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Hippocampal Subfield Volumes in Mood Disorders

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Abstract

Volume reduction and shape abnormality of the hippocampus have been associated with mood disorders. However, the hippocampus is not a uniform structure and consists of several subfields, such as the cornu ammonis (CA) subfields CA1–4, the dentate gyrus (DG) including a granule cell layer (GCL) and a molecular layer (ML) that continuously crosses adjacent subiculum and CA fields. It is known that cellular and molecular mechanisms associated with mood disorders may be localized to specific hippocampal subfields. Thus, it is necessary to investigate the link between the *in vivo* hippocampal subfield volumes and specific mood disorders, such as bipolar disorder (BD) and major depressive disorder (MDD). In the present study, we used a state-of-the-art hippocampal segmentation approach, and we found that patients with BD had reduced volumes of hippocampal subfields, specifically in the left CA4, GCL, ML, and both sides of the hippocampal tail, compared to healthy subjects and patients with MDD. The volume reduction was especially severe in patients with bipolar I disorder (BD-I). We also demonstrated that hippocampal subfield volume reduction was associated with the progression of the illness. For patients with BD-I, the volumes of the right CA1, ML and Sub decreased as the illness duration increased, and the volumes of both sides of the CA2/3, CA4, and hippocampal tail had negative correlations with the number of manic episodes. These results indicated that among the mood disorders the

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Author Contributions:

Dr. Cao designed the study, processed, quality-controlled and analyzed the data, drafted the manuscript, and critically edited the draft of the manuscript.

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Dr. Mwangi was involved in designing the study, processed the data, and critically edited the draft of the manuscript.

Dr. Amaral-Silva implemented the pipeline of quality control and independently finished the quality control of the hippocampal subfield segmentation.

Ms. Tannous independently did the quality control of the hippocampal subfield segmentation.

Dr. Wu partly processed the data and critically edited the draft of the manuscript.

Dr. Zunta-Soares coordinated the subject enrollment and data collection.

Dr. Soares supervised the study, provided financial and instrumental support, collected the data, and critically edited the draft of the manuscript.

Conflict of Interest

Dr. Cao, Dr. Passos, Dr. Mwangi, Dr. Amaral-Silva, Ms. Tannous, Dr. Wu and Dr. Zunta-Soares reported no biomedical financial interests or potential conflicts of interest.

hippocampal subfields were more affected in BD-I compared to BD-II and MDD, and manic episodes had focused progressive effect on the CA2/3 and CA4 and hippocampal tail.

Introduction

Bipolar disorder (BD) affects 2% of the world's population, with subthreshold forms affecting another 2%.¹ On the other hand, major depressive disorder (MDD) has a lifetime prevalence of 16.6%. Both disorders are leading causes of disability-adjusted life years worldwide according to The Global Burden of Disease study and the World Health Organization.^{2,3} In addition, they have been independently associated with missed workdays,⁴ comorbid cardiovascular⁵ and endocrine diseases,⁶ neurocognitive impairment, and suicide attempts.⁷ Therefore, understanding the pathophysiological mechanisms that underlie the development of both disorders is crucial for alleviating the impact of these devastating illnesses on public health.

The hippocampus is essential for the acquisition, consolidation and retrieval of memory.⁸ It is involved in verbal memory functions and other complex behaviors, including stress responses, emotions, sensorimotor integrations, and goal-directed activity, all of which may be disrupted in mood disorder.^{9,10} Noticeably, studies of hippocampal volumes in patients with BD have been contradictory so far, showing no changes^{11–13}, smaller volumes^{14–16}, and even larger volumes in BD patients as compared to healthy subjects^{17,18}. These inconsistent results could be related to the use of certain medication with neuroprotective effect, such as lithium and the heterogeneity of BD types in these studies.^{19–22} A recent study, however, reported that patients with BD have reductions in hippocampus according to prior morbidity (number of manic episodes and hospitalization).²³ Regarding MDD, a recent meta-analysis of 32 magnetic resonance imaging (MRI) studies have confirmed the difference in hippocampal volume between patients and controls, but only among patients with MDD whose duration of illness was longer than two years or who had more than one mood episode.²⁴ These findings point to a progressive reduction of the hippocampus as a function of prior morbidity in mood disorders.

However, it is known that the hippocampus is not a uniform structure and consists of subfields with distinct morphology: the cornu ammonis (CA) subfields CA1–4, the dentate gyrus (DG), the fimbria, and the adjacent subiculum and presubiculum.⁹ It is also known that cellular and molecular mechanisms associated with mood disorders may be localized to specific hippocampal subfields.^{25–27} Therefore, it is necessary to investigate to which extent *in vivo* hippocampal subfield volumes differ between BD, MDD, and healthy subjects to better understand the role of the hippocampus in mood disorders.

Previous studies have made great advancement in understanding the morphometric and volumetric changes in the hippocampus in mood disorders using surface-based shape analyses^{14,28,29} or an automated method of labeling the subfields based on an *in vivo* atlas.^{30,31} However, the surface-based shape analysis could not reach deep structures of the hippocampus. The *in vivo* atlas was derived from MRI scans with limited contrast and the validity of the atlas was not confirmed with the actual tissues.³² The method used to segment the hippocampal subfields in the present study was developed based on *ex vivo* hippocampal

tissues scanned with ultra-high field strength.³³ The resolution and accuracy of the segmentation were proved to be higher than the previous method using *in vivo* atlas,^{33,34} which will help us to observe the localized changes within hippocampus related to mood disorders and their progression.

Therefore, the aim of the present study was to investigate diagnostic differences in hippocampal subfield volumes in a large sample of patients with MDD, patients with BD, and healthy subjects. We hypothesized that patients would have smaller hippocampal subfield volumes than healthy control subjects and that patients with BD would have smaller volumes than patients with MDD. Moreover, we conducted post hoc analyzes of associations between selected subfields and illness duration and number of mood episodes. We hypothesized smaller volumes to correlate with increased illness duration and a higher number of prior mood episodes.

Materials and Methods

Participants

Subjects were recruited through flyers, radio, and newspaper advertisements from the community and outpatient psychiatric clinics from 2002 to 2006. Patient inclusion criteria were subjects with bipolar I disorder (BD-I), bipolar II disorder (BD-II) or major depressive disorder (MDD) according to DSM-IV. Exclusion criteria included head trauma with residual effects, neurological disorders, and uncontrolled major medical conditions based on self reports. We used a medication history form to obtain history about prior medication use from all patients based on their self-reports (Supplementary Materials). We also obtained a urine drug test to detect any current drug abuse, whenever applicable. Healthy controls (HC) were excluded if they had a history of any Axis I disorder, had a first-degree relative with any Axis I disorder, or used psychoactive medication less than two weeks before the study. The schedule of patients and HC being recruited and scanned were mixed, so that the date of the scanning was not related to the diagnostic groups. Subjects were evaluated through a socio-demographic history form for age, gender, years of education, as well as occupational status. Axis-I diagnoses and clinical characteristics were assessed with the Structured Clinical Interview for DSM-IV (SCID), administered by research assistants or postdoctoral fellows supervised by an experienced research psychiatrist. Inter-rater reliability was checked periodically by having raters do interviews together. Current mood symptoms were assessed with the Hamilton Depression Scale (HAM-D)³⁵ and the Young Mania Rating Scale (YMRS).³⁶ A power analysis indicated that for three-group (HC, BD and MDD) F tests, to achieve an effect size f of 0.25 with type I error at 0.05 and power at 0.95, the ideal sample size should be at least 252 in total. No hardware upgrade of the scanner was performed during the study. The study protocol was approved by the local Institutional Review Board and informed consent was obtained from all the participants.

MRI data acquisition and preprocessing

The structural T1-weighted scan of each subject was acquired on a Philips 1.5 Tesla MRI scanner (Philips Medical System, Andover, MA, USA) with a three-dimensional axial fast field echo sequence with the following parameters: repetition time (TR) = 24 ms, echo time

(TE) = 5 ms, flip angle = 40°, field of view (FOV) = 256 mm, slice thickness = 1 mm, matrix size = 256–256 and 150 slices. All scans were visually inspected to rule out gross artifacts.

Subcortical reconstruction and segmentation were first performed with the FreeSurfer software suite version 5.3.0 (<http://surfer.nmr.mgh.harvard.edu>). The procedure including motion correction, intensity normalization, automated topology corrections and automatic segmentations of cortical and subcortical regions is documented elsewhere.^{37–39}

A novel automated algorithm from FreeSurfer that will be released in the next version was used to segment the hippocampal subfields. The subfield atlas was derived from high resolution (0.13 mm) *ex vivo* MRI data of postmortem medial temporal tissue from a 7-T scanner (Figure 1).³³ This algorithm was proved to be more accurate than the previous method³² and was able to reliably identify granule cell layer (GCL) within the dentate gyrus (DG), and the molecular layer (ML) within the subiculum and the CA fields. The algorithm could also provide a better estimation of CA volumes.³⁴ In the current study, we included eight hippocampal subfields: CA1, CA2 and CA3 (noted as CA3 due to the indistinguishable MR contrast between CA2 and CA3), CA4, GCL, ML, presubiculum (Presub), subiculum (Sub) and the hippocampal tail (Tail; the posterior end of the hippocampus).

We used a two-step quality control protocol, similar to the ENIGMA protocol (<http://enigma.ini.usc.edu/>).^{22,40,41} To be brief, any outlier (five standard deviations) of any hippocampal subfield was excluded. Then each segmented image, overlaid on the corresponding brain structural image, was visually inspected by two co-authors independently (BC and HT), in order to exclude segmentations with poor registration to the hippocampus location or with apparent wrong assignment of the subfields. We did not exclude any image because we did not find any outlier or bad segmentation of hippocampal subfields with the novel algorithm.

Statistical Analyses

Analysis on the effect of diagnosis—Statistical analyses were conducted using SPSS (Version 23.0; IBM Corp., Armonk, NY). For each hippocampal subfield, we used a general linear model (GLM) to investigate the effect of mood disorder diagnosis. Diagnosis group (HC, BD, and MDD) was entered as an independent variable, while the whole hippocampal volume and the hippocampal subfield volumes were entered as a dependent variable. We used age, gender, and the intracranial volume (ICV) as covariates. Because we observed no effect of ethnicity in the preliminary analysis, we did not include it as a covariate. Bonferroni correction was performed across the 16 regions. *Post-hoc* t-tests on the estimated subfield volumes adjusted for the covariates were performed between the three diagnosis groups to identify the pairwise group differences. The p values of the three pairwise comparisons between the diagnosis groups were corrected with Bonferroni correction. Further *Post-hoc* analysis was performed to identify which subtype of BD was driving the effect from BD. We considered p-values < 0.05 significant.

Analysis on the effect of illness progression—The illness progression was considered to be represented by two typical measurements: the illness duration and the number of mood episodes. Based on several studies on the neuroprogression of bipolar disorder and major depressive disorder, the number of episodes was consistent with several aspects of the disorder, such as the brain atrophy and the general functioning.^{23,42–46} The partial correlations were performed between the hippocampal subfield volumes and the illness duration, as well as the numbers of manic, hypomanic, mixed and depressive episodes for BD-I, BD-II, and MDD controlling for age, gender, and ICV. Because a significant portion of patients reported more than 30 mood episodes, we considered the numbers of episodes as ordinal variables instead of scale variables in the correlation analysis. We considered p-values < 0.05 significant.

Results

Demographics

A total of 371 subjects were recruited (152 HC, 133 BD, and 86 MDD). Age ($p=0.005$), education ($p<0.001$), HAMD ($p<0.001$), and YMRS ($p<0.001$) were significantly different between the groups (Table S1). Patients with BD had significantly higher HAMD ($p=0.043$) and YMRS ($p<0.001$) than patients with MDD.

Findings between patients with mood disorders and healthy controls

We found significant diagnosis group effect in left ($F_{2,365}=6.551$; $p=0.002$) and right ($F_{2,365}=4.569$; $p=0.011$) whole hippocampal volumes. *Post-hoc* t-tests found that the group effect was primarily due to lower hippocampal volumes of patients with BD compared to HC and MDD, while hippocampal volumes in HC and MDD were not significantly different from each other.

We found significant diagnosis group effect in left CA1 ($F_{2,365}=3.369$; $p=0.035$), CA3 ($F_{2,365}=3.517$; $p=0.031$), CA4 ($F_{2,365}=6.626$; $p=0.001$), GCL ($F_{2,365}=6.930$; $p=0.001$), Presub ($F_{2,365}=3.192$; $p=0.042$), and both sides of ML (left: $F_{2,365}=6.196$; $p=0.002$; right: $F_{2,365}=3.786$; $p=0.024$) and Tail (left: $F_{2,365}=7.209$; $p=0.001$; right: $F_{2,365}=6.271$; $p=0.002$). *Post-hoc* t-tests found that the group effect was primarily due to lower hippocampal subfield volumes of patients with BD compared to HC and MDD (Table 1). Only the results in left CA4, GCL, ML and both sides of Tail would survive the Bonferroni correction for the multiple comparisons across the sixteen subfields.

Findings between bipolar disorder subtypes and healthy controls

With further *post-hoc* t-tests within the BD subtypes, we found that the lower hippocampal subfield volumes of BD were majorly driven by patients with bipolar I disorder (BD-I), although patients with bipolar II disorder (BD-II) showed non-significant decrease of the hippocampal subfield volumes (Table S1). The hippocampal subfield volumes in HC, BD-I, BD-II, and MDD are shown in Figure 2 (Figure S1).

Hippocampal subfield volume changes associated with progression of mood disorders

We investigated hippocampal subfield volume changes associated with progression of mood disorders. The progression of mood disorders was represented by the illness duration and the number of mood episodes. With partial Pearson correlation that controlled for age, gender, and ICV, we found that right CA1 ($r=-0.270$; $p=0.025$), ML ($r=-0.265$; $p=0.028$), and Sub ($r=-0.213$; $p=0.040$) were negatively correlated with the illness duration of patients with BD-I (Figure S2). No correlations of illness duration and any of the subfield volumes were found in patients with BD-II and MDD.

We found significant negative correlations in patient with BD-I between the number of manic episodes and both sides of CA3 (left, $r=-0.256$, $p=0.016$; right, $r=-0.284$, $p=0.007$), CA4 (left, $r=-0.240$; $p=0.024$; right, $r=-0.250$, $p=0.019$) and hippocampal tail (left, $r=-0.237$, $p=0.026$; right, $r=-0.233$, $p=0.029$) (Figure S3), and non-significant trend GCL (left, $r=-0.192$, $p=0.073$; right, $r=-0.195$, $p=0.069$). No significant correlation between the number of hypomanic, mixed and depressive and hippocampal subfield volumes was found in patients with BD-I. Besides a positive correlation between the left hippocampal tail volume and the number of hypomanic episodes in BD-II patients ($r=0.386$, $p=0.043$), no correlation between the number of any mood episodes and hippocampal subfield volumes was found in patients with BD-II or MDD (Table S2).

Discussion

In the present study, with a state-of-the-art hippocampal segmentation approach, we showed that patients with BD had reduced volumes of hippocampal subfields, specifically in the left CA4, GCL, ML, and both sides of the hippocampal tail, compared to healthy subjects and patients with MDD. The volume reduction was relatively more severe in patients with BD-I than BD-II, which spread across all the subfields of the hippocampus. We also demonstrated that hippocampal subfield volume reduction was associated with the progression of the illness. Specifically, in patients with BD-I, the volumes of the right CA1, ML, and Sub decreased as the illness duration increased, and the volumes of both sides of the CA2/3, CA4, and hippocampal tail were negatively correlated with the number of manic episodes. These results indicated that among the mood disorders the hippocampal subfields were more affected in BD-I compared to BD-II and MDD, and manic episodes had focused progressive effect on the CA2/3 and CA4, as well as the tail of the hippocampus.

Our findings that the CA4 and GCL showed reduced volumes were consistent with the previous studies using the *in vivo* atlas, in which the two subfields were not differentiable.³¹ Cells in GCL are important to functional neurogenesis during brain development and adulthood.⁴⁷ The reduced neurogenesis is linked with stress and mood disorders and can be recovered by certain interventions, such as antidepressant treatments.⁴⁸ The reduced GCL volume in BD observed in our study was in line with this theory. The CA4 is the hilar region and is a polymorphic layer that contains different types of interneurons within the DG. CA4 cannot be presented with surface-based shape reconstruction. Postmortem studies showed that mRNAs of the complexins I and II that are important to synaptic transmission⁴⁹ were lower in CA4 of patients with BD,^{26,27} a similar finding to that in schizophrenia.²⁶ The mRNA associated with the brain-derived neurotrophic factor (BDNF) was also lower in CA4

of patients with BD,^{27,50} which is important for the survival and growth of neurons and synapses.^{51,52} Moreover, the reelin, a protein involved in cell migration and cortical lamination⁵³, and reelin-positive cell counts were also lower in CA4 of patients with BD.^{27,54} The reelin protein levels might decrease progressively, which is in line with our finding that CA4 volume was negatively correlated with the number of manic episodes in BD. The CA4 labeled with the new method also includes the molecular layer of DG, which receives the major excitatory input from the cortex and is the first synaptic connection of the trisynaptic circuit of the hippocampus. Thus, the reduction of CA4 in our study may also indicate synaptic atrophy between the cortex and hippocampus. These findings indicate that BD may involve pathology of synapses and neurogenesis, which causes systematic cytoarchitectural abnormality in neurons, dendrites or axons that are linked with the morphometric alterations detected by brain imaging.⁵⁵

The volume reduction of ML in BD was a novel finding, because ML was not labeled using the previous method based on *in vivo* atlas^{31,33} and was only partially observable by the surface-based method. The ML labeled in the new method is the molecular layer in subiculum and CA fields, consisting interneurons synaptic connections of these subfields.⁵⁶ The interneurons play an important role of regulating the activities within the hippocampus.⁵⁷ Considering that the ML was involved in illness progression together with CA fields in BD-I, the reduced ML volume in BD may further indicate pathology of synapses between the pyramidal cells and interneurons in BD.

The reduced volume in the subfield of the hippocampal tail was strongly associated with BD, especially BD-I. The hippocampal tail volume was also negatively correlated with the illness duration and the number of manic episodes, indicating a progressive atrophy. These findings were not observed with the previous method with *in vivo* atlas,³¹ because the atlas did not work well at the hippocampal head or tail.³³ However, these findings were consistent with previous studies using surface-based method.²⁹

It is worth mentioning that our study was able to consider for two important variables in the study of hippocampus changes in patients with BD, such as the lithium effect on the hippocampus (Supplementary Materials) and the effect of BD types. Indeed, several important studies, including meta-analyses reported the neuroprotective effect of lithium in the hippocampus.^{19,58,59} Regarding BD type effect on the hippocampus, our previous work showed that manic episodes are important clinical correlates of hippocampus reductions.²³ In addition, a recent study from the ENIGMA Bipolar Disorder Working Group with more than 4000 participants showed that patients with BD-I have decreased hippocampus volume compared to healthy controls while patients with BD-II showed no difference in the hippocampus volume compared to healthy controls.²² We think that these two moderators may explain why some previous studies found that patients with MDD may have decreased hippocampus compared to patients with BD.^{20,21} Both studies did not control for BD type, while Kempton and colleagues were not able to control for the lithium effect. On the other hand, Wise and colleagues performed a meta-regression analysis with lithium use as a moderator, and found that lithium use was not able to explain the between-study heterogeneity.²¹ This finding may indirectly suggest that lithium is not associated with hippocampus volume, which may need further investigation, given the large body of

literature that points to a neuroprotective and neurotrophic effect of lithium in patients with BD. Therefore, future replication studies and meta-analyses may further discuss the effect of lithium use and BD type on the hippocampus subfields of patients with mood disorder.

Our findings point to a crucial role of manic episodes, but not the depressive ones, in the degeneration of hippocampus subfields. This is in line with recent studies, which suggested that the number of manic episodes seems to be the clinical marker more robustly associated with brain changes and neuroprogression in BD.^{46,55,60} Moreover, our previous work that included only patients with BD-I also reported that reductions in the total hippocampus volume were associated with manic episodes.²³ Of note, the impact of the manic episode on brain changes is not only associated with hippocampus. For instance, a 6-year follow-up study in patients with BD-I showed decreased frontal cortical volume (dorsolateral prefrontal and inferior frontal cortex) as a function of previous manic episodes.⁶¹ Finally, another interesting finding from our work is that changes in hippocampus subfields were found in patients with BD but not in those ones with MDD. Noticeably, the effect size in patients with BD was largely driven by those ones with BD-I. In line with this finding, some studies, including the work of Hibar and colleagues,²² showed a BD type effect in reductions of hippocampus and other areas, such as frontal lobe.⁶² In conclusion, it seems that the pathophysiological underpinnings of BD-I are more consistent compared to patients with BD-II or MDD regarding neuroanatomical changes.

Our findings also have therapeutic and diagnostic implications for future studies in patients with mood disorders. The reductions of hippocampus subfields presented here might be used as therapeutic targets or biomarkers of treatment response. In this sense, it was reported that lithium has neurotrophic and neuroprotective effects on the hippocampus of patients with bipolar disorder.^{19,58} A recent cross-sectional study, which included only patients with BD-I, showed that long-term, but not short-term, exposure to lithium treatment was associated with larger total hippocampal volumes and bilateral CA2–3, left CA4-DG, left presubiculum, and right subiculum volumes.⁶³ In addition, it was shown that erythropoietin was associated with memory improvement and reversal of brain matter loss in the left hippocampal CA1–3 and subiculum in patients with mood disorders.⁶⁴ Regarding diagnostic implications, future studies should consider the hippocampus subfield changes presented in the current study as well as other relevant brain regions that are altered in mood disorders to build a neuroanatomical network signature using machine learning techniques, so that we are able to differentiate patients with mood disorders in regards to the diagnosis and stage of the disorder.^{65,66}

The present study has a cross-sectional design and causality cannot be established between hippocampus subfields reduction and diagnoses, mood episodes or illness duration. In addition, recall bias and the influence of current symptoms may have interfered with our findings. Specifically, our reliance on retrospective self-report for the number of mood episodes may be influenced by biases such as the fact that patients with greater severity of illness may have been more likely to identify previous mood episodes. Moreover, we were not able to control for some confounders, such as medication status due to the heterogeneous medication types and histories among the patient groups (see Supplementary Materials for further analyses). Although some medications, such as lithium, might prevent the volume

reduction of the hippocampus in BD,⁶⁷ no patient with MDD and only eight patients with BD were taking lithium. We did not find any correlation between the illness duration and the hippocampal subfield volumes in MDD compared to previous studies on the whole hippocampal volume.²⁴ However, in several studies that investigated the relationship between the illness duration and whole hippocampal volume and included patients similar with our study with respect to the illness duration, number of depressive episodes and hospitalization (Supplementary Materials), one found negative correlation only in the left hippocampus,⁶⁸ one found the correlation was significant only when calculated non-linearly,⁶⁹ one did not find any correlation,⁷⁰ and two used a different measurements, treated and untreated depressed days, which could be more sensitive but were only a subset period compared to illness duration.^{71,72} Thus, further studies will be necessary to investigate these inconsistencies in MDD and the corresponding results need to be interpreted with caution.

In summary, the present study provides evidence of hippocampus subfield volume reductions in patients with BD, mainly in those ones with BD-I. Moreover, it adds to the notion of neuroprogression, since changes in specific regions of hippocampus were associated with number of manic episodes and illness duration. Longitudinal studies will help to clarify the causal relationship between manic episodes and volumetric changes in hippocampus subfields, and further cellular and molecular studies integrating structural imaging will help to understand the biological mechanisms underlying this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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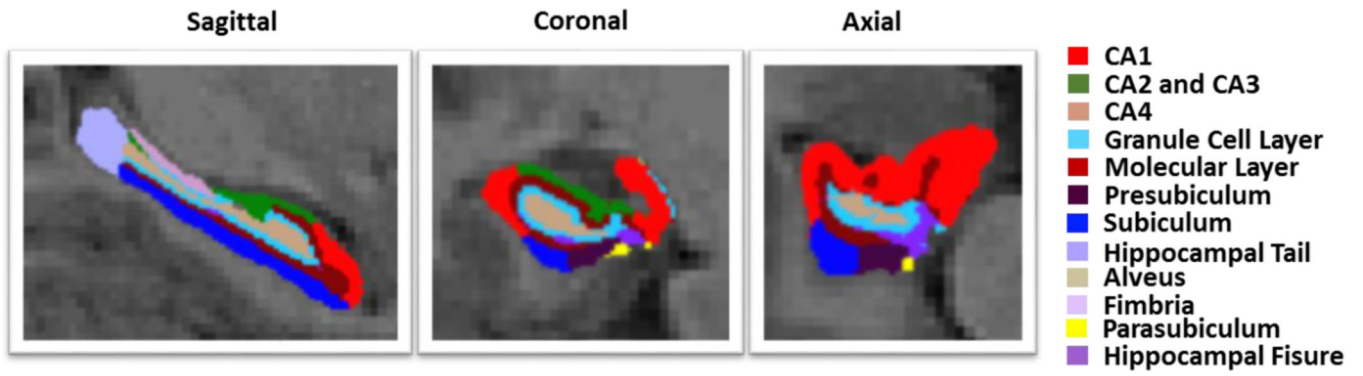


Figure 1.
An illustration of left hippocampal subfield segmentation using the novel method.
Abbreviation: CA, cornu ammonis.

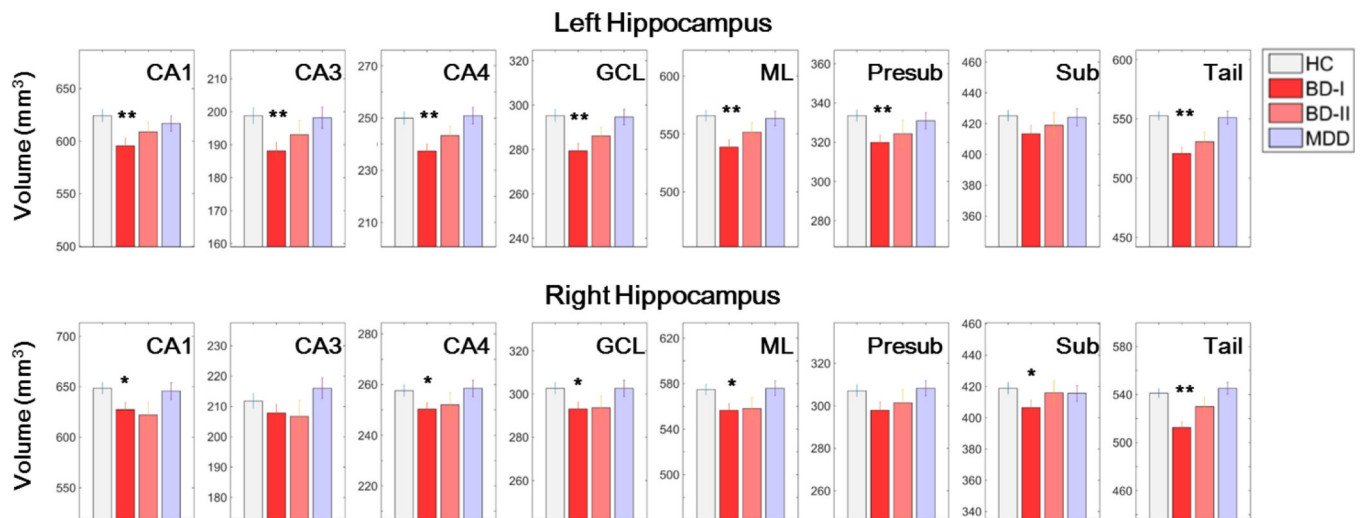


Figure 2.

Hippocampal subfield volumes in HC, BD-I, BD-II and MDD. * $p < 0.05$; ** $p < 0.005$. Error bar indicates one standard error. Abbreviations: BD-I, bipolar I disorder; BD-II, bipolar II disorder; HC, healthy controls; MDD, major depressive disorder; CA, cornu ammonis; GCL, granule cell layer; ML, molecular layer; Presub, presubiculum; Sub, subiculum and Tail, hippocampal tail.

Table 1

Demographic Information of all the subjects

	HC (n=152)	BD (n=133)	MDD (n=86)	F/X ²	P value
Age (years)*	35.4±12.43	38.8±12.0	41.2±12.2	5.432	0.005
Gender					
Male	36.8%(56)	31.6%(42)	30.2%(26)	1.395	0.498
Female	63.2%(96)	68.4%(91)	69.8%(60)		
Handedness					
Left	5.9%(9)	4.5%(6)	9.3%(8)	3.088	0.543
Right	91.4%(139)	91.0%(121)	88.4%(76)		
Ambidextrous	2.6%(4)	4.5%(6)	2.3%(2)		
Education (years)*	16.4±3.0	13.6±3.5	14.8±2.4	25.384	<0.001
Ethnicity*					
Hispanic	41.4%(63)	24.8%(33)	33.7%(29)	3.67	0.011
Non-Hispanic	57.9%(88)	75.2%(100)	66.3%(57)		
Current mood status					
Euthymic	-	25.6%(34)	46.5%(40)		
Depressed	-	50.4%(67)	53.5%(46)		
Manic	-	4.5%(6)	-		
Hypomanic	-	6.0%(8)	-		
Mixed	-	12.8%(17)	-		
Undetermined	-	0.8%(1)	-		
HAMD*	0.7±1.1	12.7±7.9	10.5±8.4	124.167	<0.001
YMRS*	0.3±0.8	6.3±6.8	2.5±2.9	58.845	<0.001

Hippocampal subfield volume difference between patients with mood disorders and healthy controls

Table 2

	All Groups		BD vs. HC		BD vs. MDD		MDD vs. HC	
	F _{2,365}	p ^a	t	p ^a	t	p ^a	t	p ^a
Left Hippocampus								
CA1	3.369	0.035	-2.335	0.060	-2.052	0.123	0.025	1.000
CA3	3.517	0.031	-2.276	0.070	-2.230	0.079	0.255	1.000
CA4	6.626	0.001	-2.725	0.020	-3.372	0.002	1.013	0.935
GCL	6.930	0.001	-2.985	0.009	-3.318	0.003	0.731	1.000
ML	6.196	0.002	-2.838	0.014	-3.126	0.006	0.666	1.000
Presub	3.192	0.042	-2.144	0.098	-2.149	0.097	0.289	1.000
Sub	1.131	0.324	-0.815	1.000	-1.494	0.408	0.793	1.000
Tail	7.209	0.001	-3.266	0.004	-3.184	0.005	0.350	1.000
Right Hippocampus								
CA1	2.914	0.056	-1.990	0.142	-2.107	0.107	0.381	1.000
CA3	1.914	0.149	-0.826	1.000	-1.956	0.154	1.248	0.638
CA4	2.369	0.095	-1.673	0.285	-1.990	0.142	0.541	1.000
GCL	2.947	0.054	-1.981	0.145	-2.137	0.100	0.420	1.000
ML	3.786	0.024	-1.968	0.150	-2.597	0.029	0.895	1.000
Presub	2.359	0.096	-1.151	0.751	-2.162	0.094	1.171	0.727
Sub	0.768	0.465	-1.072	0.853	-1.033	0.907	0.103	1.000
Tail	6.271	0.002	-2.803	0.016	-3.183	0.005	0.754	1.000

^aBonferroni corrected for multiple comparisons between the groups.

Abbreviations: BD, bipolar disorder; HC, healthy controls; MDD, major depressive disorder; CA, cornu ammonis; GCL, granule cell layer; ML, molecular layer; Presub, presubiculum; Sub, subiculum and Tail, hippocampal tail.