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ORIGINAL ARTICLE

Hippocampal subfields in remitted schizophrenia

Ying-Jay Liou[a,b], Mu-N. Liu[a,b], Kai-Chun Yang[a,b], Li-Yu Hu[a,b], Wen-Chi Hsieh[a,c], Yuan-Hwa Chou[b,d,*]

[a]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Department of Psychiatry, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Department of Industrial and Systems Engineering, Chung Yuan Christian University, Taoyuan, Taiwan, ROC; [d]Department of Psychiatry, Taichung Veterans General Hospital, Taichung, ROC

Abstract

Background: Current evidence of volume changes in hippocampal subdivisions in schizophrenia remains inconsistent, and few studies have investigated the relationship between regional hippocampal volumes and symptom remission.

Methods: In this cross-sectional study, we recruited 31 patients with schizophrenia and 31 healthy controls (HCs). Symptomatic remission in schizophrenia was determined according to Remission in Schizophrenia Working Group criteria. The volumes of hippocampal longitudinal subregions and transverse subfields were measured using manual and automatic techniques, respectively. Between-group regional hippocampal volume differences were analyzed using multivariate analysis of covariance followed by univariate analysis of covariance.

Results: Compared with the HCs, the patients with schizophrenia had smaller bilateral heads and tails along the longitudinal axis; they also had reduced volumes of the bilateral CA1, CA3, CA4, GC-ML-DG, molecular layer, tail, left subiculum, left HATA, and right parasubiculum along the transverse axis in the hippocampus (all corrected $p < 0.05$). Furthermore, compared with the HCs and patients with remitted schizophrenia, the patients with nonremitted schizophrenia had smaller bilateral hippocampal tail subfields (corrected $p < 0.05$).

Conclusion: Our results indicated that the pathophysiology and symptomatic remission of schizophrenia are related to changes in the volumes of hippocampal subdivisions. These volume changes might be clinically relevant as biomarkers for schizophrenia identification and treatment.

Keywords: Antipsychotics; Magnetic resonance imaging; Schizophrenia

1. INTRODUCTION

Schizophrenia is a psychiatric illness characterized by positive symptoms, negative symptoms, and cognitive dysfunction. Hippocampal dysfunction has been implicated in the pathophysiology of schizophrenia on the findings showing that the hippocampus is involved in hyperactive dopaminergic neurotransmission,[1] and that psychotic symptoms are associated with neurological disorders, lesions, or electrical stimulation of certain hippocampal regions and adjacent structures.[2,3]

The hippocampus can be segmented into the head, body, and tail subregions along its longitudinal (anteroposterior) axis.[4–6] Findings regarding the association of the reduction in hippocampal subregion volume with susceptibility to schizophrenia are inconsistent. Some reports have suggested that among patients with schizophrenia, volume reduction is more prominent in the anterior parts,[7,8] whereas other studies have observed volume reduction in the mid- and posterior-regions of the hippocampus.[9,10]

* *Address correspondence: Dr. Yuan-Hwa Chou, Department of Psychiatry, Taichung Veterans General Hospital, 1650, Section 4, Taiwan Boulevard, Taichung 407, Taiwan, ROC. E-mail addresses: c520608@ms64.hinet.net; c520608@gmail.com (Y.-H. Chou).*

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Apart from its longitudinal segmentation, the hippocampus can be divided into distinct subfields on its transverse axis based on the basis of cytoarchitectural and magnetic resonance imaging (MRI) findings,[11–14] such as the cornu ammonis (CA) 1-3, CA4, dentate gyrus (DG), and subiculum complex (the presubiculum, parasubiculum, and subiculum). These subfields play specific roles in cognitive processing, mood regulation, and neurological plasticity.[14–16] Compared with HCs, patients with schizophrenia exhibited volume reductions in the CA1, CA2/3, DG/CA4, and subiculum, suggesting that the volume reduction is widespread over the hippocampal subfields in patients with schizophrenia.[14–16]

Antipsychotic drugs remain a major treatment for the positive symptoms of schizophrenia. Several studies have examined the relationship of hippocampal volumes and antipsychotic treatment outcome in schizophrenia. In patients with first-episode schizophrenia (FES), antipsychotic treatment was associated with reduced volumes of the bilateral whole hippocampal and several subfields (such as the bilateral molecular layers [MLs], granular cell layers of the DG and tails; left CA1 and CA3, and fimbria), but increased the subiculum volume.[17,18] Bodnar et al[19] showed decreased volumes over bilateral hippocampal tails were associated with inadequate symptomatic remission defined by the Remission in Schizophrenia Working Group (RSWG)[20] in patients with FES after 12-month antipsychotic treatment. However, the association of symptomatic remission after antipsychotic treatment with volume changes in the hippocampal tail or other subdivisions has not been studied in patients with chronic schizophrenia.

The present study investigated volume differences in hippocampal subregions and subfields between patients with

schizophrenia and HCs. In addition, we also investigated which of the hippocampal subregions and subfields was associated with RSWG-defined symptomatic remission in patients with chronic schizophrenia receiving antipsychotic treatment.

2. METHODS

2.1. Participants

We recruited 31 unrelated patients with schizophrenia diagnosed per the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) by two board-certified senior psychiatrists according to information obtained from clinical interviews with the patients and their families, clinical observations, and chart reviews. The age of the patients ranged from 20 to 65 years. We excluded patients who had a history of substance abuse (amphetamine, ketamine, 3,4-methylenedioxymethamphetamine, opioids, or alcohol); other psychiatric illness (schizophreniform disorder, schizoaffective disorder, mood disorder, psychotic disorder due to general medical conditions, mental retardation, or dementia); and severe medical illness, including cardiovascular, hepatic, or renal diseases, poorly controlled hypertension, and diabetes mellitus. Women who were pregnant or breastfeeding were also excluded. We included 31 healthy controls (HCs) who had no symptoms or history of psychiatric illness through face-to-face interviews conducted by board-certified psychiatrists. All the participants were Han Chinese. The study followed the principles of the Declaration of Helsinki and was approved by the Ethics Review Committee of Taipei Veterans General Hospital, Taiwan. Before enrollment, the study aims and procedures were explained to the participants, and their written informed consent was obtained.

The patients in the schizophrenia group were stratified into remitted (SC-R) and nonremitted (SC-NR) groups according to symptomatic remission criteria for schizophrenia developed by the RSWG,[20] which consist of two elements: time criteria (6 months) and symptom-based severity criteria. The symptom-based severity criteria encompass eight diagnostically relevant symptoms of schizophrenia from the Positive and Negative Syndrome Scale (PANSS-8): delusion (P1), conceptual disorganization (P2), hallucinatory behavior (P3), mannerisms/posturing (G5), unusual thought content (G9), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6). Patients who score ≤3 points (mild symptom intensity) for ≥6 months on all the eight core items are considered to have symptomatic remission.[20] The PANSS-8 has been validated in both clinical trials and clinical practice.[21,22] All the patients in the schizophrenia group were followed up monthly for ≥6 months, during which the class and daily dose of prescribed antipsychotics were maintained. Symptomatic remission was determined by the severity scores for each item in the PANSS-8 at the sixth month of antipsychotic treatment.

2.2. MRI acquisition

Structural brain MRI data were collected using a 1.5-T GE Scanner Excite-II system (GE Medical Systems, Milwaukee, WI). T1-weighted images were acquired using the following parameters: spoiled gradient-echo sequence; repetition time (TR), 8.54 millisecond; echo time (TE), 1.836 millisecond; inversion time (TI), 400 millisecond; flip angle, 15°; matrix size, 256×256; field of view (FOV), 260 mm; 124 axial slices with 1.5-mm slice thickness; and resolution, 1.02 mm × 1.02 mm × 1.5 mm.

2.3. Measurement of subregion volumes along the hippocampal longitudinal axis

Manual hippocampal tracing was performed on the T1-weighted image by using PMOD 3.0 software (https://www.pmod.com/web/). Tracing was mainly performed on the coronal plane and the axial and sagittal planes to determine boundaries when necessary. The volume was measured from the most posterior slice of the hippocampal tail to the most anterior limit of the hippocampal head, and the hippocampus was segmented into three subregions (head, body, and tail) along the anteroposterior axis (Fig. 1A). For hippocampal tracing, we followed methods and landmarks described in a previous study.[5] All measurements were performed by a single rater (WCH), and the intrarater reliability was examined at 1-week intervals. The intrarater reliability and intraclass correlation coefficients for hippocampal subregion segmentation were 0.98 and 0.99 for the right/left head, 0.99 and 0.98 for the right/left body, and 0.90 and 0.96 for the right/left hippocampal tail volume, respectively.

2.4. Measurement of subfield volumes along the hippocampal transverse axis

An automatic procedure implemented in the FreeSurfer 7.0 software package (Massachusetts General Hospital, Boston, MA; https://surfer.nmr.mgh.harvard.edu/fswiki/ReleaseNotes) was used to measure the volume of the hippocampal subfield in T1 imaging. With the automated method, both the hippocampi of each patient were segmented into 12 subfields: parasubiculum, presubiculum, subiculum, CA1, CA3, CA4, granule cell (GC), and ML of the DG (GC-ML-DG), ML, hippocampus–amygdala transition area (HATA), fimbria, tail, and fissure (Fig. 1B). In this automated segmentation tool, a single computational atlas of the hippocampal formation is constructed using a Bayesian algorithm with labels from in vivo and ex vivo data. The resulting atlas then can be used to automatically segment the hippocampal subfields in structural MRI images. The technical details for automated segmentation and volume quantification for the eight hippocampal subfields were described in a previous study.[23]

2.5. Statistical analyses

Statistical analyses were performed using SPSS (version 21; SPSS, Chicago, IL). Categorical variables were compared between groups by using the Chi-square test (Fisher's exact test if necessary), and continuous variables were compared using the two-tailed independent *t* test or one-way analysis of variance. A series of multivariate analyses of covariance (MANCOVAs) were performed to determine differences in the mean volumes of the hippocampal subregions or subfields between groups. In the MANCOVA, the hippocampal subregions or subfields were included as dependent variables and the groups were included as independent variables. Other variables, specifically age, years of education received, sex, and estimated total intracranial volume (eTIV), which may differ significantly between groups, were included as covariates. Once the multivariate null hypothesis was rejected, the main group effect on a specific subregion or subfield volume was analyzed by performing univariate analysis of covariance (ANCOVA) after controlling for the effects of the covariates. For all univariate ANCOVA analyses, Benjamini-Hochberg-adjusted (corrected) $p < 0.05$ was considered statistically significant to account for multiple comparisons (https://tools.carbocation.com/FDR).

3. RESULTS

3.1. Demographic and clinical characteristics

Table 1 lists the clinical and demographic characteristics of the HCs and patients with schizophrenia. The patients with schizophrenia were treated with the following antipsychotic drugs: aripiprazole (N = 10), risperidone (N = 8), ziprasidone (N = 2), paliperidone (N = 3), amisulpride (N = 4), olanzapine (N = 1), and clozapine (N = 3). The HCs had more mean education years received than the SC-NR (post hoc Bonferroni $p = 0.015$).

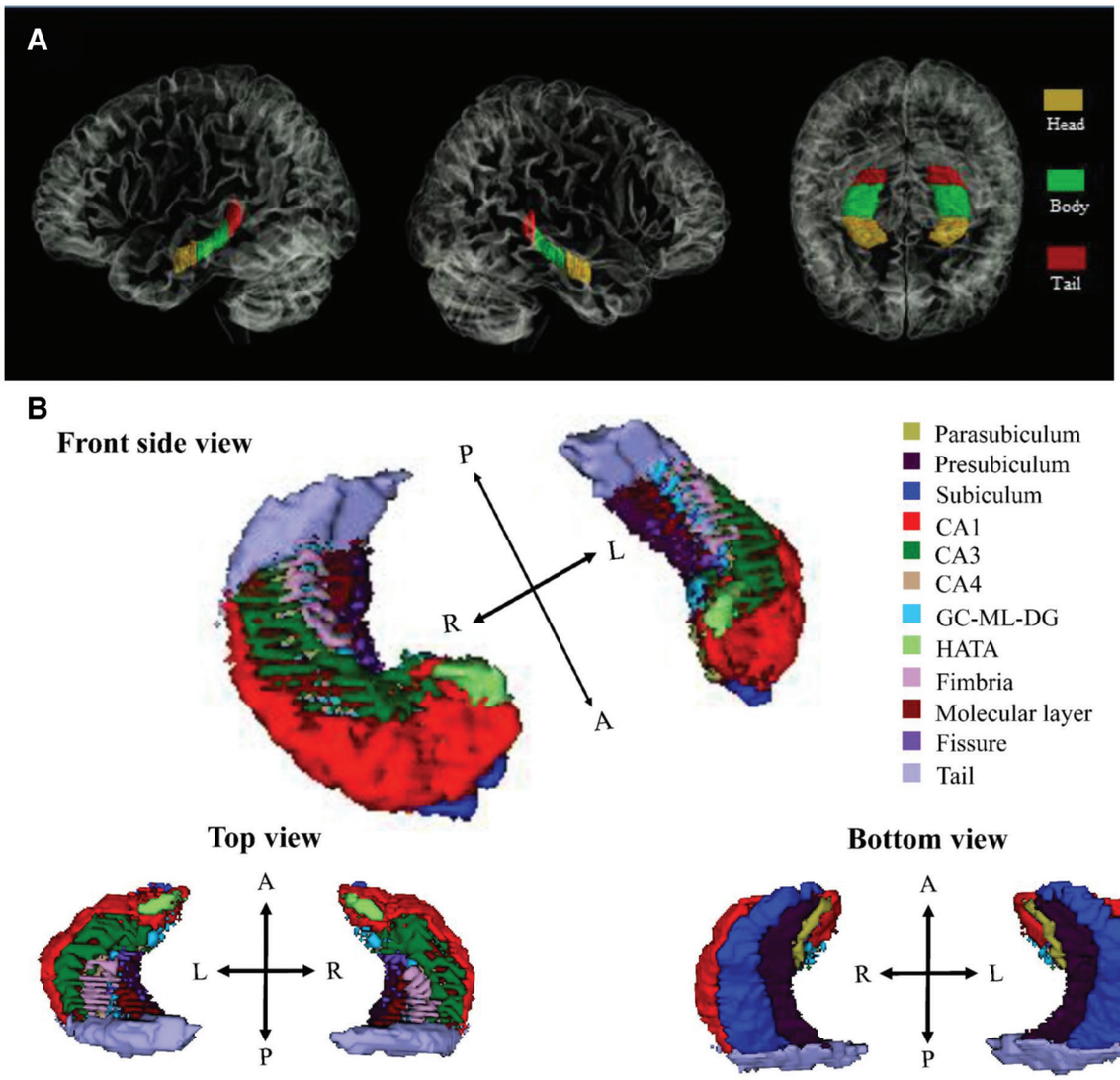

Fig. 1 Hippocampal segmentation. A, Manual hippocampus tracing. The hippocampus was segmented along the anteroposterior axis in the three subregions: head, body, and tail. B, Automated hippocampal segmentation (3D view). The hippocampus was segmented into 12 subfields: parasubiculum, presubiculum, subiculum, CA1, CA3, CA4, GC-ML-DG, molecular layer, HATA, fimbria, tail, and fissure. CA = cornu ammonis; GC-ML-DG = granule cell (GC) and molecular layer (ML) of the dentate gyrus (DG); HATA = hippocampus—amygdala-transition area.

The SC-NR group had significantly more men, fewer education years, and higher total scores in the PANSS-8 than the SC-R group (Table 1, all $p < 0.05$).

3.2. Volume differences in hippocampal subregions and subfields between the schizophrenia and HC groups

The left/right whole hippocampal volumes were $2.79 \pm 0.51/3.01 \pm 0.51\,cm^3$ in the patients with schizophrenia and $3.44 \pm 0.48/3.59 \pm 0.54\,cm^3$ in the HCs. Compared with the HCs, the patients with schizophrenia had a significantly smaller hippocampus bilaterally after age, sex, education years, and eTIV were controlled for and corrected multiple comparisons (left hippocampus: corrected $p < 0.001$; right hippocampus, corrected $p < 0.01$).

Table 2 lists the volumes of hippocampal subregions and subfields in the patients with schizophrenia and HCs. In the MANCOVA, a significant main group effect was noted on the volume of hippocampal subregions (Pillai's trace = 0.453, $F = 7.51$, $p < 0.001$) and subfields (Pillai's trace = 0.601, $F = 2.32$, $p = 0.01$) between the HCs and patients with schizophrenia. The bilateral head and tail subregions were significantly smaller in the patients with schizophrenia than in the HCs, as determined through follow-up ANCOVA (Fig. 2A, Table 2, all corrected $p < 0.05$). Regarding the hippocampal subfields, follow-up ANCOVAs indicated that the volumes of the left (L.) subiculum, CA1, CA3, CA4, GC-ML-DG, ML, HATA, and tail and right (R.) parasubiculum, CA1, CA3, CA4, GC-ML-DG, ML, and tail of the patients with schizophrenia were significantly smaller than those of the HCs (Fig. 2B, Table 2, all corrected $p < 0.05$).

3.3. Volume differences in hippocampal subregions and subfields between the SC-NR, SC-R, and HCs

After the education years were controlled for, a significant main group effect was observed on the volume of the subregions

Table 1

Demographic and clinical characteristics of patients with schizophrenia and healthy controls

			Statistical analysis, *F*, *t*, or χ^{2a}		
	SC, N = 31 (SC-NR (a), N = 14; SC-R (b), N = 17)[b]	HCs (c), N = 31	SC vs HCs	a vs b	a vs b vs c
Gender, M/F	15/16 (10/4; 5/12)	15/16	$\chi^2 = 1.00$, $p = 1.00$	$\chi^2 = 5.43$, $p = 0.020$	$\chi^2 = 5.43$, $p = 0.066$
Age, y	44.2 ± 10.7 (44.6 ± 10.4; 44.4 ± 11.5)	44.6 ± 10.4	$t = 1.32$, $p = 0.895$	$t = 0.11$, $p = 0.917$	$F = 0.014$, $p = 0.986$
Education, y	11.9 ± 3.2 (10.6 ± 2.7; 12.9 ± 3.2)	13.4 ± 3.0	$t = 1.95$, $p = 0.056$	$t = 2.16$, $p = 0.038$.	$F = 4.37$, $p = 0.017$
eTIV, cm^3	1460 ± 200 (1510 ± 100; 1410 ± 100)	1500 ± 200	$t = 1.23$, $p = 0.266$	$t = -2.02$, $p = 0.053$	$F = 2.65$, $p = 0.079$
Age of onset, y	31.9 ± 13.3 (28.9 ± 13.0; 34.4 ± 13.3)	n.a.		$t = 1.15$, $p = 0.259$	
CPZ, mg/d	225.7 ± 200.7 (286.7 ± 248.6; 175.5 ± 139.2)	n.a.		$t = -1.57$, $p = 0.127$	
PANSS-8	14.1 ± 5.0 (18.8 ± 3.3; 10.2 ± 1.9)	n.a.		$t = -8.62$, $p < 0.001$	

Continuous data are presented as mean ± SD.

χ^2 = Pearson Chi-square value; CPZ = chlorpromazine equivalent dose; df = degree of freedom; eTIV = estimated total intracranial volume; F = female; HCs = healthy controls; M = male; n.a. = not applicable; PANSS-8 = the eight-item version of the Positive and Negative Syndrome Scale; SC = schizophrenia; SC-NR = nonremitted schizophrenia; SC-R = remitted schizophrenia.

[a]Analysis of variance or independent *t* test for continuous data, and χ^2 analysis or Fisher's exact test for categorical data.

[b]Data in the parentheses indicate the corresponding information of SC-NR and SC-R, respectively.

Table 2

Hippocampal subdivision volumes of patients with schizophrenia and healthy controls

Orientation	Side	Subregion/subfield	SC, N = 31	HCs, N = 31	*p*[a]	Corrected *p*[b]
Longitudinal, mm^3	Left	Head	1345.8 ± 321.5	1606.8 ± 339.3	0.003	**0.006**
		Body	972.3 ± 284.5	1080.7 ± 290.0	0.143	
		Tail	467.6 ± 160.0	753.6 ± 215.1	2.0e−07	**1.2e-06**
	Right	Head	1481.6 ± 328.3	1849.0 ± 411.0	0.0003	**0.0009**
		Body	1020.7 ± 424.0	1105.8 ± 331.3	0.382	
		Tail	511.6 ± 166.8	638.4 ± 186.2	0.006	**0.009**
Transverse, mm^3	Left	Parasubiculum	133.6 ± 13.1	137.1 ± 14.6	0.3233	
		Presubiculum	298.5 ± 44.1	310.8 ± 41.0	0.2602	
		Subiculum	430.0 ± 43.7	457.7 ± 48.5	0.0217	**0.040**
		CA1	621.6 ± 67.3	680.4 ± 82.7	0.0032	**0.0097**
		CA3	209.1 ± 29.7	231.1 ± 29.7	0.0050	**0.0133**
		CA4	264.4 ± 27.9	288.1 ± 30.1	0.0021	**0.0082**
		GC-ML-DG	289.9 ± 31.1	317.0 ± 32.9	0.0015	**0.0117**
		Molecular layer	545.2 ± 56.1	594.4 ± 61.1	0.0016	**0.0077**
		HATA	57.8 ± 7.7	63.3 ± 10.1	0.0191	**0.0383**
		Fimbria	85.6 ± 18.9	84.5 ± 15.8	0.7713	
		Tail	547.1 ± 92.8	618.6 ± 88.5	0.0029	**0.0100**
		Fissure	140.6 ± 21.8	132.9 ± 22.4	0.1754	
	Right	Parasubiculum	53.2 ± 8.4	59.2 ± 11.7	0.0232	**0.0398**
		Presubiculum	281.3 ± 34.1	296.7 ± 34.8	0.0825	
		Subiculum	438.9 ± 46.2	462.8 ± 52.0	0.0599	
		CA1	658.1 ± 79.0	727.6 ± 76.7	0.0008	**0.0203**
		CA3	233.6 ± 30.3	251.0 ± 31.7	0.0313	**0.0500**
		CA4	264.5 ± 29.9	283.1 ± 29.2	0.0162	**0.0353**
		GC-ML-DG	306.6 ± 34.0	328.3 ± 33.8	0.0145	**0.0348**
		Molecular layer	572.3 ± 61.1	623.7 ± 60.5	0.0015	**0.0091**
		HATA	59.0 ± 9.6	63.4 ± 9.9	0.0811	
		Fimbria	83.1 ± 20.4	84.8 ± 15.5	0.7256	
		Tail	576.4 ± 76.4	644.5 ± 76.6	0.0009	**0.0104**
		Fissure	147.1 ± 27.6	145.6 ± 23.4	0.8078	

Continuous data in the cells are presented as mean ± SD. Bold values indicate $p < 0.05$.

ANCOVA = analysis of covariance; CA = cornu ammonis; GC-ML-DG = granule cell (GC) and molecular layer (ML) of the dentate gyrus (DG); HATA = hippocampus–amygdala transition area; HCs = healthy controls; SC = schizophrenia.

[a]*p* Value of follow-up post hoc ANCOVAs.

[b]Corrected *p* value after correction for multiple comparisons with the Benjamini-Hochberg approach.

(Table 3, Pillai's trace = 0.553, $F = 3.444$, $p < 0.001$) and subfields (Pillai's trace = 1.154, $F = 2.046$, $p = 0.003$) between the SC-NR, SC-R, and HCs.

For the subregions, significant mean volume differences were noted in the bilateral heads and tails, as indicated by follow-up ANCOVAs (Table 3, all corrected $p < 0.05$). Post hoc analyses indicated that the patients with schizophrenia, regardless of remission status, had significantly smaller volumes in the four subregions than did the HCs.

For the hippocampal subfields, follow-up ANCOVA revealed that the mean volume of the L. CA1, L. CA3, L. CA4, L. GC-ML-DG, L. molecular layer, L. tail, R. CA1, R. molecular

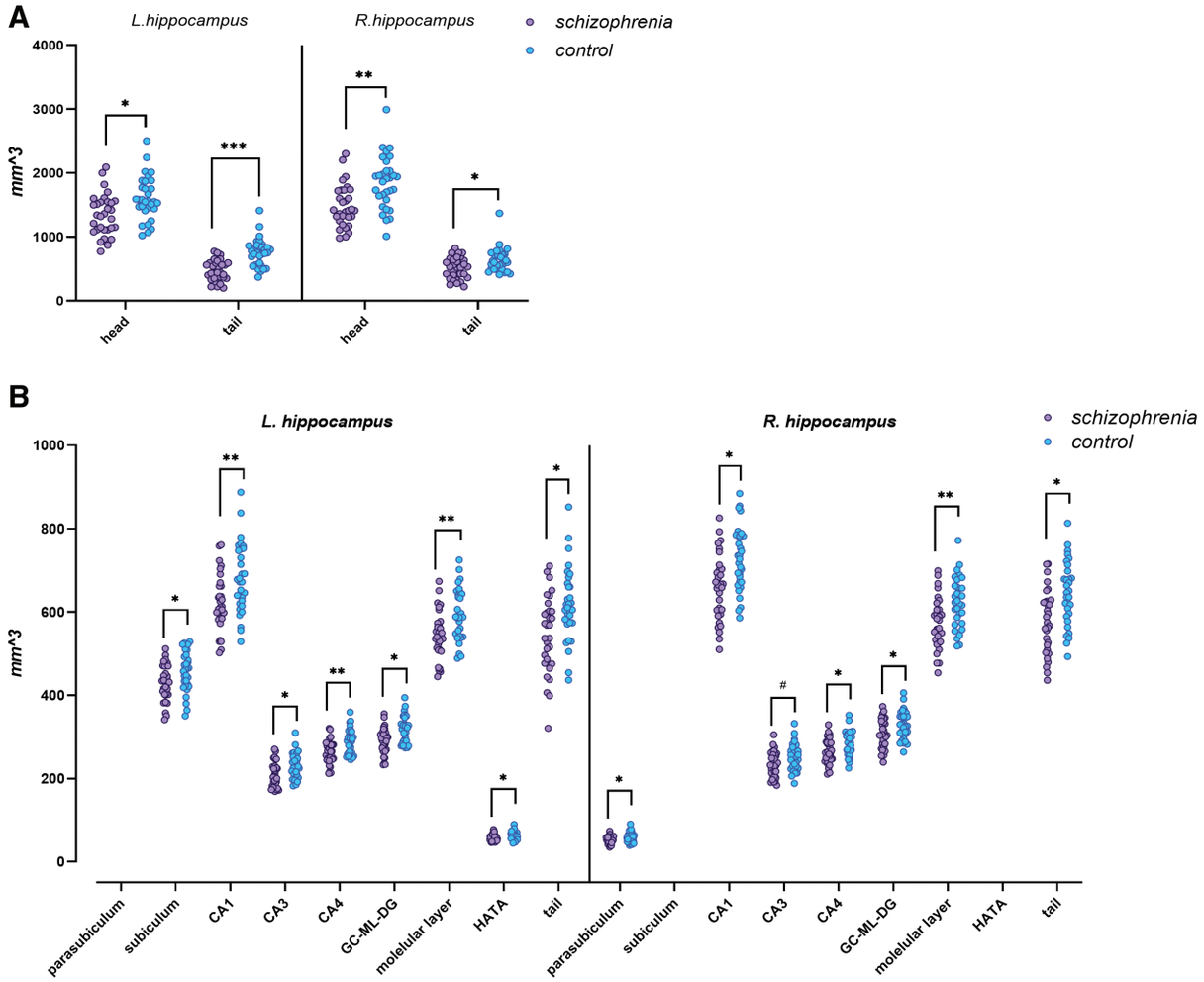

Fig. 2 Hippocampal subdivisional volumes that were significantly different in patients with schizophrenia and healthy controls. A, Hippocampal subregions. B, Hippocampal subfields. (# corrected $p = 0.05$; * corrected $p < 0.05$; ** corrected $p < 0.01$; *** corrected $p < 0.001$). HCs = healthy controls; L. = left; R. = right; SC = schizophrenia.

layer, and R. tail significantly differed between the SC-NR, SC-R, and HCs (Table 3, all $p < 0.05$). However, only the between-group mean volume difference in the bilateral tail subfields remained significant after correction for multiple testing (all corrected $p < 0.05$). The SC-NR had statistically smaller bilateral hippocampal tail subfields than the HCs and SC-R (Fig. 3, for L. tail, SC-NR vs SC-R: $p = 0.007$ and SC-NR vs HCs: $p = 0.00007$; for R. tail, SC-NR vs SC-R: $p = 0.019$ and SC-NR vs HCs: $p = 0.00008$).

4. DISCUSSION

In this study, compared with the HCs, the patients with schizophrenia had smaller volumes in the bilateral head and tail subregions. The patients with schizophrenia also had smaller volumes in the bilateral CA1, CA3, CA4, GC-ML-DG, ML, tail, L. subiculum, L. HATA, and R. parasubiculum than the HCs. Our results further indicated the SC-NR had significantly smaller volumes in these subfields relative to the HCs and SC-R. Our results suggested that decreased regional hippocampal volumes are involved in the pathophysiology of schizophrenia and associated with the remission of symptoms during antipsychotic treatment.

Our finding of decreased volumes over the posterior hippocampus (including tail subregions and subfields) is consistent with those of previous studies.[17,24–29] The posterior hippocampus projects to the dorsolateral prefrontal cortex, another brain area usually implicated in the pathophysiology of schizophrenia.[30,31] Atrophy in the posterior relative to the anterior hippocampus has been identified in schizophrenia.[9] Notably, in a study using shape analysis, patients with schizophrenia exhibited deformation in the hippocampal tail, resulting in a less bent tail relative to those of the controls.[32] Decreased posterior hippocampal volume may related to decreased pyramidal neuronal size and density in the subregion in schizophrenia.[9] These pieces of evidence and our results collectively suggest that a smaller posterior hippocampus is related to vulnerability to schizophrenia. In addition to the tail subregions, the bilateral heads in the anterior hippocampus were smaller among patients with schizophrenia than among the HCs in this study (Table 2). Some studies have reported that hippocampal volume reduction in schizophrenia mainly affects the anterior region.[7,33–35] But this was not found in other studies.[9,36] As suggested in previous studies, the hippocampal head is related to positive symptoms and dopaminergic dysfunction in schizophrenia.[37,38] Our results for the longitudinal axis suggest that both the anterior and posterior hippocampus are involved in the pathophysiology of schizophrenia and support that

Table 3

Comparisons for the hippocampal subdivision volumes between patients with nonremitted and remitted schizophrenia and healthy controls

Orientation	Side	Subregion/subfield	SC-NR, N = 14 (a)	SC-R, N = 17 (b)	HCs, N = 31 (c)	p^a	Corrected p^b
Longitudinal, mm^3	Left	Head	1305.0 ± 322.0	1379.4 ± 326.9	1606.8 ± 331.3	0.025, a < c, b < c	**0.037**
		Body	875.7 ± 279.6	1057.8 ± 270.9	1080.7 ± 290.0	0.096	
		Tail	467.7 ± 186.2	468.2 ± 140.7	753.6 ± 215.0	2.6e-6, a < c, b < c	**1.8e−5**
	Right	Head	1403.6 ± 230.4	1545.9 ± 386.2	1849.0 ± 411.3	0.002, a < c, b < c	**0.006**
		Body	1120.7 ± 561.3	928.2 ± 255.1	1105.9 ± 331.3	0.270	
		Tail	498 ± 176.9	522.3 ± 162.7	638.4 ± 186.2	0.017, a < c, b < c	**0.034**
Transverse, mm^3	Left	Parasubiculum	138.3 ± 11.9	129.7 ± 13.0	137.1 ± 14.6	0.2473	
		Presubiculum	313.9 ± 53.6	285.8 ± 30.5	310.8 ± 41.0	0.2006	
		Subiculum	436.1 ± 41.4	428.0 ± 46.2	457.7 ± 48.5	0.0688	
		CA1	622.9 ± 62.5	620.5 ± 72.9	680.4 ± 82.7	0.0250	
		CA3	213.0 ± 26.5	205.8 ± 32.5	231.1 ± 29.7	0.0190	
		CA4	267.3 ± 27.8	262.0 ± 28.5	288.1 ± 30.1	0.0222	
		GC-ML-DG	293.6 ± 31.6	286.9 ± 31.2	317.0 ± 32.9	0.0152	
		Molecular layer	550.0 ± 54.2	541.1 ± 58.9	594.4 ± 61.1	0.0138	
		HATA	57.4 ± 8.1	58.1 ± 7.6	63.3 ± 10.1	0.1234	
		Fimbria	86.5 ± 14.9	85.2 ± 22.1	84.5 ± 15.8	0.9868	
		Hippocampal_tail	501.3 ± 89.5	584.8 ± 79.4	618.6 ± 88.5	0.0010, a < b, a < c	**0.012**
		Hippocampal-fissure	145.5 ± 20.1	136.7 ± 23.1	132.9 ± 22.3	0.3853	
	Right	Parasubiculum	54.3 ± 7.7	52.2 ± 8.9	59.2 ± 11.7	0.0729	
		Presubiculum	284.9 ± 42.3	278.3 ± 26.6	296.7 ± 34.8	0.3275	
		Subiculum	448.7 ± 46.8	430.8 ± 45.5	462.8 ± 52.0	0.1870	
		CA1	656.5 ± 74.8	659.4 ± 84.7	727.6 ± 76.6	0.0115	
		CA3	233.1 ± 28.6	234.1 ± 32.5	251.0 ± 31.7	0.2050	
		CA4	265.1 ± 27.9	264.0 ± 32.3	283.1 ± 29.2	0.1045	
		GC-ML-DG	307.3 ± 33.3	306.0 ± 35.6	328.3 ± 32.8	0.1139	
		Molecular layer	575.9 ± 60.9	569.3 ± 63.0	623.7 ± 60.5	0.0185	
		HATA	56.6 ± 10.1	60.9 ± 9.0	63.3 ± 9.9	0.2065	
		Fimbria	81.0 ± 13.5	84.9 ± 25.1	84.8 ± 15.5	0.4769	
		Hippocampal_tail	542.0 ± 71.9	604.7 ± 69.9	644.6 ± 76.6	0.0009, a < b, a < c, b < c	**0.021**
		Hippocampal-fissure	144.5 ± 21.4	149.4 ± 32.3	145.6 ± 23.4	0.6768	

Continuous data in the cells are presented as mean ± SD. Bold values indicate $p < 0.05$.

ANCOVA = analysis of covariance; CA = cornu ammonis; DG = dentate gyrus; GC-ML-DG = granule cell (GC) and molecular layer (ML) of the dentate gyrus (DG); HATA = hippocampus–amygdala transition area; HCs = healthy controls; SC = schizophrenia; SC-NR = nonremitted schizophrenia; SC-R = remitted schizophrenia.

[a]p Values of follow-up post hoc ANCOVAs.

[b]Corrected p value after correction for multiple comparisons with the Benjamini-Hochberg approach.

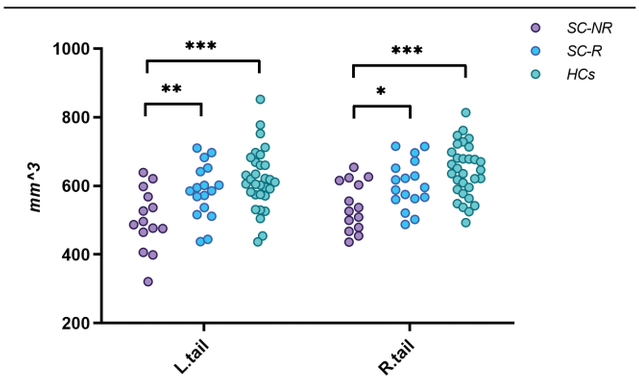

Fig. 3 The volumes of bilateral hippocampal tail subfields in patients with nonremitted and remitted schizophrenia and the healthy controls. (* corrected $p < 0.05$; ** corrected $p < 0.01$; *** corrected $p < 0.001$). HCs = healthy controls; L. = left; R. = right; SC-NR = nonremitted schizophrenia; SC-R = remitted schizophrenia.

chronic psychosis is related to the volumes of several hippocampal subregions.[29,35]

Considerable evidence exists on volume changes in other hippocampal subfields in schizophrenia including the CA1, CA2/3, CA4 (or DG/CA4), and subiculum.[15,16,39] Furthermore, hippocampal subfields become smaller with the progression of schizophrenia.[15,16,39] The CA1 and anterior hippocampal subregion might be the first subfields to be affected upon the onset of schizophrenia—earlier than other subfields, including the subiculum.[15,16,39] Although the illness stage at study recruitment, study design (cross-sectional vs longitudinal), participants' clinical characteristics (eg, age, first-episode-psychosis status, and the presence of other psychiatric disorders such as schizoaffective and bipolar disorders), and volumetric methods used differ from those of previous studies,[15,16,39] our results indicating smaller volumes of the bilateral CA1, CA3, CA4, GC-ML-DG, MLs, L. subiculum, and R. parasubiculum in patients with schizophrenia demonstrate the involvement of these subfields in the pathophysiology of the disease.

We investigated the relationship between hippocampal volumes and symptomatic remission defined by RSWG during antipsychotic treatment in the patients with schizophrenia.[20] Our results revealed that compared with the HCs, the SC-NR exhibited numerically smaller bilateral heads and tail subregions (Table 3). Furthermore, our findings indicated that among the hippocampal subfields, only the bilateral tail subfields were smaller in the SC-NR group than in the HCs or SC-R group (Fig. 3). In a study on FES, Bodnar et al[19] demonstrated that the SC-NR had smaller hippocampal tails bilaterally than did

SC-Rand controls. Although the patients in our study, who had schizophrenia for an average of 12.4 ± 7.7 years, were not FES, our results suggested that the observation of lower posterior hippocampal volumes in symptomatic remission applies not only to FES, as reported by Bondar et al,[19] but also to chronic schizophrenia. The results also suggested that decreased posterior hippocampal volume can serve as a generalized neuroanatomical marker for indicating antipsychotic treatment response. Consistently, Maller et al[9] revealed that patients with treatment-resistant schizophrenia exhibited a decreased smaller tail section of the hippocampus. If future studies can replicate our findings, we believe that the association of smaller hippocampal subregions and subfields with symptomatic remission can be another neuroanatomical surrogate marker for antipsychotic response in schizophrenia.[40]

This study has several limitations. First, the small sample size was unable to provide adequate statistical power to uncover between-group hippocampal volume differences given the small to medium effect size of the group effect. Second, we used a 1.5-T MRI scanner; a higher resolution scan would allow a more accurate measurement and separation of the hippocampal subregions and subfields.[41–43] Third, the cross-sectional design precluded the investigation of the temporal relationships of the illness stage, long-term antipsychotic treatment, or other nonpharmacological factors with long-lasting volume changes in hippocampal subfields. Fourth, although all the recruited patients with schizophrenia were regularly followed up for at least 6 months, we did not examine the duration of untreated psychosis or medication adherence in these patients. Finally, the study focused on regional hippocampal volume changes in schizophrenia or the symptomatic remission of schizophrenia. Further research using multimodality imaging integrating structural, functional, metabolic, and biochemical information can help elucidate the role of the hippocampus in schizophrenia pathophysiology and the implication in symptomatic remission to treatment.[15,43]

In conclusion, the volumes of hippocampal subfields are associated with schizophrenia and remission status. Our findings showed that reduced regional hippocampus volumes are related to the remission of symptoms following antipsychotic therapy and are implicated in the pathogenesis of schizophrenia. These volumes are thus a promising biomarker for indicating not only the presence of schizophrenia but also the patient's response to schizophrenia treatment.

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