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Original article

Hippocampal subfield volumes in major depressive disorder and bipolar disorder

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ABSTRACT

Background: The hippocampus is not a uniform structure, but rather consists of multiple, functionally specialized subfields. Few studies have explored hippocampal subfield volume difference in the same sample of major depressive disorder (MDD) and bipolar disorder (BD) cases. We aimed to investigate the difference of hippocampal subfield volume between patents with MDD and BD and healthy controls (HCs).

Methods: A total of 102 MDD and 55 BD patients and 135 HCs were recruited and underwent T1-weighted image. Hippocampal subfield volume was calculated by automated segmentation and volumetric procedures developed by Iglesias et al. and implemented in FreeSurfer. Volume differences between the groups were analyzed using the analysis of covariance and controlling for age, sex, and total intracranial cavity volume.

Results: Patients with MDD had significantly reduced volumes in the bilateral cornu ammonis 1 (CA1), CA4, the granule cell layer (GCL), molecular layer (ML), whole hippocampus, the left CA2/3, and right presubiclum and subiculum. Patients with BD had significantly reduced volumes in the right CA1, GCL, and the whole hippocampus as compared to HCs. No significant volume differences were observed between the MDD and BD groups. Illness duration was negatively correlated with volumes of the left CA1, CA4, ML, presubiculum, subiculum, and the whole hippocampus in patients with BD.

Conclusion: We observed hippocampal subfield volume reductions in both MDD and BD, a finding which more prominent in MDD. The inverse correlation between BD illness duration and hippocampal subfield volume may evidence the neuroprogressive nature of BD.

1. Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are lifelong episodic mental disorders with a lifetime prevalence of about 16% and 1%, respectively [1,2]. They cause enormous socioeconomic burden by increasing functional impairment, decreasing quality of life, and increasing mortality and suicidality in affected individuals [3,4]. Mood disorders are characterized by multifaceted neurobiological etiologies. However, more recently, it has been reported that structural and functional alterations in neural circuits involved in emotion and cognition may be a mechanism that underpins the development of MDD and BD [5,6].

The hippocampus is a limbic structure that has a critical role in multiple cognitive functions, especially including learning and memory acquisition and consolidation, as well as declarative memory retrieval [7]. In addition to its role in memory processes, the hippocampus is also involved in emotion regulation, motivational behaviors, and the neuroendocrine stress response [8,9]. Furthermore, all of these functions are impaired in MDD and BD [1,2]. Within emotion regulation functioning, the hippocampus is involved in multiple automatic emotional regulatory processes [9]. It works with medial prefrontal regions including the anterior cingulate, orbitofrontal, and dorsomedial prefrontal cortices via automatic cognitive control processes [9]. As a primary neural regulator of the neuroendocrine stress system [the hypothalamus-pituitary-adrenal (HPA) axis], hippocampal disruptions can lead to

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HPA axis dysregulation, characterized by elevated glucocorticoid levels and impaired negative feedback, which is deeply involved in the pathophysiology of both MDD and BD [8,10].

Chronic stress and hypersecretion of cortisol in mood disorders can exert neurotoxic effects on the hippocampus [8]. Hippocampal atrophy is one of the most consistent neuroimaging finding in MDD [11]. Although less consistent than results in MDD, numerous structural MRI studies have reported hippocampal volume losses in BD [12]. Moreover, illness duration and number of mood episodes were reported to be correlated with degree of hippocampal volume reduction in MDD [13] and BD [14]. However, the hippocampus is not a uniform structure but consists of multiple subfields which are demarcated by distinct cytoarchitectural differences and functional specializations. These include the *cornu ammonis* (CA)1–4, dentate gyrus (DG), subiculum (Sub), presubiculum (Presub), and hippocampal tail [15]. Previous postmortem and preclinical studies have suggested that chronic stress and high glucocorticoid levels affect hippocampal subfield-specific neuronal plasticity [16]. For example, in the DG, where most hippocampal adult neurogenesis occurs, is particularly sensitive to the neurotoxic effects of chronic stress and high glucocorticoid level [8].

With substantial advances in structural magnetic resonance imaging (MRI) tools, new hippocampal segmentation algorithms have made it possible to label hippocampal subfields and automatically provide volumetric information for each based on an *in vivo* atlas [17]. Several studies have reported hippocampal subfield-level volume reductions in MDD [18] and BD [15] using this technique. However, in the approach developed by Van Leemput et al. (2009), in which *in vivo* hippocampal subfield atlases are derived from MRI data, contrast properties are limited because their validity was not confirmed with actual hippocampal tissue [19]. More recently, an automated hippocampal segmentation approach developed by Iglesias et al. [20] achieved advances in both subfield identification validity and reliability using a new atlas from *ex vivo* hippocampal tissues scanned with an ultra-high resolution MRI. However, until now, few studies have investigated hippocampal subfield volumes in MDD and BD using this approach [21,22]. Furthermore, there has been only one study exploring hippocampal subfield volume differences between MDD, BD, and healthy controls (HCs) using a single adult sample [19]. This type of investigation may provide comprehensive insights into subfield-level hippocampal volume changes in mood disorders.

Given this background, the present study sought to investigate the diagnostic efficacy of hippocampal subfield volumes in a sample of patents with MDD or BD and HCs. Our *a priori* hypothesis was that patients with MDD or BD would have smaller CA and DG volumes than HCs. We also performed post hoc analyses to examine the correlation between illness duration and hippocampal subfield volumes in patients with MDD or BD. Here, we hypothesized that illness duration would be inversely correlated with subfield volume in patients with MDD or BD. We also investigated the association of antidepressant or lithium treatment, BD type, remission state, and prior history of psychotic symptoms with hippocampal subfield volumes in patients with MDD or BD and hypothesized that these factors would affect hippocampal subfield volumes.

2. Methods

2.1. Sample subjects

A total of 102 MDD and 55 BD patients were recruited from the outpatient psychiatry clinic at Korea University Anam Hospital in Seoul, Republic of Korea between February 2010 and December 2017. Patients with MDD or BD were adults aged 19–64 years, with a diagnosis (i.e., MDD, BD I, or BD II) that was confirmed by board-certified psychiatrists (i.e., Ham BJ and Won E) using a structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I disorders (SCID-I). Among patients with BD, only those with in an ongoing euthymic or depressive state were included in the present study. The concordance rate for the diagnosis of MDD and BD by the two board-certified psychiatrists was above 0.95. Our exclusion criteria for patients with MDD or BD were as follows: i) Any other major psychiatric comorbidity, including personality or substance use disorders; ii) Current psychotic symptoms (e.g., delusions or hallucinations) in patients with MDD or BD or a prior history of psychotic symptoms in patients with MDD; iii) History of a serious and unstable medical illness; iv) Primary neurological illness, including head trauma with residual effects; and v) Any contraindication to MRI, such as metal implants or claustrophobia. The current and prior history of psychotic symptoms (i.e., hallucinations, delusions, delusional ideas, or thought disturbances) in patients with MDD or BD was assessed by board-certified psychiatrists during a full psychiatric interview. Patients with BD were considered to have a prior history of psychotic symptoms if they had any previous SCID-verified mood episodes with psychotic features [23]. We assessed participant illness durations using the life-chart methodology as well as their psychotropic medication history and current status. Illness duration was defined as the elapsed time (months) since the subjects had experienced their first mood episode regardless of inter-episodic periods.

During the same period as patient recruitment, 135 HCs between 19–64 years of age were recruited from the community via an advertisement. Board-certified psychiatrists performed full psychiatric assessments of HCs to confirm that none had a current or past history of psychopathology. The same exclusion criteria that were applied to the patient groups were applied to the HC group. All patients' and HCs severity of depressive symptoms were evaluated using the 17-item Hamilton Depression Rating Scale (HDRS) at the time of MRI scanning [24]. *A priori* power analysis using G*Power (version 3.1) yielded an ideal sample size of at least 252 participants to detect differences in the three groups using an F test and a desired effect size (i.e., Cohen's *f*) of 0.25, type I error of 0.05, and power of 0.95 [25]. These analyses were based on the data collected from 43 patients with MDD and 74 HCs in a previous study by our group [21]. The present study's protocol was approved by the Institutional Review Board of the Korea University Anam Hospital. In accordance with the Declaration of Helsinki, all participants provided written informed consent prior to participation.

2.2. MRI data acquisition

T1-weighted images were obtained using a 3.0-Tesla Trio™ whole-body imaging system (Siemens Healthcare GmbH, Erlangen, Germany). T1-weighted images were acquired parallel to the anterior-commissure–posterior-commissure line using a 3D T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: repetition time of 1900 ms; echo time of 2.6 ms; 220 mm field of view; 256×256 matrix size; 1 mm slice thickness; 176 coronal slices (without gaps); $0.86 \times 0.86 \times 1\ mm^3$ voxel size; 16° flip angle; one excitation.

2.3. Image processing

Automatic procedures for hippocampal subfield segmentation and volumetric measurements of participants' T1 images were performed using a method developed by Iglesias et al. [20], operated and implemented in FreeSurfer 6.0 version (Laboratory

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for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA; http://surfer.nmr.mgh.harvard.edu). Before hippocampal subfield segmentation, reconstruction and segmentation of subcortical structures were performed in FreeSurfer, with detailed procedures described previously [26,27]. A Bayesian model-based automated algorithm developed by Iglesias et al. [20] was employed, which uses the statistical atlas of hippocampal subfields derived from ultra-high resolution (0.13 mm, 7.0 T scanner), *ex vivo* MRI data from post-mortem hippocampal samples. This algorithm yields elaborate demarcations of subregions, especially of the granule cell layer (GCL) of the dentate gyrus and the molecular layer (ML) in the subiculum and CA fields, with greater segmentation accuracy than a previous method developed by Van Leemput et al. [17,19]. Detailed segmentation algorithm parameters were described previously [20].

Although the selection of hippocampal subfields as regions of interest (ROIs) for analysis has had no consensus, the CA1, CA2/3, CA4, DG, Sub, Presub, and hippocampal tail subfields have been commonly investigated by previous mood disorder studies [18,19,22,28–31]. The segmentation method by Iglesias et al. [20] can demarcate the GCL of the DG as well as the ML of the CA and Sub. Thus, we selected the CA1, CA2/3, CA4, GCL, ML, Presub, Sub, and hippocampal tail subfields as well as the whole hippocampus as our regions of interest (Fig. 1). CA2/3 was combined into one ROI due to the lack of contrast between CA2 and CA3 on MRI. Recent studies using the Iglesias et al. [20] segmentation method also selected these subfields as their ROIs [19,22]. The volume of the whole hippocampus was automatically calculated. For segmentation quality control, we adopted a protocol used in a previous study by Cao et al. (2017) and which is similar to the ENIGMA protocol (http://enigma.ini.usc.edu/). First, we excluded outlier (beyond five standard deviations) hippocampal subfields. Next, two co-authors (Ham BJ and Tae WS) independently visually inspected the segmented hippocampal images, which overlapped with corresponding T1-images, to achieve accurate co-registration and assignment of hippocampal subfields. Using this process, no outliers or instances of incorrect segmentation were revealed, and thus no images were excluded.

2.4. Statistical analyses

The relationship between diagnosis and hippocampal subfield volumes was calculated using a general linear model (one-way analysis of covariance) approach with the following variables: 16 hippocampal subfields and two total volumes as dependent variables; diagnosis (MDD vs. BD vs. HC) as an independent variable; age, sex, and total intracranial cavity volume (TICV), obtained from FreeSurfer as covariates according to previous studies [19,22]. Pair-wise comparisons of hippocampal subfield volumes (i.e. MDD vs. HC; BD vs. HC; MDD vs. BD) were performed post-hoc using the same method as was used for primary analyses. We applied a Bonferroni correction to these analyses and post-hoc pair-wise comparisons to minimize type I error risk ($P < 0.05/18 = 0.00278$). For demographic and clinical characteristics, differences in age and HDRS scores between the three groups (MDD, BD, HC) were analyzed using analyses of variance (ANOVAs) and differences in illness duration between the two mood disorder groups were further assessed via independent t-tests. Differences in the distribution of sex and education level were examined using chi-squared tests. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corporation, Armonk, NY, USA).

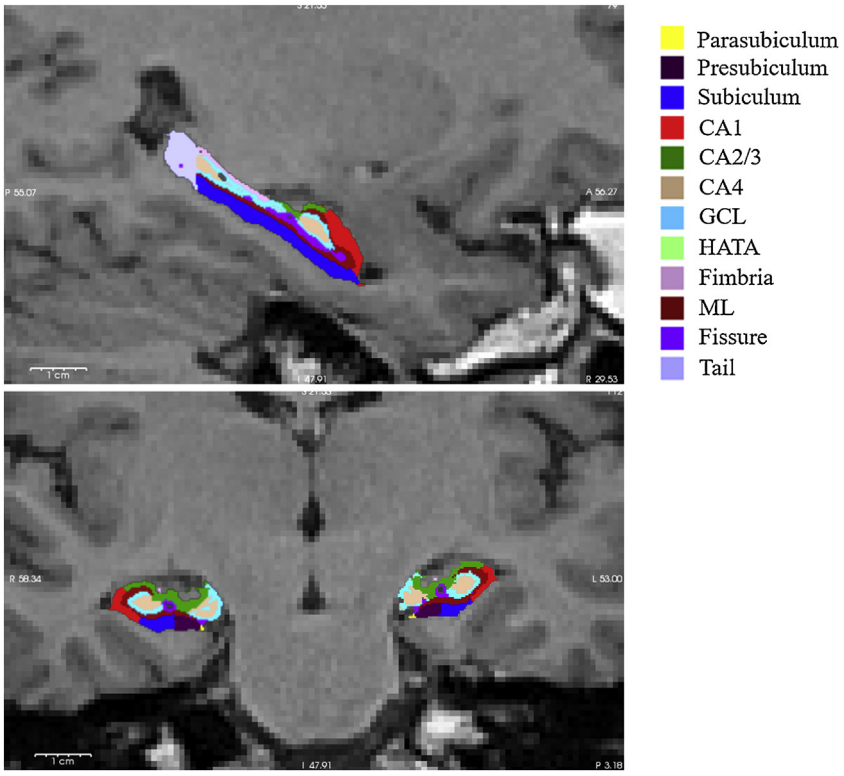

Fig. 1. Atlas for automated segmentation of hippocampal subfields. Corresponding color labels were coded via automatically-delineated hippocampal subfields in coronal and sagittal views of the hippocampus. Among the presented hippocampal subfield regions, the volumes of the CA1, CA2/3, CA4, GL, ML, subiculum, presubiculum, hippocampal tail, and whole hippocampus were used for analyses. CA, *cornu ammonis*; GCL, granule cell layer; ML, molecular layer; HATA; hippocampus-amygdala-transition-area.

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3. Results

3.1. Demographic and clinical characteristics

Information regarding the participants' age, sex, education level, HDRS scores, BD subtypes (i.e., BD I or BD II), mood state (i.e., euthymic/remission state or depressive state), illness duration, psychotropic medication at enrollment status, psychopharmacological treatment types (e.g., antidepressants, mood stabilizers, and antipsychotics), and TICV are presented in Table 1. There were no significant differences in age, sex, education level, and TICV between the three groups ($P > 0.1$; Table 1). Of the 102 patients with MDD, 25 patients (24.5%) were experiencing their first major depressive episode.

3.2. Hippocampal subfield volume differences in patients with mood disorders and healthy controls

We found significant differences in the volumes of bilateral CA1 (left: $P = 0.001$; right: $P = 1.57 \times 10^{-5}$), CA4 (left: $P = 1.06 \times 10^{-4}$; right: $P = 8.25 \times 10^{-4}$), GCL (left: $P = 1.82 \times 10^{-5}$; right: $P = 1.11 \times 10^{-4}$), ML (left: $P = 3.13 \times 10^{-5}$; right: $P = 3.86 \times 10^{-5}$), and whole hippocampus (left: $P = 2.74 \times 10^{-5}$; right: $P = 2.31 \times 10^{-5}$) as well as the volume of the Presub of the right hemisphere ($P = 6.90 \times 10^{-4}$) between the three groups after Bonferroni correction (Table 2).

Post hoc pair-wise comparisons (Table 2,Fig. 2) showed that patients with MDD had significantly smaller bilateral CA1 (left: $P = 8.48 \times 10^{-4}$; right: $P = 1.73 \times 10^{-5}$), CA4 (left: $P = 5.68 \times 10^{-5}$; right: $P = 0.002$), GCL (left: $P = 1.65 \times 10^{-5}$; right: $P = 3.12 \times 10^{-4}$), ML (left: $P = 1.60 \times 10^{-5}$; right: $P = 3.54 \times 10^{-5}$), whole hippocampus (left: $P = 2.40 \times 10^{-5}$; right: $P = 4.01 \times 10^{-5}$), left CA2/3 ($P = 0.002$), and right Presub ($P = 0.002$) and Sub ($P = 0.002$) volumes compared to those of HCs. Patients with BD had smaller right CA1 ($P = 0.002$), GCL ($P = 0.001$), and whole hippocampus ($P = 0.002$) volumes compared to those of HCs. There were no significant differences in hippocampal subfield or whole hippocampus volumes between the MDD and BD groups (Table 2). Detailed information on the hippocampal subfield volumes of each group is described in Table S1.

3.3. Exploration of the association between illness progression and hippocampal subfield volumes

We next assessed the correlation between illness duration and hippocampal subfield volumes in MDD and BD groups using a Pearson's partial correlation analysis. Age, sex, and TICV were used as covariates (Table 3). We found that illness duration was significantly inversely correlated with left CA1 ($r = -0.351$, $P = 0.011$), CA4 ($r = -0.274$, $P = 0.049$), ML ($r = -0.374$, $P = 0.006$), Presub ($r = -0.358$, $P = 0.009$), Sub ($r = -0.281$, $P = 0.044$), and whole hippocampus ($r = -0.373$, $P = 0.007$) volumes in patients with BD. There were no significant correlations in the MDD group.

3.4. Hippocampal subfield volume differences by BD subtype

As a post hoc analysis, we performed pair-wise comparisons between the BD I ($n = 29$) and BD II ($n = 26$) subgroups and HCs using the same statistical methods applied in the primary analyses (Table S2). We found that hippocampal subfield volume differences between the BD I and HC groups largely contributed to the differences between the BD and HC groups in the primary analyses. After Bonferroni correction, patients with BD I had significantly smaller left GCL ($P = 0.001$), hippocampal tail ($P = 6.37 \times 10^{-4}$), and whole hippocampus volumes compared to those of HCs ($P = 0.002$). However, there were no significant differences between the BD II and HC or BD I and BD II groups (Table S2).

Table 1
Demographic and clinical characteristics of patients with mood disorders and healthy controls.

Characteristics	MDD (n = 102)	BD (n = 55)	HC (n = 135)	P-value (F, t, χ^2)
Age	36.04 ± 11.35	33.29 ± 11.32	35.99 ± 12.61	0.316 (F = 1.155)
Sex (female / male)	60 / 42	24 / 31	78 / 57	0.144 (χ^2 = 3.874)
Education level				
Elementary and middle school	7	0	7	0.207 (χ^2 = 5.898)
High school or college/university	87	51	111	
Graduate/professional school or beyond	8	4	17	
HDRS-17 score	13.93 ± 6.44	6.31 ± 4.87	1.56 ± 1.85	<0.001 (F = 216.746)
BD I / BD II	NA	29 / 26	NA	NA
Euthymic (or remission) state / depressive state	18 / 84	37 / 18	NA	NA
Duration of illness (months)	44.76 ± 42.20	45.29 ± 64.38	NA	0.951 (t=-0.062)
Drug-treated patients (n)	80	55	NA	NA
Medication, n				
SSRI	33	8	NA	NA
SNRI	12	2		
NDRI	5	7		
NaSSA	6	1		
Combination of AD	21	0		
Lithium	4	7		
AED	6	38		
Lithium + AED	0	4		
AED + AED	1	1		
AP	23	25		
Combination of AP	6	23		
TICV (mm^3)	1441850 ± 143183	1444253 ± 131053	1459807 ± 155567	0.609 (F = 216.746)

Data are mean ± standard deviation for age, HDRS-17 scores, and duration of illness.
P-values for distribution of sex and education level were obtained using a chi-squared test.
P-values for age comparisons obtained using analyses of variance.
P-values for comparisons with HDRS-17 scores were obtained using independent t-tests.
MDD, major depressive disorder; BD, bipolar disorder; HC, healthy controls; HDRS-17, 17-item Hamilton Depression Rating Scale; BD I, bipolar I disorder; BD II, bipolar II disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; Combination of ADs, combination of two or more types of antidepressants; AEDs, anti-epileptic drugs; APs, antipsychotics; ADs, antidepressants.

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Table 2
Hippocampal subfield volume differences between patients with mood disorders and healthy controls.

Hippocampal volumes	All groups			MDD vs. HC			BD vs. HC			MDD vs. BD		
	$F_{(2, 286)}$	P-value	Cohen's *f*	$F_{(1, 232)}$	P-value	Cohen's *f*	$F_{(1, 185)}$	P-value	Cohen's *f*	$F_{(1, 152)}$	P-value	Cohen's *f*
Left hemisphere												
CA1	6.825	**0.001**	0.218	11.429	$\mathbf{8.48 \times 10^{-4}}$	0.222	6.031	0.015	0.181	0.087	0.769	0.024
CA2/3	5.210	0.006	0.191	9.850	**0.002**	0.206	2.807	0.096	0.123	0.455	0.501	0.055
CA4	9.447	$\mathbf{1.06 \times 10^{-4}}$	0.257	16.822	$\mathbf{5.68 \times 10^{-5}}$	0.269	6.508	0.012	0.188	0.257	0.613	0.041
GCL	11.341	$\mathbf{1.82 \times 10^{-5}}$	0.282	19.355	$\mathbf{1.65 \times 10^{-5}}$	0.289	8.791	0.003	0.218	0.065	0.798	0.021
ML	10.758	$\mathbf{3.13 \times 10^{-5}}$	0.274	19.431	$\mathbf{1.60 \times 10^{-5}}$	0.289	6.870	0.009	0.193	0.578	0.448	0.062
Presub	6.084	0.003	0.206	8.242	0.004	0.188	7.354	0.007	0.199	0.453	0.502	0.055
Sub	3.766	0.024	0.162	7.466	0.007	0.179	0.202	0.653	0.033	2.611	0.108	0.131
Hippocampal tail	4.425	0.013	0.176	5.793	0.017	0.158	6.014	0.015	0.180	0.366	0.546	0.049
Whole hippocampus	10.901	$\mathbf{2.74 \times 10^{-5}}$	0.276	18.592	$\mathbf{2.40 \times 10^{-5}}$	0.283	8.411	0.004	0.213	0.123	0.727	0.028
Right hemisphere												
CA1	11.500	$\mathbf{1.57 \times 10^{-5}}$	0.284	19.257	$\mathbf{1.73 \times 10^{-5}}$	0.288	10.051	**0.002**	0.233	0.004	0.951	0.005
CA2/3	3.078	0.048	0.147	5.650	0.018	0.156	2.422	0.121	0.114	0.159	0.690	0.032
CA4	7.279	$\mathbf{8.25 \times 10^{-4}}$	0.226	10.181	**0.002**	0.209	7.979	0.005	0.208	0.412	0.522	0.052
GCL	9.405	$\mathbf{1.11 \times 10^{-4}}$	0.256	13.398	$\mathbf{3.12 \times 10^{-5}}$	0.240	10.502	**0.001**	0.238	0.487	0.486	0.057
ML	10.533	$\mathbf{3.86 \times 10^{-5}}$	0.271	17.789	$\mathbf{3.54 \times 10^{-5}}$	0.277	8.466	0.004	0.214	0.004	0.949	0.005
Presub	7.468	$\mathbf{6.90 \times 10^{-4}}$	0.229	9.463	**0.002**	0.202	8.856	0.003	0.219	1.294	0.257	0.092
Sub	4.870	0.008	0.185	9.548	**0.002**	0.203	2.480	0.117	0.116	0.194	0.661	0.036
Hippocampal tail	3.139	0.045	0.148	5.053	0.026	0.148	2.809	0.095	0.123	0.011	0.916	0.009
Whole hippocampus	11.083	$\mathbf{2.31 \times 10^{-5}}$	0.278	17.534	$\mathbf{4.01 \times 10^{-5}}$	0.275	9.773	**0.002**	0.230	0.088	0.768	0.024

Bonferroni correction was applied: $P < 0.05/18 = 0.00278$.
Significant hippocampal subfield volume differences are presented in a bold face.
MDD, major depressive disorder; BD, bipolar disorder; HC, healthy controls; CA, cornu ammonis; GCL, granular cell layer; ML, molecular cell layer; Presub, presubiclum; Sub, subiculum.

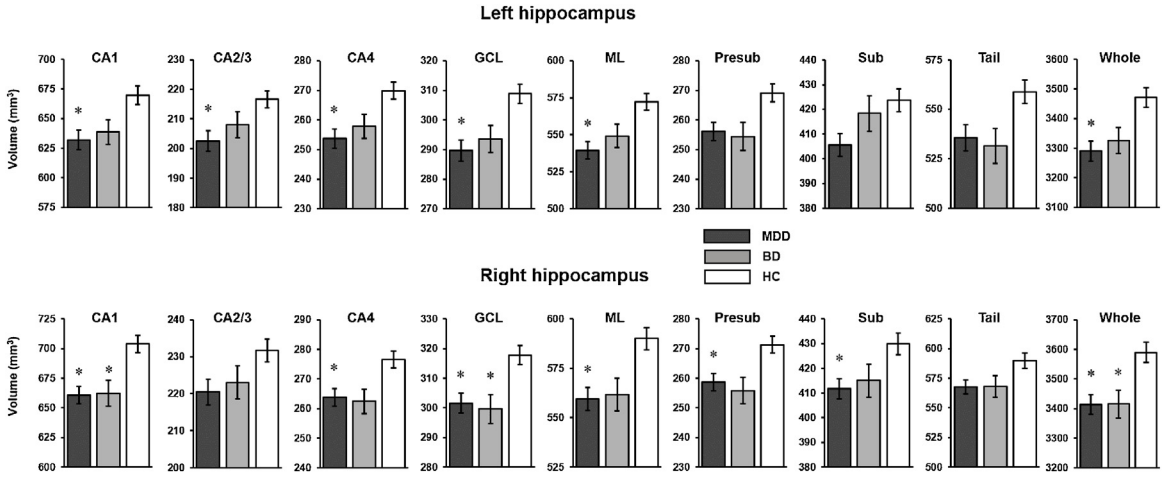

Fig. 2. Comparisons of hippocampal subfield volumes between MDD, BD, and HC groups. Asterisk represents significantly different volume versus HC group after Bonferroni correction. Error bar represents one standard error. MDD, patients with major depressive disorder; BD, patients with bipolar disorder; HC, healthy control participants; CA, cornu ammonis; GCL, granule cell layer; ML, molecular layer; Presub, presubiculum; Sub, subiculum; Tail, hippocampal tail; Whole, whole hippocampus.

3.5. Hippocampal subfield volume differences after lithium treatment in BD or antidepressant treatment in MDD

An ANCOVA with age, sex, TICV, illness duration, and HDRS score as covariates showed that there were no significant subfield volume differences between drug-naïve (n = 24) and antidepressant-treated (n = 78) patients with MDD (all, $P > 0.05$, Table S3). Moreover, there were no significant subfield volume differences between lithium-treated (n = 11) and non-treated (n = 44) patients with BD using the same statistical method ($P > 0.05$; Table S4).

3.6. Hippocampal subfield volume differences according to the remission state and prior history of psychotic symptoms

As the secondary analysis, we investigated the difference of in hippocampal subfield volumes with respect to the remission state of each patient group using an ANCOVA with age, sex, and TICV included as covariates. The results of this analysis showed no significant difference between patients with remission and non-remission in the MDD and BD groups (all, $P > 0.05$; Table S5). Using the same statistical method as the main analysis, we performed an additional analysis comparing the hippocampal subfield volumes between the MDD, BD, and HC groups with those from the sample of non-remitted patients and HCs (MDD, n = 84; BD, n = 18; HC, n = 135). This analysis showed a similar pattern to our main findings; however, reduced volume was only observed for the comparison between the MDD and HC groups after Bonferroni correction (Table S6). Using the same statistical methods, we examined the relationship between a prior history of psychotic symptoms and hippocampal subfield volumes in the BD group. There were no significant volume differences in BD patients with a prior history of psychotic symptoms (n = 22) and

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Table 3
Correlation between illness duration and hippocampal subfield volumes in patients with mood disorders.

Hippocampal volumes	MDD		BD	
	r	P-value	r	P-value
Left hemisphere				
CA1	0.046	0.653	−0.351	**0.011**
CA2/3	−0.045	0.661	−0.220	0.117
CA4	−0.063	0.534	−0.274	**0.049**
GCL	−0.084	0.409	−0.259	0.063
ML	−0.015	0.881	−0.374	**0.006**
Presub	0.072	0.479	−0.358	**0.009**
Sub	0.031	0.764	−0.281	**0.044**
Hippocampal tail	−0.046	0.653	−0.178	0.206
Whole hippocampus	−0.013	0.899	−0.373	**0.007**
Right hemisphere				
CA1	−0.030	0.769	−0.112	0.428
CA2/3	0.080	0.431	0.041	0.772
CA4	0.106	0.295	−0.044	0.757
GCL	0.059	0.564	−0.029	0.837
ML	0.041	0.687	−0.073	0.605
Presub	0.171	0.090	−0.186	0.188
Sub	0.013	0.901	−0.070	0.623
Hippocampal tail	−0.019	0.853	−0.202	0.150
Whole hippocampus	0.042	0.683	−0.116	0.415

Significant correlations are presented in a bold face.
MDD, major depressive disorder; BD, bipolar disorder; HC, healthy controls; CA, cornu ammonis; GCL, granular cell layer; ML, molecular cell layer; Presub, presubiclum; Sub, subiculum.

those without a psychotic symptom history (n = 33; all, P > 0.05; Table S7).

4. Discussion

The present *in vivo* study primarily showed that the volumes of multiple hippocampal subfields (i.e., bilateral CA1, CA4, GCL, and ML, left CA2/3, and right Presub and Sub [MDD] and right CA1 and GCL [BD]) in patients with MDD or BD were smaller than those in HCs. Decreased subfield volumes in the BD group were primarily driven by patients with BD I. Furthermore, there was no significant difference in the subfield volumes of patients with MDD and those with BD. There was a significant, inverse correlation between illness duration and left CA1, CA4, ML, Presub, and Sub volumes in patients with BD.

Our MDD findings are supported by previous studies that have reported similar volume reductions in CA1 [32,33], CA2/3 [18,32,34], CA4 [32], GCL [31], and the Sub [18,33] in MDD patients compared to HCs. Using the state-of-the-art method developed by Iglesias et al. [20], Doolin et al. [32] reported volume reductions in the left CA1, bilateral CA2/3, and the right CA4 in MDD in a sample of 48 patients with MDD and 27 HCs. However, a study by Cao et al. [19], which used the same approach but in a larger sample (86 MDD, 133 BD, and 152 HCs), did not find significant hippocampal subfield volume differences between patients with MDD and HCs but did between those with BD and HCs.

Subfields that exhibited volume losses in patients with MDD in the present study are implicated in modulatory interactions between the hippocampus and HPA axis (ventrally) and integration of basal HPA axis activity information (dorsally) [16]. Preclinical evidence has indicated that chronic stress exposure and increased glucocorticoid levels exert detrimental effects on hippocampal neuroplasticity per subfield via dendritic retraction, death of pyramidal cell, and suppression of neurogenesis, and the neurogenic hypothesis of MDD suggests that a reduced rate of neurogenesis in the DG is a key pathoetiology of MDD [16]. We are the first to report volume reductions in the ML in MDD because this region goes unlabeled in the existing hippocampal segmentation method used in prior studies [17]. The new method developed by Iglesias et al. [20] and used here labeled the molecular layer of CA and Sub (i.e., ML). Critically, the ML consists of interneuron synapses, which play a pivotal role in synaptic wiring and temporal event processing in the hippocampus [35]. A recent study by Cao et al. (2017) reported volume reductions in the MLs of patients with BD (but not MDD) as compared to HCs. Given the paucity of similar studies, however, further work is required.

Our second main finding revealed reduced CA1, GCL, and total hippocampal volumes in BD. This may underlie disruptions to hippocampal involvement in declarative memory, stress reactivity, emotion and mood regulation, and regulation of goal-directed activity in BD [15]. Furthermore, besides recurrent alternations between (hypo)manic and depressive episodes, BD can be characterized by global neurocognitive deficits, particularly to declarative memory during both acute and euthymic (i.e. remission) states [12]. Previous structural MRI studies have consistently suggested smaller hippocampal volumes in BD versus HC groups [36–39]. Our findings also support previous hippocampal subfields studies that have reported CA1 [15,40] and GCL [19] volume reductions in BD. Additionally, Cao et al. (2017) reported volume reductions in the left CA4 and GCL and bilateral ML and hippocampal tails in BD using the same automatic segmentation method employed here. A similar study using the same segmentation approach in children and adolescents with BD also reported smaller right CA1, CA4, subiculum and bilateral GCL, ML, and hippocampal tail volumes [22].

In the present study, we also found that subfield volume reductions were more prominent in BD I than in BD II (versus HCs), as was also reported by Cao et al. (2017). There, the authors reported that volume reductions were observed in BD I but not in BD II. They also observed that hippocampal subfield volumes (CA2/3, CA4, and hippocampal tail) were inversely correlated with the number of manic episodes (but not hypomanic, mixed, or depressive episodes). Similarly, a recent large-scale neuroimaging study by the ENIGMA Bipolar Disorder Working Group, which included data from over 4000 subjects, indicated significant hippocampal volume reductions in patients with BD I compared to HCs; however, hippocampal reduction was not observed in patients with BD II [41]. These findings implicate hippocampal and subfield neurostructdural alterations in the pathophysiology of BD I more than in that of BD II. Thus, it is possible that the cumulative effect of manic episodes in BD I may exert particularly detrimental effects on hippocampal neuroplasticity [19].

In a secondary analysis, we found a significant inverse correlation between illness duration and volumes of the CA1, CA4, ML, Presub, Sub, and the whole hippocampus in the left hemisphere among patients with BD but not MDD. Several reports have similarly found that illness duration was inversely correlated with hippocampal volume in patients with BD [14,42]. Furthermore, Cao et al. (2017) first reported an inverse correlation between illness duration and hippocampal subfield volumes (right CA1, ML, and Sub) among patients with BD, results that supports our own. The neuroprogressive model of BD represents illness progression in two ways: illness duration and number of mood episodes. The model contests that these are associated with symptomatology severity, neurocognitive deficits, functional impairments, and recurrence risk [43]. The progression of BD is further associated with hippocampal atrophy via putative neurobiological mediation pathways and a disturbed HPA axis, reduced brain-derived neurotropic factor (BDNF), and increased oxidative stress and neuroinflammatory markers [44]. Despite reports of hippocampal subfield-specific effects of HPA axis dysregulation (e.g. increased glucocorticoid levels) [45], *BDNF* genotype [34], oxidative stress [30], and inflammatory pathways [32] in patients

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with MDD, few have investigated whether the neuroprogression of BD is specific to hippocampal subfields. Further studies are required to clarify this.

No significant hippocampal subfield volume differences were observed between MDD and BD groups. To the best of our knowledge, only two prior studies have directionally compared MDD and BD–one used adults [19], and the other children and adolescents [22]. Using the same segmentation method, neither observed any significant difference in hippocampal subfield volumes with the mood disorders. Additionally, one previous meta-analytic study investigated total hippocampal volume in mood disorder patients and reported smaller volumes in patients with MDD versus BD [46], while, included studies in the meta-analysis did not consider subtypes of BD or lithium treatment which could affect hippocampal volumes [19]. Future meta-analytic studies that consider the effects of these two potential moderators are therefore important.

In the present study, we could not find any significant effect of remission or non-remission state on hippocampal subfield volumes in patients with MDD or BD. Several previous studies have reported that remitted patients with MDD had larger hippocampal volumes compared to patients with active depression [46–48], however, no studies have shown significant differences in hippocampal subfield volumes between such patients. To our knowledge, there have been no studies that have reported hippocampal volume differences between remitted and non-remitted patients with BD. Nevertheless, in this study, a substantial proportion of our sample (18 patients with MDD [17.6%] and 37 patients with BD [67.3%]) was in remission and we cannot exclude the possibility that the remission state of these patients may have affected our results. We also observed that a previous history of psychiatric symptoms did not affect the hippocampal subfield volumes in the BD group. A previous study reported that patients with BD and a history of psychosis showed a significantly lower verbal memory, which was significantly associated with the hippocampal structure, compared to those without a history of psychosis [23]. However, a recent study by Haukvik et al. [15], which used a hippocampal segmentation method by Van Leemput et al. [17], found no significant differences in hippocampal subfield volumes between psychotic and non-psychotic patients with BD. Therefore, further studies are required to resolve these discrepant findings.

The present study has several limitations. First, we were unable to fully control for antidepressant and lithium treatment in patients with MDD and BD, respectively, due to the heterogeneity of concomitant medication types, dosage, and duration, which may affect our results as potential confounding factors. Furthermore, we did not observe any significant differences in hippocampal subfield volumes between lithium-treated and untreated patients with BD or antidepressant-treated and drug-naïve patients with MDD. However, previous reports have indicated that antidepressants and lithium may affect hippocampal volumes in MDD and BD [49,50]. For example, Yucel et al. [51] reported that 2–4 years of lithium treatment was associated with a 4–5% increase in hippocampal volume in patients with BD. Moreover, Sani et al. [52] found that patients with BD with long-term exposure (i.e., > 24 months) to lithium treatment had larger hippocampal volumes compared to those without exposure to lithium treatment. A previous post-mortem study reported that antidepressant treatment in patients with MDD was associated with increased DG volume and granule neuron numbers [50]. Our null finding for the effect of medication on hippocampal subfield volume may be due to sample heterogeneity in lithium or antidepressant treatment duration or dosage. Thus, we cannot exclude the possibility that the antidepressant or lithium treatment status of the patients studied may have confounded our findings. Second, rather than the number of mood episodes, we assessed illness duration in the patients here. Previous studies have reported that the number of mood episodes is associated with hippocampal subfield volumes in MDD [53] and BD [19]. Furthermore, our duration of illness assessment was susceptible to recall bias, a possible source of inaccuracy. Lastly, the present study employed a cross-sectional design and thus any causal relationship between hippocampal subfield volume alterations and onset of mood disorders was unassessed.

In summary, we observed hippocampal subfield volume reduction in the MDD and BD groups compared to the HC group. Moreover, the extent of volume reduction was greater in the MDD group. Reduced hippocampal subfield volumes in BD were mainly driven by reductions in BD I. The significant inverse correlation between BD illness duration and hippocampal subfield volume reported here may evidence the neuroprogressive nature of BD. Future studies should consider antidepressant/lithium treatment and BD subtypes, as well as utilize a longitudinal design to clarify a causal relationship between subfield volume and disease state. Furthermore, neurobiological mechanisms of subfield-specific hippocampal atrophy may be elucidated via more comprehensive studies that integrate neuroimaging and cellular/molecular makers.

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Conflict of interest

The authors have no potential or actual conflict of interest.

Contributors

K.-M. Han wrote the manuscript as the first author. K.-M. Han managed the literature search and performed statistical analysis of the data. K.-M. Han, A. Kim, W. Kang, Y. Kang, J. Kang, E. Won, W.-S. Tae, and B.-J. Ham contributed to the analysis and interpretation of the data. B.-J. Ham conceived and designed the study and wrote the protocol as the corresponding author. All authors contributed significantly to and have approved the final manuscript.

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None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurpsy.2019.01.016.

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