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Bilateral Hippocampal Volume Increase in Patients with Bipolar Disorder and Short-term Lithium Treatment

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Most previous magnetic resonance imaging (MRI) studies of patients with bipolar disorder (BD) report similar hippocampus (HC) volumes across patients and controls, but because patients studied were heterogeneous with respect to course of illness variables and medication status, the conclusions of these studies remain equivocal. Lithium (Li) is the reference-standard drug for BD and its role as an important agent in neuroprotection and neurogenesis has been documented in human and in animal studies. We compared the volume of the HC, hippocampal head (Hh), and body/tail (Hbt) in three groups with no history of medication use before entry into this study: (a) a group of patients treated with Li for 1–8 weeks and then scanned; (b) a group comprised of patients who were unmedicated at the time of scan; and (c) a group of patients treated with either valproic acid or lamotrigine. Healthy age- and sex-matched comparison subjects were also scanned. HC volumes did not differ between the unmedicated and healthy comparison groups. There was a bilateral increase in volumes of HC and Hh in the Li-treated group compared to the unmedicated group, an effect that was apparent even over a brief treatment period. Our study provides further confirmation that Li can exert structural effects on the HC, which are detectable *in vivo*. The study emphasizes the need to control for even brief exposure to medication in volumetric studies of the HC.
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INTRODUCTION

The hippocampus (HC) is a key component of fronto-temporal neural networks involved in memory (McKinnon *et al*, 2007) and in emotional regulation (Mayberg, 1997). As such, it is implicated in the cognitive and affective abnormalities observed in mood disorders. There have been two recent meta-analyses reporting bilateral HC volume reduction in patients with major depressive disorder (MDD) compared to healthy controls using magnetic resonance imaging (MRI; Campbell *et al*, 2004; Videbech and Ravnkilde, 2004). In contrast, results from studies of persons with bipolar disorder (BD) are heterogeneous. There is, however, a tendency to conclude that HC volume is preserved in patients with BD (eg Geuze *et al*, 2005), despite research reporting both smaller (Blumberg *et al*, 2003) and larger (Beyer *et al*, 2004) HC volumes. As the patients included in these studies were heterogeneous with respect to course of illness variables and medication status, the conclusions of these studies remain equivocal (see Table 1). Medication history, in particular, is an important confounding factor in studies of patients with BD (Dickstein *et al*, 2005; Strasser *et al*, 2005; Frazier *et al*, 2005; Rajkowska, 2002).

Lithium (Li) is the reference-standard drug for acute and prophylactic treatment of BD, although the exact mechanism of its effect is unknown (Bachmann *et al*, 2005). Nonetheless, its role as an important agent in neuroprotection and neurogenesis has been documented in human and in animal studies. For example, Chen *et al* (2000) demonstrated enhancement of hippocampus neurogenesis in the dentate gyri of Li-treated mice. In a more recent study, Frey *et al* (2006) reported that Li increased hippocampus brain-derived neurotrophic factor (BDNF) levels in an animal model of mania. The HC has been implicated as a site for cellular plasticity and Li appears to be involved in this process (Chen and Manji, 2006).

Sassi *et al* (2002; mean of 27 weeks duration) and Moore *et al* (2000a; mean of 4 weeks duration) reported increased total gray matter volume following Li exposure. No change in HC volume was apparent in patients treated with Li when compared to patients treated with medication other than Li (Chen *et al*, 2004) or drug-free patients (Brambilla *et al*,

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Table 1 Populations Studied, Findings and Approaches in Analyzing the Volumetric Data in HC Volumetric Studies with Bipolar Patients

Author (year)	Sample	Age (Mean ± SD)	Results	HC protocol	Medication status
McDonald *et al* (2006)	38 BD, 52 relatives, 54 controls	41 ± 11.7, 44 ± 15.4, 40.2 ± 15.3	No change in HC volumes	Miscellaneous papers cited	Mixed
Velakoulis *et al* (2006)	22 BD, 87 controls	21.7 ± 2.4, 26.9 ± 10	No change in HC volumes	Alveus excluded, posterior: Watson's last slice (Watson *et al*, 1992)	Mixed
Strasser *et al* (2005)	23 psychotic BD, 15 non-psychotic BD, 44 controls	36.4 ± 11.6, 40.8 ± 14.1, 39.6 ± 11.7	A trend for a smaller left HC in psychotic BD	Alveus included, full extent of HC measured	Majority in the treatment program
Blumberg *et al* (2003)	36 BD (14 adolescents, 22 adults), 56 controls (23 adolescents, 33 adults)	31 ± 14.1, 28.3 ± 13.7	A trend for smaller HC volumes in both BD groups	Alveus and some parts of fornix included, full extent of HC measured	Mixed (36% of adults were free of medication, 43 % of adolescents were free of medication)
Brambilla *et al* (2003)	24 BD, 36 controls	35 ± 10, 37 ± 10	No change in HC volumes	From one slice posterior, to the slice where the mamillary body became visible to the slice in which superior colliculus completely connected with the thalamus	Nine drug-free, 13 Li treated
Strakowski *et al* (2002)	18 first epi BD, 17 multiple epi BD, 32 controls	22 ± 6, 25 ± 6, 24 ± 6	A trend for smaller HC volumes in first epi pts with BD	Alveus excluded, the last coronal slice was that in which the right and left superior colliculi were jointly visualized.	Mixed (all medicated)
Hauser *et al* (2000)	25 BD I pts, 22 BD II pts, 19 controls	41.8 ± 10.5, 39.4 ± 10.2, 33.2 ± 7.1	No change in HC volumes	From the slice where IHLV and the anterior commissure are both still present.	No data
Strakowski *et al* (1999)	24 BD, 22 controls	27 ± 6, 28 ± 6	HC volume slightly larger with a small effect size	From the slice where alveus was seen till the slice where superior and inferior collucili were jointly visualized	Mixed
Swayze *et al* (1992)	48 BD, 47 controls	33.41 (men with BD), 34.63 (women with BD	Right HC smaller in pts with BD	N/A	N/A
Altshuler *et al* (2000)	24 men with BD, 18 controls	50.2 ± 12.7, 53.4 ± 11.1	No change in HC volumes	From the first slice in which the alveus was well visualized to the first slice where all four colliculi could be well visualized. Alveus excluded	Mixed
Beyer *et al* (2004)	36 BD, 29 controls	58.2 ± 7.8, 61.0 ± 5.5	Larger left HC in older pts with BD	From the slice in which the the ILV appeared horizontally without any body of gray matter visible below them to the slice in which pulvinar thalami obscured the crura fornicis	Mixed
Dickstein *et al* (2005)	20 pediatric BD, 20 controls	13.4 ± 2.5, 13.3 ± 2.3	No change in HC volumes	VBM analysis	All but one were taking psychotropic medications
Frazier *et al* (2005)	43 pediatric BD, 20 controls	11.3 ± 2.7, 11.0 ± 2.6	Smaller HC in young BD	A semi-automated method	Mixed (26% Li)
Chen *et al* (2000)	16 pediatric BD, 21 controls	16 ± 3, 17 ± 4	No change in HC volumes	From the slice where the third ventricle splits from the cistern by the hypothalamus to the slice where the superior colliculus joined the thalamus	Mixed

Abbreviations: BD, bipolar disorder; epi, episode; pts, patients; HC, hippocampus; IHLV, inferior horn of the lateral ventricle; ILV, inferior lateral ventricles; TBV, total brain volume; TCV, total cerebral volume; VBM, voxel-based morphometry.

2003). Similarly, Sax *et al* (1999) found no differences in HC volumes between medicated and unmedicated patients with BD. A recent study by Velakoulis *et al* (2006) found no change in HC volumes of patients experiencing their first-episode of mood-related psychosis; excluding those patients using Li from the data did not change this pattern. In contrast, Beyer *et al* (2004) found a correlation between Li use and an increase in HC sizes in an older patient population.

Despite the fact that a medication naïve population is critical for understanding the structural changes that may reflect the pathophysiology of BD, the association between HC volumes and treatment has not been previously investigated using controlled exposure to medication in people with BD. We, therefore, used a sample with no history of medication use before entry into the study and compared the HC volumes of patients with BD treated with Li (Li^+ group) to those of patients who were either unmedicated (UM group) or treated with one of the anticonvulsants, valproic acid or lamotrigine (AC group).

MATERIALS AND METHODS

Subjects

Twenty-eight subjects (13 men and 15 women) were recruited from the mood disorders clinic at St. Joseph's Healthcare Hamilton. Subjects provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Research Ethics Boards of St. Joseph's Hospital (ON, Canada) and Hamilton Health Sciences Corporation (ON, Canada). The diagnosis of BD was confirmed by the Structured Clinical Interview for DSM-IV (SCID; First *et al* 2001). All patients were medication naïve, having never received psychopharmacological treatment for psychiatric illness before entry into the study. Three groups were examined: (i) a Li^+ group comprised of 12 patients (mean age = 25.73, SD = 6.2; five women) treated with Li for 1 to 8 weeks duration (mean = 26.67 days; SD = 13.50); (ii) a non-Li group (AC) comprised of seven patients (mean age = 25.55, SD = 8.5; four women) treated for 1–8 weeks duration (mean = 30.29 days; SD = 13.61) with valproic acid or lamotrigine and (iii) an unmedicated (UM) group of nine patients (mean age = 24.36, SD = 8.4; six women) who were either untreated with medication ($n = 5$) or who received medication (ie Celexa, Zoloft, Lamictal, or Li) for less than 5 days (mean = 1.33; SD = 1.89) at the time of scanning.

The control group comprised of 30 healthy comparison subjects matched to the patients in terms of age (mean age = 25.28, SD = 7.8) and gender distributions (14 males and 16 females).

Exclusion criteria for patients and comparison subjects were: (i) substance-use related disorder within the past 6 months as determined by the SCID; (ii) lifetime history of substance dependence as measured by the SCID; (iii) posttraumatic stress disorder as determined by the SCID; (iv) use of alcohol or illicit psychoactive substance within 48 h of testing; (v) untreated medical illness such as uncontrolled diabetes or other endocrine disorders; (vi) history of head injury with loss of consciousness; (vii) history of neurological disease; and (viii) past treatment with psychotropic medication, electroconvulsive therapy, transcranial magnetic stimulation or a formal course of psychotherapy. See Table 2 for a summary of demographic and clinical variables.

Table 2 Demographic and Clinical Characteristics of Study Sample

	Controls ($n = 30$)	Li^+ ($n = 12$)	AC ($n = 7$)	UM ($n = 9$)
Characteristic				
Sex				
Male	14	7	3	3
Female	16	5	4	6
Diagnosis				
BD I		6	1	0
BD II		2	3	5
Undifferentiated		4	3	4
Previous Hx of psychotic episode(s)[a,b]				
Yes		4	3	3
No		7	2	4
Family Hx of BD				
Positive		6	3	3
Negative		1	0	2
Unknown		5	4	4
	Mean	*Mean*	*Mean*	*Mean*
Age	25.3 (7.8)	25.7 (6.2)	25.6 (8.6)	24.4 (8.4)
Li level[a]		0.64 (0.26)	N/A	N/A
Ham-D 17 score at baseline[b]		11.8 (11.1)	16.7 (5.9)	13 (8.4)
YMS score at baseline[b]		11.5 (11.2)	10.6 (12.5)	5.3 (6.5)
Number of affective episodes[b]		9.7 (15.2)	8.6 (7.1)	6.4 (3.6)
Age at onset of illness[a,b]		19.3 (8.7)	16 (4.5)	15.5 (7.7)
Duration of illness (years)[a,b]		7 (7.1)	9.4 (7.0)	9.4 (7.2)
Duration of medication (days)		26.7 (13.5)	30.3 (13.6)	1.3 (1.9)

Abbreviations: BD I, bipolar disorder 1; BD II, bipolar disorder 2; Hx, history; HAM-D 17, 17-item Hamilton Rating Scale for Depression; YMS, Young Mania Scale.
[a]Data not available for all subjects.
[b]Patient groups did not differ significantly on any of these variables ($ps > 0.05$).

MRI Image Acquisition and Analysis

Fifty-three of the MRI scans were obtained on a 1.5-T. Sigma GE Genesis-based Echo-Speed scanner (General Electric Medical Systems, Milwaukee, WI) running version 5.7 software and using a standard 30cm circularly polarized head coil. Sagittal anatomic images were acquired by using a 3D/FSPGR/20 sequence (flip angle, 20°; echo delay time

in-phase (TE), minimum repetition time (TR), 300 msec; inversion recovery, 300 msec; matrix, 512×256; field of view (FOV), 24 cm; scan thickness, 1.2 mm). The remaining five subjects were scanned on a 3-T MRI Sigma GE Genesis (General Electric Medical Systems, Milwaukee, WI). Here, sagittal T-1 weighted images were acquired using a 3D FSPGR-IR sequence, (TR/TE $= 10.3/2.1$ ms, flip angle, 20°, inversion time, 300 ms, and FOV $= 24$ cm, slice thickness $= 1.2$ mm. Briellmann *et al* (2001) reported no difference in HC volumes measurements in the MRI scans of eight healthy adults performed at 1.5 and 3 T. Hence, we treated the images acquired in our study at 1.5 and 3 T as a single data set.

The AFNI software package (National Institute of Mental Health, Bethesda, Maryland, USA; http://afni.nimh.nih.gov/afni/) was used to analyze these data. Our images were T1-weighted, but we were able to utilize the *swap* feature in AFNI to create a negative image of the original scan, approximating a T-2 weighted image (eg the alveus which is white on T1-weighted images but looks black using this function). This allowed us to examine the images on both the sagittal, coronal, and axial plane, using the T1-weighted and negative images.

Total Cerebral Volume Measurement

Total cerebral volume (TCV) was defined as the gray and white matter of both hemispheres spanning the midbrain superior to the pons, a border chosen for its easy identification. Here, the inter-rater reliability (intraclass correlation coefficient (ICC)) between two raters was 0.99.

Hippocampal Measurement

A detailed description of the measurement protocol can be found at the website http://physics.stjosham.on.ca/~kaan/HippoProtocol.pdf. The HC was defined anatomically as the hippocampus proper (Ammon's horn), dentate gyrus, and most of the subiculum. The alveus, fimbria, and fornix were excluded from these measurements. The sagittal plane was the primary reference plane where the majority of the traces were made. The coronal and axial planes were used as required. The HC was further subdivided into the HC head (Hh), HC body, and tail (Hbt) (Kim *et al,* 1994). HC volumes were measured by one rater (KY) with reliability confirmed by a second investigator (VHT), falling within 5% between raters. The ICC values were 0.97 for right HC and 0.99 for left HC. HC volumes were obtained with raters who were blind to group membership.

Statistical Analyses

HC volume data were analyzed using one-way ANOVAs where group (Li^+, AC, UM, and Control) was treated as a between-subjects variable. Tukey's honestly significant difference *post-hoc* test with α set at 0.05 was used for follow-up pairwise comparisons. Volumetric differences across male and female subjects were compared using independent-samples *t*-test treating sex as a between-subjects variable.

RESULTS

Subject Demographics and Clinical Characteristics

There were no differences in age or sex across the patient and healthy comparison groups ($p > 0.05$). Furthermore, the patient groups did not differ significantly from one another at the time of enrollment with respect to number of previous affective episodes, age at onset of first psychiatric episode, psychosis or duration of psychiatric illness ($p > 0.05$). Baseline scores on the 17-item Hamilton Rating Scale for Depression (HAM-D) and Young Mania Scale (YMS) did not differ significantly across the three patient groups ($p < 0.05$). In subjects for whom handedness data were available (45 of 58 subjects), 96% of controls and 83% of patients (across all three groups) were right handed or ambidextrous. Hence, there were too few left-handed subjects in each group to examine reliably differences in HC volume across left- and right-handed subjects.

Total Cerebral Volume

There was a marginally significant main effect of group on TCV ($F(3,57) = 2.66$, $p = 0.06$). Numerically, healthy comparison subjects had the largest TCVs. When TCV was included in the analyses of HC volume described below, there was no impact on the pattern of results for HC volumes.

Volumetric Differences Between Groups

There was a significant main effect of group on left ($F(3,57) = 3.25$, $p = 0.03$) and on right ($F(3,57) = 3.65$, $p = 0.02$) HC volumes (see Table 3). These effects were evident in the Hh (hippocampal head), but not Hbt (hippocampal body-tail). Specifically, there was a main effect of group on left Hh volume ($F(3,57) = 4.12$, $p = 0.01$); this effect was marginally significant for right Hh volume ($F(3,57) = 2.59$, $p = 0.06$). By contrast, no significant group differences emerged for left and right Hbt

Table 3 Mean Hippocampal Volumes Across Groups

Group	Left HC (mm^3)	Right HC (mm^3)	Left Hh (mm^3)	Right Hh (mm^3)	Left Hbt (mm^3)	Right Hbt (mm^3)
Control	2626.4 (338.8)	2748.6 (317.7)	1208.8 (230.2)	1306.9 (240.6)	1417.6 (232.5)	1441.7 (203.5)
Li^+	2851.1 (365.9)	2966.8 (442.3)	1375.7 (281.1)	1466.9 (281.9)	1475.4 (185.5)	1499.9 (254.2)
AC	2711.6 (131.3)	2691.3 (167.8)	1301 (197.8)	1338.9 (152.5)	1410.5 (144.0)	1352.4 (122.0)
UM	2438.4 (174.1)	2497.4 (244.9)	1031.5 (169.5)	1169.8 (266.1)	1407.0 (109.2)	1327.6 (146.6)

($p > 0.05$). *Post-hoc* testing indicated that the volumes of left ($p = 0.02$) and of right HC ($p = 0.01$), and of left Hh ($p < 0.01$) and right Hh ($p = 0.04$), were larger in the Li^+ group than in the UM group. Means and SD for each of these variables are included in Table 3.

Because there was a marginally significant main effect of group on TCV, we repeated our analysis using TCV as a co-variate in an ANCOVA design. All effects remained significant at the $p < 0.05$ level in this analysis, and controlling for TCV enhanced the difference between groups such that the difference in right Hh became significant ($p = 0.03$).

Volumetric Differences Between Men and Women

Healthy men ($n = 14$) had larger right and left HC ($p < 0.01$), right ($p < 0.01$) and left Hh ($p = 0.04$), and left Hbt ($p = 0.002$) than healthy women ($n = 16$). Right Hbt volume, however, did not differ between men and women in the comparison group ($p = 0.11$). After co-varying for TCV, the left Hh and left Hbt volumes were not different between healthy men and women ($p = 0.08$). In the BD group as a whole ($n = 28$), men with BD ($n = 13$) had larger right ($p < 0.01$) and left ($p = 0.04$) Hh volumes than did women with BD ($n = 15$).

Asymmetries in Left and Right Hippocampal Volumes

Right HC and Hh volumes were larger than those of the left in patients ($p = 0.04$) and controls ($p < 0.01$). No such differences, however, emerged for the Hbt in either the patient or comparison groups ($p > 0.05$).

DISCUSSION

The key findings of this study were that medication naïve patients with BD had HC volumes that did not differ from age- and sex-matched healthy comparison subjects, while patients treated with Li had larger total HC and Hh volumes. Co-varying for TCV did not change these results. To our knowledge, this is the first study to examine systematically a medication naïve population with BD compared with short-term treatment with Li and other standard treatments for BD (valproate and lamotrigine). Because of the small sample of patients receiving Li and the relatively short-term duration of treatment, we were unable to examine relations between treatment duration and HC volumes. In the absence of a sufficient preclinical literature examining the time course whereby Li may exert effects on the HC, we are unable to predict whether increases in HC volume following Li would follow a linear function; it seems likely, however, that if the relation between treatment and HC volume is linear over the short-term, the long-term impact of Li treatment would follow a different function.

Most studies comparing patients with BD to healthy comparison subjects report no differences in HC volumes (Hauser *et al*, 2000; Altshuler *et al*, 2000; Dickstein *et al*, 2005; Chen *et al*, 2004; McDonald *et al*, 2006; Velakoulis *et al*, 2006; Brambilla *et al*, 2003). This contrasts with other neuropsychiatric disorders such as schizophrenia, Alzheimer's disease, post-traumatic stress disorder, borderline personality disorder, and major depressive disorder that are associated with small HC volumes (Campbell and MacQueen, 2006; Geuze *et al*, 2005) in those with established illness. Following diagnosis, people with BD spend one-third to half their lives with depressive symptoms (Judd *et al*, 2002, 2003). Patients with BD often have a psychotic element to their illness, and co-morbidity with anxiety disorders, including post-traumatic stress disorder, is common. These features would lead to the prediction of small HC volumes in BD and yet the results of studies to date do not support this (see Table 1). This study may provide one clue to that puzzle, with the finding that Li was associated with larger HC volumes. As studies to date have not controlled for current or previous treatment status, the effect of illness independent of medication is unknown, and it appears that Li may promote volumetric increases in the HC, possibly mitigating against or preventing illness-related changes. In human subjects, an increase in NAA levels after Li treatment in patients with BD (Moore *et al*, 2000b) suggests that Li may promote neurogenesis and neuroprotection in the HC.

An extensive number of pre-clinical studies have reported neuroprotective effects of Li. Long-term treatment with Li protects primary cultures of rat brain neurons from glutamate-induced, NMDA receptor-mediated excitotoxicity, likely by inhibition of NMDA-receptor-mediated calcium influx, upregulation of anti-apoptotic Bcl-2, down-regulation of pro-apoptotic p53 and Bax, and activation of cell (see Shaltiel *et al*, 2007; Chen and Manji, 2006; Chuang, 2004, 2005 for detailed reviews). Li also induces the expression of BDNF in rat HC (Hashimoto *et al*, 2002; Frey *et al*, 2006) and induces activation of its receptor trkB (Rantamaki *et al*, 2006), which may be necessary for the neuroprotective effects of this medication. Furthermore, a number of animal disease models have found that Li can reduce ischemic damage (Xu *et al*, 2006). Li-induced increases in the number of astrocytes in rodent hippocampus have been reported (Rocha *et al*, 1998), as well as enhancement of hippocampus neurogenesis in the dentate gyri of Li-treated mice (Chen *et al*, 2000). Additionally, Cadotte *et al* (2003) reported that several weeks of Li treatment inhibited pilocarpine-induced mossy fiber sprouting in rat HC. The ability of Li to attenuate this activation-induced reorganization in the HC supports its role as a neuroprotective agent in an *in vivo* model that may be relevant to its clinical effects in BD.

We did not find any change in HC size between the AC group and the UM group or healthy comparison group. This small group comprised of only seven patients using valproic acid and patients using lamotrigine, however, and therefore, the lack of a difference between the UM group and those treated with an anticonvulsant must be considered very preliminary. There is one report that valproate-treated patients with BD had larger cingulate gyrus volumes than medication-naïve patients (Atmaca *et al*, in press) but to our knowledge there are no similar reports of HC volumes in anticonvulsant treated patients. A number of preclinical studies suggest that valproate may share some of the neuroprotective properties that Li appears to possess (Shaltiel *et al*, 2007; Chen and Manji, 2006), but at least one recent study reported distinct differences between Li and valproate in cultured cerebellar granule cell models, with valproate potentiating cell death in conditions where

Li appeared neuroprotective (Jin *et al*, 2005). Both the preclinical and clinical data supporting a role for valproate and lamotrigine as neuroprotective agents thus require further investigation.

Hh Volume and BD

Our results suggest that the effect of Li is most prominent in the head of the HC. When we divided the HC into its head and body/tail, only this region showed a bilateral volume increase in patients treated with Li compared to unmedicated patients. There have been relatively few MRI studies concerning Hh volume. In these studies, Hh volume has been found to be smaller in patients with post-traumatic stress disorder (Vythilingam *et al*, 2005), schizophrenia (Csernansky *et al*, 2002), temporal lobe epilepsy (Bernasconi *et al*, 2003; Bronen *et al*, 1995), and age-associated memory impairment (Mega *et al*, 2002). To our knowledge, our study is the first study in which Hh volume has been measured in patients with BD.

There is evidence suggesting that the neuroanatomic circuit between prefrontal cortex and HC might be involved in the affective symptoms and cognitive deficits associated with BD (Sax *et al*, 1999). Hippocampal CA1 neurons that project to the medial prefrontal cortex are found predominantly in the Hh in primate models (Barbas and Blatt, 1995; Carmichael and Price, 1995). In one influential model, Mayberg (1997) postulates that the affective and cognitive abnormalities of mood disorders arise from dysregulation in the co-ordinated interaction of HC, prefrontal cortical regions, and anterior cingulated cortex. Our results suggest that the Hh may be particularly responsive to Li treatment and further investigation will be required to specify more precisely the relation between Hh changes and changes in cognitive and affective symptoms following Li treatment.

CONCLUSIONS

Hippocampal volumes did not differ between medication naïve subjects with BD and age and sex-matched healthy comparison subjects. An effect of Li treatment on HC volume was apparent even over a brief treatment period spanning 1–8 weeks. Notably, this increase was apparent in the Hh, but not in the Hbt. It will be of interest for future studies to determine whether there are effects of Li on HC volume over longer periods of treatment (ie months to years) and whether there is a relation between HC volume increases and markers of clinical or cognitive outcome in larger samples of participants.

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