated patients was adjusted for age, gender, years of education, age at first episode, years of disease course, and number of manic-depressive episodes. The correlations between serum lithium levels and normalized brain volumes were assessed with Pearson's correlation coefficients (*R*). Results with *P*-values ≤.05 were considered significant. Data were analyzed with Aabel 20/20 data vision 3 (Vista Data Vision, Reykjavik, Iceland), Statgraphics Centurion XVI (Statgraphics, Warrenton, VA, USA) and Statistical Package for Social Science (SPSS) 15.0 (International Business Machines Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Demographic and clinical variables

The three study groups – long-term lithium-treated BD-I patients, unmedicated BD-I patients, and healthy controls – had similar socio-demographic characteristics (education, age and gender) with no statistically significant differences. Regarding the clinical variables, both the lithium-treated and the unmedicated groups had an average of 17 years of illness duration. The number of manic and depressive episodes, however, was significantly lower in the unmedicated group than in the lithium-treated patients (*P*=.010). No significant differences were found between medicated and unmedicated subjects in HDRS and YMRS scores (Table 1).

3.2 | Comparisons between groups

3.2.1 | Comparison among the three groups

Age-adjusted ANCOVA showed significant differences among the three groups in the volumes of the left amygdala (*P*=.0003), right amygdala (*P*=.030), left hippocampus (*P*=.022), left thalamus

(*P*=.022), right thalamus (*P*=.019) and posterior half corpus callosum. Differences in white matter hypointensities were also identified among the three study groups (*P*=.012), but no significant differences were found in the other brain regions under study (the prefrontal cortex, pallidum, caudate, accumbens and cingulate gyrus) or in the volume of the lateral ventricles (left, *P*=.053 and right, *P*=.236). In the comparison of global brain volume, no significant differences were found (*P*=.546) (Table 2).

3.2.2 | Comparison between long-term lithium-treated and unmedicated bipolar patients

Multivariable analysis (including age, gender, years of education, age at first episode, years of disease course, and number of manic-depressive episodes) demonstrated a significantly larger volume in lithium-treated BD-I patients vs unmedicated patients for the left amygdala (*P*=.002), right amygdala (*P*=.04), left thalamus (*P*=.023) and right thalamus (*P*=.007). A significantly smaller volume was found for lithium-treated BD-I patients compared to unmedicated patients for the central corpus callosum (*P*=.017) and the anterior half corpus callosum (*P*=.036). The patients from the lithium group had a greater number of white matter hypointensities than unmedicated patients. There were no differences between the two groups in global brain volume (*P*=.273) and volume of the hippocampus or of the other brain structures under study (Table 3).

3.2.3 | Comparison between lithium-treated bipolar patients and control subjects

Multivariable analysis demonstrated that lithium-treated BD-I patients had significantly larger volumes than control subjects for the left amygdala (*P*=.025), right amygdala (*P*=.025), left thalamus (*P*=.022), right thalamus (*P*=.020) and left hippocampus (*P*=.007). Lithium-treated BD-I patients did not show differences in the volume of the corpus callosum in comparison with the control group. The lithium group had a greater number of white matter hypointensities than healthy controls. No differences were reported between the two groups in the volume of basal ganglia or in global brain volume (*P*=.499).

3.3 | Correlation between volume and serum lithium levels

Three patients in the lithium-treated group had lithium serum levels below the therapeutic range (<0.6 mEq/l) and only one of them had lithium levels below 0.4 mEq/l. The median serum lithium level was 0.76 mEq/l (0.44). When the correlation was assessed between serum lithium values and the volumes of the amygdala, hippocampus and thalamus, a direct association was found only between lithemia and magnetic resonance (MR) volumetry of the right amygdala (*R* = .4863). This suggests that the linear model is possibly appropriate (*P*=.0561) but must be tested in other studies with larger patient samples and longitudinal measurements of serum lithium levels.

4 | DISCUSSION

In the present study, significant differences were found when comparing amygdala, thalamus and hippocampal volumes among lithium-treated BD-I patients, unmedicated BD-I patients, and healthy controls. The study is unique in that all patients were receiving long-term lithium monotherapy; this reduced the confounding factors present in other structural neuroimaging studies, in which a high percentage of patients were receiving combined pharmacotherapy. A volumetric increase was observed in the bilateral amygdala, left hippocampus and bilateral thalamus in lithium-treated BD-I patients compared to healthy controls, data being adjusted for age, gender and years of education. When compared with unmedicated BD-I patients, long-term lithium-treated BD-I patients demonstrated significant volume differences in the amygdala and bilateral thalamus, even after multivariable adjustment, which suggests that the increase in the volume of these structures is due to long-term lithium exposure rather than a consequence of the underlying physiopathology of the disorder.

Our findings are consistent with previous studies and recent meta-analyses which demonstrate that the subgroup of patients who receive lithium may show increased amygdala and hippocampal volumes.[7,9,17–19,30–33] Lithium treatment has been associated with increased hippocampal head volume, which is not seen with other medications such as valproate or lamotrigine,[18,33] and with increased volume of the right hippocampus in bipolar adolescents compared to healthy controls.[18] Longitudinal studies show a 4–5% increase in hippocampal volume in lithium-treated patients throughout a 2–4-year follow-up period.[17,33,34] It has been reported that lithium-treated patients have larger brain volumes, by 7.6%, compared with patients not taking lithium.[7,35] In our results, however, no significant differences were found in global brain volume between long-term lithium-treated patients and unmedicated patients, or in the size of the lateral ventricles in patients with BD relative to controls.

A relevant finding, replicated in other studies and reported in several meta-analyses, is the increase in white matter hyperintensities in patients with BD: a 2.5-fold higher probability of white matter hyperintensities has been reported for patients with BD compared to subjects without the disorder.[7,9,35,36] Our study showed an increase in white matter hypointensities in patients on lithium compared to unmedicated patients and healthy controls. Further studies are needed to ascertain the relevance of this finding and its correlation with anatomic connectivity and neurocognitive performance.

No direct correlation was found between serum lithium levels and changes in the volume of the brain areas under study, in spite of the fact that medicated BD-I patients had been on lithium for 180 months on average and that serum levels were obtained from a single serum sample. The strength of the association was greater for the right amygdala, with a value close to 0.05. In the present study, the average level of lithium was 0.76 mg/L, but it could be as low as 0.32 mg/L. Another aspect possibly associated with increased volume of some brain structures is the time of exposure to lithium. This variable, however, was

TABLE 2 Analysis of brain region normalized volumes in each study group

Brain region	Lithium-treated BD-I patients (n=16)	Unmedicated BD-I patients (n=16)	Healthy control subjects (n=20)	*P*-value*
Left amygdala	8.29 ± 1.68	6.26 ± 1.36	7.21 ± 0.84	0.0003, *F*: 9.74
Right amygdala	8.51 ± 1.63	7.72 ± 1.17	7.12 ± 1.67	0.030, *F*: 3.76
Left hippocampus	23.91 ± 2.53	22.10 ± 2.62	21.70 ± 2.00	0.022, *F*: 4.13
Right hippocampus	24.44 ± 3.85	22.34 ± 3.31	22.86 ± 2.09	0.148, *F*: 1.98
Left thalamus	49.68 ± 7.55	44.53 ± 4.40	44.60 ± 5.79	0.022, *F*: 4.15
Right thalamus	47.65 ± 6.83	42.16 ± 5.90	42.68 ± 5.52	0.019, *F*: 4.29
Left caudate	60.46 ± 4.07	20.09 ± 2.39	20.27 ± 2.39	0.933, *F*: 0.07
Right caudate	21.75 ± 3.22	21.23 ± 2.45	21.17 ± 3.16	0.765, *F*: 0.27
Left putamen	31.32 ± 6.24	30.15 ± 4.30	29.57 ± 4.79	0.467, *F*: 0.77
Right putamen	31.80 ± 6.59	29.76 ± 4.63	28.55 ± 4.88	0.129, *F*: 2.14
Left pallidum	10.47 ± 2.25	9.73 ± 1.28	9.49 ± 1.17	0.185, *F*: 1.75
Right pallidum	10.77 ± 2.02	10.03 ± 1.13	9.85 ± 1.39	0.180, *F*: 1.77
Left accumbens	3.38 ± 0.96	3.29 ± 0.78	3.37 ± 0.64	0.974, *F*: 0.03
Right accumbens	2.86 ± 0.49	2.65 ± 0.85	2.76 ± 0.63	0.691, *F*: 0.37
Brain volume	1496203 ± 93972.79	1526900 ± 76755.29	1515787 ± 69515.51	0.546, *F*: 0.61
Intracranial volume	1403533 ± 173742.6	1363206 ± 141253.6	1332076 ± 123517.3	0.323, *F*: 1.16
Left anterior cingulate	11.47 ± 2.56	12.01 ± 3.49	12.52 ± 2.92	0.609, *F*: 0.50
Right anterior cingulate	15.57 ± 4.16	14.74 ± 5.16	16.09 ± 3.81	0.763, *F*: 0.27
Left lateral orbitofrontal	49.26 ± 6.47	51.64 ± 5.32	50.84 ± 3.64	0.355, *F*: 1.06
Right lateral orbitofrontal	47.59 ± 5.46	50.17 ± 5.75	51.52 ± 5.41	0.108, *F*: 2.33
Left medial orbitofrontal	36.89 ± 4.36	37.11 ± 5.71	37.21 ± 3.88	0.967, *F*: 0.03
Right medial orbitofrontal	34.30 ± 3.79	35.26 ± 3.55	36.08 ± 3.55	0.380, *F*: 0.99
Left posterior cingulate	19.43 ± 2.72	20.03 ± 3.98	20.63 ± 2.29	0.355, *F*: 0.64
Right posterior cingulate	20.13 ± 2.81	20.92 ± 3.86	21.89 ± 2.78	0.277, *F*: 1.32
Left rostral anterior cingulate	18.14 ± 3.51	17.20 ± 2.25	17.91 ± 2.48	0.642, *F*: 0.45
Right rostral anterior cingulate	15.27 ± 3.83	15.16 ± 2.76	14.37 ± 3.23	0.561, *F*: 0.58
Left rostral medial cingulate	109.17 ± 11.76	104.58 ± 11.03	105.21 ± 10.03	0.318, *F*: 1.17
Right rostral medial cingulate	113.05 ± 11.74	110.09 ± 15.05	109.84 ± 8.91	0.664, *F*: 0.41
Left superior frontal	154.47 ± 14.84	151.25 ± 10.52	152.79 ± 15.15	0.810, *F*: 0.21
Right superior frontal	147.47 ± 15.69	147.01 ± 13.51	144.86 ± 13.27	0.741, *F*: 0.30
Left lateral ventricle	48.54 ± 16.76	41.28 ± 15.89	36.45 ± 10.15	0.053, *F*: 3.12
Right lateral ventricle	50.22 ± 21.32	42.27 ± 26.86	38.03 ± 12.70	0.236, *F*: 1.49
White matter Hypointensities	14.42 ± 8.24	9.66 ± 3.32	9.33 ± 2.95	0.012, *F*: 4.90
Posterior corpus callosum	6.47 ± 1.34	6.26 ± 1.28	6.49 ± 0.99	0.764, *F*: 0.27
Medial posterior corpus callosum	2.50 ± 0.57	3.06 ± 0.62	3.00 ± 0.400	0.008, *F*: 5.35
Central corpus callosum	2.74 ± 0.55	3.26 ± 0.79	3.04 ± 0.49	0.069, *F*: 2.83
Medial anterior corpus callosum	2.83 ± 0.44	3.34 ± 0.79	3.06 ± 0.53	0.063, *F*: 2.93
Anterior corpus callosum	5.99 ± 1.35	6.53 ± 1.24	5.79 ± 1.04	0.188, *F*: 1.73

Results are presented as mean ± standard deviation. *ANCOVA adjusted by age. BD-I, bipolar disorder type I.

not included in our analysis. The strength of the current study is the comparison between lithium-treated patients, unmedicated patients, and healthy controls, and the exclusion of patients with psychotropic drug use in the 6 months before the experiment. However, these findings must be interpreted with caution due to the sample size, which may not have been be sufficient to determine that the findings of our study were due to the effect of lithium, and to the design of the study, which does not allow one to infer causality either.

TABLE 3 Comparison of brain region normalized volume between lithium-treated patients and control subjects; and between lithium-treated and unmedicated patients

Brain region	Lithium-treated BD-I patients (n=16) vs healthy control subjects (n=20) *P*-value* (CI: 95%) Adj.R^2	Lithium-treated BD-I patients (n=16) vs unmedicated BD-I patients (n=16) *P*-value** (CI: 95%) Adj.R^2
Left amygdala	0.025 (0.137; 1.889) 15.16%	0.002 (0.930; 3.599) 41.12%
Right amygdala	0.025 (0.177; 2.433) 15.24%	0.040 (0.067; 2.511) 22.11%
Left hippocampus	0.007 (0.574; 3.382) 33.23%	0.064 (−0.137; 4.367) 0.99%
Right hippocampus	0.166 (−0,590; 3.289) 16.14%	0.104 (−0.508; 5.113) 17.71%
Left thalamus	0.022 (0.731; 8.619) 33.85%	0.023 (0.852; 10.368) 26.63%
Right thalamus	0.020 (0.764; 8.461) 27.62%	0.007 (2.133; 12.327) 21.90%
Left caudate	0.863 (−1.978; 2.347) 4.41%	0.842 (−2.451; 2.979) 3.46%
Right caudate	0.609 (−1.632; 2.739) 0.12%	0.608 (−2.710; 1.619) 17%
Left putamen	0.273 (−1.447; 4.936) 28.90%	0.763 (−3.445; 4.638) 17.66%
Right putamen	0.059 (−0.129; 6.484) 33.17%	0.585 (−3.126; 5.420) 20.10%
Left pallidum	0.091 (−0.152; 1.956) 26.69%	0.297 (−0.692; 2.172) 14.02%
Right pallidum	0.127 (−0.248; 1.905) 19.60%	0.222 (−0.510; 2.088) 12.10%
Left accumbens	0.826 (−0.541; 0.435) 19.94%	0.748 (−0.787; 0.572) 12.57%
Right accumbens	0.582 (−0.285; 0.499) 0.53%	0.240 (−0.232; 0.881) 8.70%
Brain volume	0.499 (−77048.17; 38356.1) 7.03%	0.273 (−114866; 33963.02) 6.74%
Intracranial volume	0.147 (−21966.92; 140189.4) 38.95%	0.537 (−69053.91; 129148.3) 43.49%
Left anterior cingulate	0.220 (−3.098; 0.742) 0.30%	0.577 (−3.187; 1.817) 2.65%
Right anterior cingulate	0.782 (−3.193; 2.425) 7.41%	0.845 (−2.980; 3.613) 28.08%
Left lateral orbitofrontal	0.488 (−4.773; 2.331) 2.53%	0.266 (−7.654; 2.214) 2.37%
Right lateral orbitofrontal	0.046 (−7.432; −0.071) 13.13%	0.132 (−7.945; 1.108) 29.96%
Left medial orbitofrontal	0.739 (−3.253; 2.332)	0.702 (−3.065; 4.483) 19.03%
Right medial orbitofrontal	0.093 (−4.539; 0.370) 8.61%	0.704 (−3.765; 2.581) 7.59%
Left posterior cingulate	0.137 (−2.743; 0.396) 19.18%	0.808 (−2.719; 2.141) 26.19%
Right posterior cingulate	0.072 (−3.703; 0.169) 6.34%	0.718 (−2.350; 1.642) 49.42%
Left rostral anterior cingulate	0.902 (−1.965; 2.219) 5.84%	0.611 (−1.725; 2.872) 13.39%
Right rostral anterior cingulate	0.435 (−1.533; 3.478) 7.98%	0.821 (−2.357; 2.943) 7.46%
Left rostral medial cingulate	0.208 (−2.634; 11.644) 9.60%	0.150 (−2449; 15.026) 36.06%
Right rostral medial cingulate	0.432 (−4.105; 9.370) 9.46%	0.417 (−6.742; 15.754) 0.62%
Left superior frontal	0.576 (−7.416; 13.092) 0.07%	0.635 (−7.942; 12.772) 6.41%
Right superior frontal	0.563 (−7.363; 13.288) 9.83%	0.939 (−11.724; 12.638) 21.44%
Left lateral ventricle	0.014 (2.723; 22.052) 8.48%	0.435 (−8.607; 19.361) 2.22%
Right lateral ventricle	0.049 (0.045; 24.597) 1.56%	0.468 (−12.523; 26.424) 8.01%
White matter Hypointensities	0.026 (0.598; 8.927) 10.18%	0.042 (0.225; 11.563) 3.68%
Posterior corpus callosum	0.953 (−0.727; 0.770) 10.43%	0.972 (−1.015; 1.050) 9.61%
Medial posterior corpus callosum	0.006 (−0.809; −0.149) 22.20%	0.061 (−1.007; 0.244) 10.89%
Central corpus callosum	0.106 (−0.631; 0.063) 9.65%	0.017 (−1.137; −0.126) 30.14%
Medial anterior corpus callosum	0.214 (−0.557; 0.129) 0.25%	0.036 (−1.114; −0.041) 11.01%
Anterior corpus callosum	0.430 (−0.478; 1.094) 6.38%	0.282 (−1.775; 0.539) 11.57%

*Multivariate analysis adjusted by age, gender and years of education.
**Multivariate analysis adjusted by age, gender, years of education, age at first episode, years of disease course and manic-depressive episodes.
BD-I, bipolar disorder type I; CI, confidence interval.

Among the possible explanations for the increased volumes of the amygdala, thalamus and hippocampus in lithium-treated patients relative to unmedicated patients and healthy controls, we can include hypotheses regarding neuroprotection and neurotropism. Some authors have reported that lithium might trigger regeneration in some brain regions, especially the hippocampus.[37,38] In this study,

the patients on lithium monotherapy were exposed to lithium for a mean duration of 10.8 years, which would support the hypothesis that prolonged exposure to lithium continues to promote increased brain volume. These findings may be indirectly related to the findings of studies that have demonstrated an increase in brain-derived neurotrophic factor (BDNF) in patients who are taking lithium.[39]

In this study we did not evaluate the correlation between the volumetric changes of the hippocampus and the cognitive characteristics of the patients. One small longitudinal study showed a positive correlation between improvement in verbal memory (California Verbal Learning Test) and increased size of the hippocampus[33] and some other studies have found lower risks of dementia in older adults with BD treated with lithium, compared with other medications.[40] Longitudinal studies support the conclusion that lithium may protect against cognitive decline in bipolar patients.[41]

The study has, however, some limitations. Despite the differences found in the volume of brain regions such as the amygdala, hippocampus and thalamus in long-term lithium-treated patients compared to unmedicated patients and healthy controls, and despite the persistence of such differences after adjusting for demographic and clinical variables, the authors acknowledge their inability to establish a cause–effect relationship between treatment with lithium and brain volume increase. The results of this study must be interpreted only as descriptive, exploratory findings. Moreover, given the difficulties in finding unmedicated patients and patients on long-term lithium monotherapy, the sample size is relatively small, but is still the largest to date in a study of this kind. Although many comparisons were made, the multivariate analyses allowed spurious associations to be discarded.

Further longitudinal studies with larger patient samples will permit evaluation of the consistency of lithium exposure over time and its relationship with changes in structural neuroimaging.[42,43] Another hypothesis which needs to be considered in future studies is the correlation between lithium-related increased brain volume and brain activation in functional neuroimaging, in order to assess whether the increase in volume identified is somehow correlated with brain functionality and connectivity.

This study included patients on no medication, patients on long-term lithium treatment, and healthy controls. The results are consistent with findings from previous studies regarding volumetric changes in the amygdala and hippocampus,[17,19,22,31,32] and contribute new findings regarding the effect of long-term lithium treatment on subcortical structures such as the thalamus. BD-I patients on long-term lithium treatment were compared to BD-I patients taking no medication and to healthy controls, and the three groups differed from each other in the volumes of the amygdala, left hippocampus, and thalamus, and in the number of hypointensities.

In conclusion, our findings support the hypothesis of the possible neuroprotective and neurotropic effect of long-term lithium treatment in BD-I patients and suggest a neurobiological reason to continue maintenance treatment in patients with BD even if they are euthymic.[44–46]

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STATEMENT OF INTEREST

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