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Effects of lithium on cortical thickness and hippocampal subfield volumes in psychotic bipolar disorder

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Conflict of interest

The other authors report no disclosures.

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Abstract

Relative to healthy controls, lithium free bipolar patients exhibit significant gray matter abnormalities. Lithium, the long-time reference standard medication treatment for bipolar disorder, has been proposed to be neuro-protective against these abnormalities. However, its effects on cortical thickness and hippocampal subfield (HSF) volumes remain unstudied and unclear, respectively, in bipolar disorder. This study included 342 healthy controls (HC), 51 lithium free PBD patients (NoLi), and 51 PBD patients taking lithium (Li). Regional gray matter thickness and HSF volume values were extracted from 3T MRI images. After matching NoLi and Li samples, regions where HC differed from either Li or NoLi were identified. In regions of significant or trending HC-NoLi difference, Li-NoLi comparisons were made. No significant HC-Li thickness or HSF volume differences were found. Significantly thinner occipital cortices were observed in NoLi compared to HC. In these regions, Li consistently exhibited non-significant trends for greater cortical thickness relative to NoLi. Significantly less volume was observed in NoLi compared to both HC and Li in right HSFs. Our results suggest that PBD in patients not treated with Li is associated with thinner occipital cortices and reduced HSF volumes compared with HC. Patients treated with Li exhibited significantly larger HSF volumes than NoLi, and those treated with Li were no different from HC in cortical thickness or hippocampal volumes. This evidence directly supports the hypothesis that Li may counteract the locally thinner and smaller gray matter structure found in PBD.

Keywords

Lithium; Bipolar disorder; Hippocampus; Cortical thickness; MRI; Neuro-protective

1. Introduction

Bipolar mood disorder is a common psychiatric illness, whose pathophysiology is still largely unknown. It affects approximately 5.7 million American adults, or about 2.6 percent of the U.S. population age 18 and older in a given year (Kessler et al., 2005). Lithium has been the reference standard psychopharmacological treatment for bipolar mood disorder for much of the past 50 years (Brambilla et al., 2001) and is one of only two medications known to reduce risk of suicide (Goodwin et al., 2003). After decades of intensive research, the mechanisms of lithium's action in bipolar disorder have proven to be complex and diverse and they still remain unclear (Jope, 1999; Marmol, 2008; Toker et al., 2012). Lithium has been suggested to be neuro-protective in the context of other psychiatric disorders, as studies have indicated that lithium may change disease progress in Alzheimer's patients with early symptoms (Forlenza et al., 2012; Diniz et al., 2013). It has also been suggested that lithium may stimulate increases in gray matter volume and density in bipolar patients (Moore et al., 2000, 2009; Sassi et al., 2002; Bearden et al., 2007), particularly hippocampal volume increases (Yücel et al., 2007; Hallahan et al., 2011; Hajek et al., 2012a, 2012b, 2014). However, research into the effects of lithium on the brain in bipolar disorder, particularly psychotic bipolar disorder (PBD), remains unclear and inconsistent (Kato et al., 1996;

Davanzo et al., 2001; Brambilla et al., 2004; Friedman et al., 2004; Patel et al., 2008; Dickstein et al., 2009; Seleke et al., 2013).

Several lines of evidence implicate brain structural abnormalities, particularly thinner cortex, in patients with bipolar disorder, and it has been suggested that these abnormalities may parallel phases of illness (Benedetti et al., 2011). Findings, however, have been largely inconsistent across studies. Some studies with samples consisting of bipolar patients with mixed lithium usage show significantly thinner cortices in the left rostral and right dorsal paracingulate cortex (Fornito et al., 2008) and other studies demonstrate more widespread differences in cortical thickness when compared to healthy controls (Lyoo et al., 2006). It has also been found that relative to healthy control subjects, currently euthymic lithium-free patients with bipolar disorder have significantly thinner gray matter in bilateral prefrontal cortex and the left anterior cingulate cortex, a finding that was more pronounced in patients with a history of psychosis (Foland-Ross, 2011). Thus far, the effect of lithium on this phenomenon of thinner cortex has not been studied.

The hippocampus has been implicated in affective and cognitive abnormalities in mood disorders and is routinely observed as smaller in major depressive disorder patients (Kempton et al., 2011). In previous research on bipolar disorder, patients have largely been found to exhibit hippocampal volumes similar to controls (Strakowski et al., 1999; Altshuler et al., 2000; Brambilla et al., 2003; Delaloye et al., 2009; Foland-Ross et al., 2013). However, in meta-analysis of a series of relatively small studies grouping patients according to presence and absence of lithium treatment, structural hippocampal differences were noted between controls and bipolar patients with minimal lithium exposure (Hajek et al., 2012b, 2014), raising the possibility that disease effects may be masked by medication effects in the current body of bipolar disorder literature. These disease effects may be magnified in PBD, as studies have suggested an association between psychosis and smaller hippocampi in bipolar disorder (Strasser et al., 2005).

Further studies are needed to examine the structural impact of lithium in PBD. Specifically, the medication's effects in PBD on cortical thickness should be assessed for the first time, and its effects on hippocampal volumes should be confirmed and localized in a large-scale study. This study investigated these effects of lithium in patients with PBD recruited as part of the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) study. These subjects were separated into groups of patients either treated or not treated with lithium. A previous study using the B-SNIP database did not identify lithium effects on gray matter, but used voxel-based rather than surface-based analysis and was conducted on an interim study sample which was 50% of the total study sample (Ivleva et al., 2013). We hypothesized that patients not on lithium would exhibit thinner cortices and smaller hippocampal subfields (HSFs) compared to healthy controls while patients on lithium would not. We also examined the potential confounding effect of cognitive, demographic (age, gender, race), clinical (anti-psychotic use), and social measures (socioeconomic status) on these comparisons.

2. Methods and materials

We compared MRI-derived cortical thickness data between healthy controls (HC), lithium taking probands with PBD (Li) and probands with PBD currently not on lithium (NoLi). Data were derived from B-SNIP, which represents a 6-site study (Wayne State University, Harvard University, Maryland Psychiatric Research Center, University of Chicago/University of Illinois at Chicago, University of Texas Southwestern, and the Institute of Living/Yale University).

2.1. Study participants

The study included 342 HC, 51 Li, and 135 NoLi from the B-SNIP database for whom 3.0 T MRI data, clinical measures, and demographic information were available. 19 participants (10 controls and 9 probands) were excluded due to motion and scanner artifacts. A chi-square test showed that proportion of images with artifacts did not differ significantly between groups.

All participants met the following inclusion criteria: (1) ages 15–65; (2) sufficient proficiency in English to understand task instructions; (3) no known history of neurologic disorders including head injury; (4) no history of substance abuse within the last month or substance dependence within the last 6 months; (5) negative urine toxicology screen on day of testing. Control subjects met the following additional criteria: (1) no personal or family history (first degree) of psychotic or bipolar disorders; (2) no personal history of recurrent mood disorder; (3) no lifetime history of substance dependence; (4) no history of any significant cluster A axis II personality features defined by meeting full or minus-one criteria of a Cluster A diagnosis using the Structured Interview for DSM-IV-TR Personality (SID-P) (Pfohl et al., 1997). Institutional review boards at each site approved the study and all sites used identical diagnostic, clinical, and recruitment techniques (Tamminga et al., 2013).

At the time of enrollment and assessments, patients were known to be clinically stable on current treatments. A structured medication history was administered by research staff to ascertain all medications currently taken by participants. In this study, the presence or absence of psychotropic medications was considered.

All participants underwent a diagnostic interview using the Structured Clinical Interview for DSM-IV-TR (SCID-IV) (First and Gibbon, 1997) and were categorized by diagnosis. Interviews were performed by trained clinicians who established reliability at regular intervals and met for weekly conferences to discuss difficult cases. Controls were also administered the SID-P. Diagnoses were made at each site by a consensus process led by a senior clinician that included reviews of results from clinical interviews, psychiatric and medical histories, and medical records when available. Healthy controls and patients meeting criteria for Bipolar Disorder Type I who also endorsed psychotic symptoms (with mood component more significant) were included for this analysis.

2.2. MRI-structural imaging

Subjects were scanned at six sites: Boston, MA (3.0 T, GE Signa, Pewaukee, WI); Detroit, MI (3.0 T, Siemens Allegra, Malvern, PA); Baltimore (3.0 T, Siemens Trio Tim, Erlangen, Germany); Hartford (3.0 T, Siemens Allegra, Malvern, PA); Dallas, TX (3.0 T, Philips Achieva, Andover, MA); and Chicago, IL (3.0 T, GE Signa, Pewaukee, WI). High-resolution isotropic T1-weighted MPRAGE scans (TR = 6.7 ms, TE = 3.1 ms, 8° flip angle, 256 × 240 matrix size, total scan duration = 10:52.6 min, 170 sagittal slices, 1 mm slice thickness, 1 × 1 × 1.2 mm³ voxel resolution) were obtained following the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (<http://www.loni.ucla.edu/ADNI>).

All images underwent rigorous data quality control. First, images were converted to NIFTI format and checked for scanner artifacts by trained raters. When images passed this pre-check, they were run through a first-level auto-reconstruction in FreeSurfer (Fischl, 2012). The skull stripped brains were then checked for remaining dura or sinus that could interfere with accurate segmentation. When non-brain tissue was found, images were edited manually by trained raters. All raters had inter-rater reliabilities (intra-class *r*) above 95%. When deemed sufficiently clean for segmentation by an independent rater, images were run through second- and third-level auto-reconstructions, whereby gray matter surface area, thickness, and volume measures were extracted. Average cortical thickness values were calculated in 64 anatomically defined automated cortical parcellations that covered the entire cortex (Desikan et al., 2006).

Automated hippocampal subfield (HSF) segmentation was conducted through a separate FreeSurfer processing pipeline. Extracted HSF regional volumes consisted of CA1, CA2/3, CA4/DG, presubiculum, and subiculum. This segmentation method, which employs a Bayesian probabilistic model to automatically segment the hippocampus, has been validated using manual morphometric measurements of ultra-high-resolution magnetic resonance imaging scans (Van Leemput et al., 2009). Voxel measurements of HSFs were 0.5 × 0.5 × 0.5 mm (Nelson et al., 1998). Fimbria, hippocampal fissure, and hippocampal tail were not included as measurements of smaller subfields may be unreliable (Van Leemput et al., 2009).

2.3. Statistical analyses

The NoLi sample was matched to the Li sample using a one-to-one optimal matching protocol on age, race, scanner site, and intracranial volume (ICV), which were the variables found to be significantly associated with cortical thickness, as described in the covariate selection methodology below. Consequently, analyses were conducted using a total of 444 participants (342 HC, 51 Li, 51 NoLi). Table 1 presents mean age, race distribution, sex distribution, site distribution, and mean ICV across diagnostic groups for this matched 444 participant sample. The NoLi and Li samples were matched in order to level the statistical power in assessing HC-NoLi and HC-Li differences and thereby enable direct comparison of those differences.

Cortical thickness of HC was compared to Li and to NoLi probands separately using a hierarchical approach which minimized risk of Type I error through a two step process: 1) a

selection step and 2) a selective analysis (Nanda et al., 2014). In the selection step, HC and Li or NoLi were compared bilaterally on six large functionally distinct regions of the brain (frontal, temporal, parietal, occipital, sensorimotor, and cingulate cortex). The mean cortical thickness value of each of these large regions was calculated by taking the average thickness value across the given region's component sub-regions, weighting by the sub-regions' surface areas. When a large region exhibited a trending difference ($p < 0.10$), it was retained for selective analysis. In this selective analysis, for each large region passing the selection step, HC was compared to Li or NoLi in the large region's component sub-regions, with Benjamini-Hochberg multiple comparisons correction for the number of sub-regions. To avoid "double-dipping" pitfalls, the selection step was performed on a randomly chosen 1/4 of the sample whereas the selective sub-region analysis was performed on the remaining 3/4 of the sample. The two steps were run on independent samples to ensure non-circular analysis (Kriegeskorte et al., 2009). Outliers were handled by winsorising all values greater than three standard deviations from group means.

To evaluate further the possible neuro-protective effect of lithium, Li and NoLi cortical thickness were then compared in regions where HC and NoLi were observed by the above hierarchical analysis to demonstrate significant or trending differences, with Benjamini-Hochberg multiple comparisons correction for the number of qualifying regions.

HSF volumes were analyzed by comparing Li and NoLi probands to HC in the 10 subregions of the hippocampus (right and left CA1, CA2/3, CA4/DG, presubiculum, and subiculum) with multiple comparisons adjustment. As with the cortical thickness analysis, Li and NoLi HSF volumes were compared in regions where HC and NoLi exhibited significant or trending differences, with Benjamini-Hochberg multiple comparisons correction for the number of qualifying regions.

Current cognitive function was assessed in participants using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe, 2004). BACS scores were compared between Li and NoLi by ANOVAs. Symptom severity was also measured in participants using the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). Symptoms of psychosis were compared between Li and NoLi by ANOVA using PANSS positive scores.

Sex, race, scanner site, handedness, duration of illness, current antipsychotic medication usage, current antipsychotic medication dosage (measured by chlorpromazine equivalents), age, ICV, and socioeconomic status (measured by Hollingshead index (Hollingshead, 1975)) were tested as potential covariates for analyses. To account for confounds, measures were included as covariates only when they were significantly associated with the dependent variables (by ANOVAs for categorical variables and Pearson's correlations for continuous variables). For the cortical thickness analyses, measures were evaluated as potential covariates with Benjamini-Hochberg multiple comparisons correction for the total number of cortical regions. Similarly, for the HSF analyses, measures were evaluated with adjustment for the total number of subfields. Covariates were employed in addition to the matching procedure because the HC sample was never matched to the proband groups, and it therefore necessitated the inclusion of potential confounds as covariates in analyses.

3. Results

Significant associations with cortical thickness were observed with age in 62 regions ($p < 0.05$), with race in 16 regions ($p < 0.05$), with scanner site in 55 regions ($p < 0.05$), and with ICV in 13 regions ($p < 0.05$). No significant regional thickness associations were found for sex, duration of illness, handedness, antipsychotic use, antipsychotic dosage, cognitive ability, or socioeconomic status. Consequently, age, race, scanner site, and ICV were used as covariates in all cortical thickness statistical analyses. Age, scanner site, ICV, race, and sex qualified as covariates for HSF statistical analyses, as they were significantly associated with HSF volumes.

Race, ICV, and antipsychotic use qualified as covariates for BACS analysis. In this BACS analysis, no significant differences were observed between Li and NoLi ($p > 0.8$; $d < 0.02$). Sex and anti-psychotic use qualified as covariates for PANSS positive analysis, in which no significant differences were found between Li and NoLi ($p > 0.9$; $d < 0.01$).

Mean cortical thickness values varied significantly between NoLi and HC in the right lateral occipital, right lingual, and left lateral occipital brain regions ($p < 0.01$; $d > 0.45$; Fig. 1, Table 2). In all three regions of observed significant difference, NoLi exhibited thinner cortices. NoLi also showed trending cortical thinning compared to controls in the left lingual region ($p = 0.07$; $d = 0.28$; Fig. 1; Table 2). No significant or trending differences were found between Li and HC.

In post-hoc analysis comparing Li and NoLi in the four regions of significant or trending HC-NoLi cortical thickness difference, Li consistently demonstrated thicker cortices compared to NoLi ($d > 0.14$; Table 2). This effect was observed as trending in the right lingual region ($p = 0.08$; $d = 0.37$; Table 2).

No significant or trending HSF volume differences were found between Li and HC. However, mean HSF volumes were significantly lower for NoLi compared to HC in the right CA2/3 and right CA4/DG regions ($p < 0.05$; $d > 0.45$; Table 3; Fig. 2). In post-hoc analysis of these two regions, mean HSF volumes were also significantly lower for NoLi compared to Li ($p < 0.05$; $d > 0.39$; Table 3).

4. Discussion

Results of the study are notable for finding cortical thickness and HSF volume deficits in NoLi relative to HC and Li and for not finding any significant HC-Li differences. These results indicate that lithium may potentially bear a neuro-protective effect in PBD and medication effects may obscure disease effects in PBD studies.

Significantly thinner cortices were observed in NoLi compared to HC in occipital regions, supporting prior findings of thinner cortices in bipolar disorder. Notably, the observed localization of this thinning does not match past research, as it is neither frontal, nor cingulate-based, nor global. This discrepancy could be due to the selective choice of the NoLi bipolar group, which was exclusively lithium free and psychotic, or it could be due to the sample size of NoLi, which was deliberately reduced by matching in order to hone

comparison to Li. Within the occipital regions of significant HC-NoLi difference in thickness, Li consistently exhibited increased thickness relative to NoLi, culminating in a trending increase in thickness in the right lingual region. The HC-NoLi and Li-NoLi results together indicate that providing Li may compensate for disease-related cortical thinning. Indeed, cortical thickness in subjects exposed to Li was indistinguishable from cortical thickness in HC.

Since the hippocampus has been implicated in affective and cognitive abnormalities in mood disorders and because the hippocampus is routinely observed as smaller in major depressive disorder patients (Kempton et al., 2011), we examined potential structural differences between PBP and HC HSF volumes. We found that NoLi had significantly decreased volume of the right CA2/3 and the right CA4/DG compared to HC. In these regions of HC-NoLi HSF volume difference, we also observed that subjects exposed to Li exhibited significantly greater volumes than those without Li exposure. These findings support the contention that disease effects may be masked by medication effects in PBD studies grouping patients irrespective of lithium history.

The noted decreases in cortical thickness and HSF volume of NoLi compared to Li may possibly reflect a neuro-protective effect of lithium, which has been found in clinical and animal models to enhance neurogenesis, increase neuropil, and prevent injury to nerve cells following insults (Manji et al., 2000; Moore et al., 2000; Wada et al., 2005). Several molecular pathways have been proposed as being involved in this potential effect of lithium (Shaltiel et al., 2007). In rodent models, chronic lithium treatment has been shown to upregulate synaptosomal uptake of glutamate (Dixon and Hokin, 1998) and also increase expression of proto-oncogene bcl-2 (Manji et al., 1999; Chen et al., 2002a,b), an antiapoptotic factor that inhibits cytochrome C release from mitochondria (Shimizu et al., 2000). Lithium may thereby shield cerebellar, cortical, and hippocampal neurons from glutamate-induced excitotoxicity (Nonaka et al., 1998; Nonaka and Chuang, 1998). Lithium may further protect neuronal cells by inhibiting glycogen synthase kinase-3 (GSK-3) activity (Klein and Melton, 1996) and by increasing expression of brain-derived neurotrophic factor (BDNF) and its receptor TrkB (Fukumoto et al., 2001). Lithium has also been found to enhance neurogenesis in the dentate gyri of rats through the ERK-mitogen-activated pathway, one of the pathways whereby BDNF exerts its biological effects (Chen et al., 2002a). Additionally, pilocarpine-induced mossy fiber sprouting in rat hippocampi, which causes cell damage (Mello et al., 1993) and models the increased hippocampal mossy fiber sprouting exhibited by bipolar patients (Dowlatsahi et al., 2000), has been demonstrated to be inhibited by chronic lithium treatment (Cadotte et al., 2003).

The osmotic effects of lithium, which may result in neuronal swelling, may provide an alternative explanation for the increased cortical thickness and HSF volumes in patients treated with lithium. Chronic lithium administration has been demonstrated in rats to result in elevation in tissue water content in the frontal cortex, hippocampus, and cerebellum (Phatak et al., 2006). However, in this study, the increases in cortical thickness and HSF volumes were found only in certain regions and not globally, making the osmotic explanation unlikely. Potential neurophysiological differences between responders and non-responders to lithium treatment may constitute another alternative explanation for the

observed Li-NoLi structural differences (Hajek et al., 2014). However, this explanation is unlikely as the NoLi sample, for which we have no lithium response data, likely represents a heterogeneous group of responders and non-responders, and the Li sample was not selected for unambiguous responders so that it too is likely heterogeneous.

In examining effects on cognition, we found that Li did not differ significantly in cognitive measures compared to NoLi. This observation, however, is not conclusive by itself because the cognitive measures we analyzed were neither comprehensive nor targeted for testing any specific hypothesis. Prior research has yielded mixed results (Wingo et al., 2009; Forlenza et al., 2011), calling into question the impact of lithium on cognitive function. Nonetheless, the lack of cognitive difference between Li and NoLi reduces the possibility of recall bias confounding patient reporting of prescribed medication.

We also investigated possible impact of antipsychotic medication use, because of previously suggested effects on cortical thickness (Mattai et al., 2010) and hippocampal volume (Horacek et al., 2006). However, we observed no such relationships here. The chance of antipsychotic medication playing a confounding role in this study is additionally unlikely given that the Li and NoLi samples had analogous proportions of participants using antipsychotics (69% and 67% respectively). Nonetheless, we cannot rule out effects of antipsychotic medication. Moreover, our study is limited by the lack of precise information regarding prior lithium exposure, treatment duration, lithium dose, patient compliance, and lithium serum concentration, as well as regarding other potential covariates including body mass index, educational level, and intelligence quotient. Further, we cannot exclude the possibility that the effects observed were caused not by lithium usage but rather by a third variable distinguishing Li and NoLi samples. However, this possibility is unlikely given the matching performed on the samples. Although matching the NoLi sample to the Li sample enabled more direct Li-NoLi comparison, it also necessarily diminished the NoLi sample size and thereby reduced the study's sensitivity for abnormalities in NoLi cortical thickness and subcortical volumes. The sample size also precludes investigation into differential effects of lithium based on sex, as the study lacks the statistical power needed for a meaningful stratified analysis. Nonetheless, for the purpose of investigating medication effects, the size of the study remains a strength as, to our knowledge, it is the largest study yet looking at the effects of lithium on hippocampal volume, with a lithium taking population 38% higher than the next largest study (Hajek et al., 2012b). It is also, to our knowledge, the first study examining lithium's effect on cortical thickness.

Future studies testing whether the effects of lithium on brain structure and cognitive and clinical measures span across all mental illnesses or differ based on the predominant features of these disorders (mainly psychotic or mainly affective symptoms) are necessary in order to gain a more comprehensive understanding of lithium's mechanism of action. Furthermore, the relationship between different dosages, duration of treatment with lithium, and optimal therapeutic results should be examined, although such studies would require much more fine-grained data.

Overall, our findings notably indicate that PBD patients that were not taking lithium have significantly thinner occipital cortices and smaller CA2/3 and CA4/DG volumes than

controls. However, neither this cortical thinness nor this HSF volume loss is seen for lithium-taking patients; indeed, in direct comparison, lithium-taking patients exhibit thicker occipital cortices and bigger right CA2/3 and CA4/DG volumes than their lithium-naïve counterparts. These findings raise the intriguing possibility that lithium may exert neuro-protective effects that in fact counteract the thinner occipital cortices and the smaller hippocampi seen in PBD. The absence of observed BACS and PANSS differences somewhat weakens this hypothesis, but these negative findings may be due to baseline differences between the lithium taking and naïve groups or due to the potentially global nature of PANSS and BACS effects in contrast to the regional impact of lithium. Furthermore, lithium taking patients may garner other benefits from the observed structural effects, possibly including reduced episode severity or improved primary and secondary treatment responsiveness. The potential neuro-protective effect of lithium, if confirmed and clarified by longitudinal research on neurogenesis and neuronal survival, may support the use of lithium as a beneficial prophylaxis for individuals at high-risk for psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpsychires.2014.12.00>.

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Fig. 1.
Effect sizes (Cohen's d) for regional contrasts demonstrating thinner cortex in lithium free probands relative to controls.

Fig. 2. Effect sizes (Cohen's d) for contrasts demonstrating reduced HSF volumes in lithium free probands relative to controls (HC).

Table 1

Demographics of included participants.

	Controls				Lithium Takers				Lithium Free			
n	342				51				51			
Mean age (sd)	37.1 (12.4)				35.1 (13.8)				36.2 (13.1)			
Race Distribution ^a	AA 88 26%	CA 223 65%	OT 31 9%	AA 7 14%	CA 40 78%	OT 4 8%	AA 7 14%	OT 4 8%	CA 40 78%	AA 7 14%	OT 4 8%	OT 4 8%
Gender Distribution ^b	F 186 54%	F 186 54%	M 156 46%	F 14 27%	F 14 27%	M 37 73%	F 34 67%	M 17 33%	F 34 67%	F 34 67%	M 17 33%	M 17 33%
Mean Intracranial Volume (sd)	1434 cc (194)				1436 cc (167)				1422 cc (163)			
Current Antipsychotic Usage	Yes 0 0%	Yes 0 0%	No 342 100%	Yes 35 69%	Yes 35 69%	No 16 31%	Yes 34 67%	No 17 33%	Yes 34 67%	Yes 34 67%	No 17 33%	No 17 33%
Scanner Site Distribution (%) ^c	Bo 12	De 11	Ba 15	Bo 6	De 22	Ba 12	Bo 4	De 29	Ba 10	Bo 4	De 29	Ba 10
	Da 20	Da 20	H 20	C 21	Da 20	H 22	C 33	Da 6	H 22	C 33	Da 6	H 18
	C 31	C 31	C 31	C 31	C 31	C 31	C 31	C 31	C 31	C 31	C 31	C 31

^a AA – African American; CA – Caucasian; OT – Other^b F – Female; M – Male^c Bo – Boston; De – Detroit; Ba – Baltimore; H – Hartford; Da – Dallas; C – Chicago

Descriptive and comparative statistics for cortical thickness in regions of significant and trending difference between controls and lithium free probands.

Table 2

Sub-region	Mean cortical thickness (SE) (mm) ^a			Effect sizes for contrasts		
	Controls (HC)	Lithium takers (Li)	Lithium free (NoLi)	HC-Li	HC-NoLi	Post-Hoc Li-NoLi
Right Lateral Occipital	2.05 (0.01)	2.00 (0.02)	1.97 (0.02)	N.S ^b	0.50***	0.19
Right Lingual	2.06 (0.01)	2.03 (0.02)	1.99 (0.02)	N.S ^b	0.45**	0.37 ^{\$}
Left Lateral Occipital	2.14 (0.01)	2.10 (0.02)	2.06 (0.02)	N.S ^b	0.50***	0.32
Left Lingual	2.05 (0.01)	2.02 (0.02)	2.00 (0.02)	N.S ^b	0.28 ^{\$}	0.14

**
p < 0.01.

p < 0.001

^{\$}
p < 0.10.

^aValues adjusted for age, scanner site, race, and intracranial volume by linear regression to covariates' means.

^bLarge region contrast did not justify sub-region contrast.

Table 3

Descriptive and comparative statistics for hippocampal subfield volumes in regions of significant and trending difference between controls and lithium free probands.

Sub-region	Mean volume (SE) (mm ³) ^a			Effect sizes for contrasts		
	Controls (HC)	Lithium takers (Li)	Lithium free (NoLi)	HC-Li	HC-NoLi	Post-Hoc Li-NoLi
Right CA2/3	985 (4)	974 (15)	931 (13)	0.10	0.47 *	0.39 *
Right CA4/DG	543 (4)	540 (9)	516 (8)	0.06	0.45 *	0.40 *

^{*} p < 0.05.

^a Values adjusted for age, scanner site, race, sex, and intracranial volume by linear regression to covariates' means.