Study on the sub-regions volume of hippocampus and amygdala in schizophrenia

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Background: Many studies have found volume changes in the hippocampus and amygdala in patients with schizophrenia, but these findings have not reached an agreement. Particularly, few results showed the volumes of the sub-regions of the amygdala. In this research, we aim to clarify volume changes of hippocampus and amygdala sub-regions in patients with schizophrenia.

Methods: The sample consisted of 69 patients with schizophrenia and 72 control subjects aged from 18 to 65 years. FreeSurfer 6.0 software was used on T1-weighted images to assess the volumes of hippocampus and amygdala and their sub-regions. The general linear model (GLM) was used to analyze the volume changes between the two groups. False discovery rate (FDR) correction was performed, and the significance level was set at 0.05.

Results: The hippocampus volume in schizophrenia showed reduction compared to healthy control (P<0.05). Several hippocampal subfields showed smaller volume in schizophrenia patients, including bilateral presubiculum and molecular layer, left hippocampal tail, subiculum and cornus ammonis (CA)1, and right parasubiculum (P<0.05). Left amygdala volume showed a decrease as well, sub-regions including the bilateral basal nucleus, anterior-amygdaloid-area (AAA), paralaminar nucleus and left lateral nucleus (P<0.05).

Conclusions: Several sub-regions of hippocampus and amygdala showed a volumetric decline in patients group, which suggest the key roles of these regions in the pathophysiology of schizophrenia. Based on these results, we speculate that these regions could be used to assess the early finding of schizophrenia.

Keywords: Amygdala; hippocampus; schizophrenia; sub-regions

Introduction

Schizophrenia is a chronic mental disorder characterized by distortion of thinking, language, emotion, perception, and self-behavior (1,2). It is generally believed that schizophrenia is related to genetic, environmental, psychosocial factors and social defeat (2,3). In current years, the study found that there was a significant difference in brain immune cell density of patients with schizophrenia compared with healthy people (4), and then the mild encephalitis hypothesis of schizophrenia was put forward (5). The limbic system contains several structures of the brain involving connectivity, architecture, function, and development, including the hippocampus, amygdala, parahippocampal

gyrus, internal olfactory region, dentate gyrus, cingulate gyrus and mammillary body (6). Evidence showed that there were changes in limbic system volume in patients with schizophrenia, which may serve as an early indication for the impending development of schizophrenia (7). Both of the hippocampus and amygdala have important positions in the limbic system: hippocampus can store information and is a key part of human learning and memory (8,9), and amygdala has the function of emotional processing (10-12). Sub-regions of the amygdala, including the central-medial and basolateral, are organized at the relative level of emotional processing. Though memory deficits and abnormalities of the amygdala-hippocampal complex have been reported in schizophrenia in the past (13), there was research found no group differences in the amygdala or hippocampal volume between schizophrenia and control (14). Thus, it is necessary to investigate the abnormal changes in hippocampus and amygdala in schizophrenia.

There were longitudinal studies showed that the hippocampus in patients with schizophrenia was vulnerable. Evidence has verified that the volume of the hippocampus was smaller in patients with schizophrenia compared with control (15). Another research showed that hippocampal volume decreased at the initial stage of schizophrenia, and to a lesser extent, this abnormal change occurred in first-degree relatives of schizophrenia patients (16). Furthermore, one study reported that the smaller the volume of the hippocampus, the worse the cognitive ability as well as in schizophrenia (17), which indicated the roles of hippocampus on cognition. Using Freesurfer version 5.1 or 5.2, both Mathew *et al.* (18) and Haukvik *et al.* (19) found the volume of CA1, CA2/3, CA4/DG, presubiculum, and subiculum decreased in patients with schizophrenia. Importantly, Iglesias *et al.* updated the method with a different and more reliable/detailed atlas in Freesurfer 6.0, which included cornus ammonis (CA)1, CA2/3, CA4, molecular layer, alveus, granule cell layer of the dentate gyrus (GC-DG), hippocampal amygdala transition area (HATA), subiculum, presubiculum, parasubiculum, fimbria, hippocampal tail and fissure. Based on the updated method, we make further segmentation on the hippocampus in anticipation of more detailed findings.

Differently, few studies focused on the volume changes of amygdala subregions in patients with schizophrenia, although much research has reported the abnormal volume changes of the whole amygdala (20,21). The previous study

has demonstrated that schizophrenia patients have smaller volume in bilateral amygdala and hippocampus compared with healthy control (13). The reduction in the volume of the amygdala was found in patients with early course schizophrenia (22). Another study has found a reduction in somatostatin-immunoreactive (SST-IR) neurons in the amygdala of patients with schizophrenia, which indicated that amygdala change might disrupt anxiety regulation and responses to fear in schizophrenia (23). Many studies have illustrated amygdala atrophy in schizophrenia, while due to the small size of the amygdala, it is difficult to perform sub-regional research in the vivo brain.

Moreover, most of the studies just divided the amygdala into 2–4 sub-regions. For example, Kleinhans *et al.* (24) divided amygdala into three regions, including centromedial, laterobasal and superficial. Entis *et al.* (25) divided it into four subregions: basolateral, medial, basal and cortical nucleus. These sub-regions are not fine enough, so detailed division is necessary for research.

In this study, we used the advanced technology to make a more detailed segmentation of hippocampus and amygdala in Freesurfer software on 141 subjects. We hope to identify volume alteration in hippocampus and amygdala in schizophrenia more clearly and provide more reliable results.

Methods

Participants

All participants data were acquired from the Center for Biomedical Research Excellence (COBRE) database (http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html). A total of 141 samples were obtained, including 69 patients with schizophrenia (11 females and 58 males) and 72 control subjects (21 females and 51 males), aged from 18 to 65 years (patients average age =37.739±13.634; control average age =35.857±11.656).

Image acquisition

All data were acquired on the Siemens Trio Tim 3T scanner. The following parameters were collected by the magnetization-prepared rapid gradient echo (MPRAGE) sequence. TE (echo time) =1.64 ms, TR (repetition time) =2,530 ms, FOV (field of view) =256 mm resolution =256×256, 7° flip angle, slice thickness =1.0 mm, Matrix =256×256×176, Voxel size =1×1×1 mm.
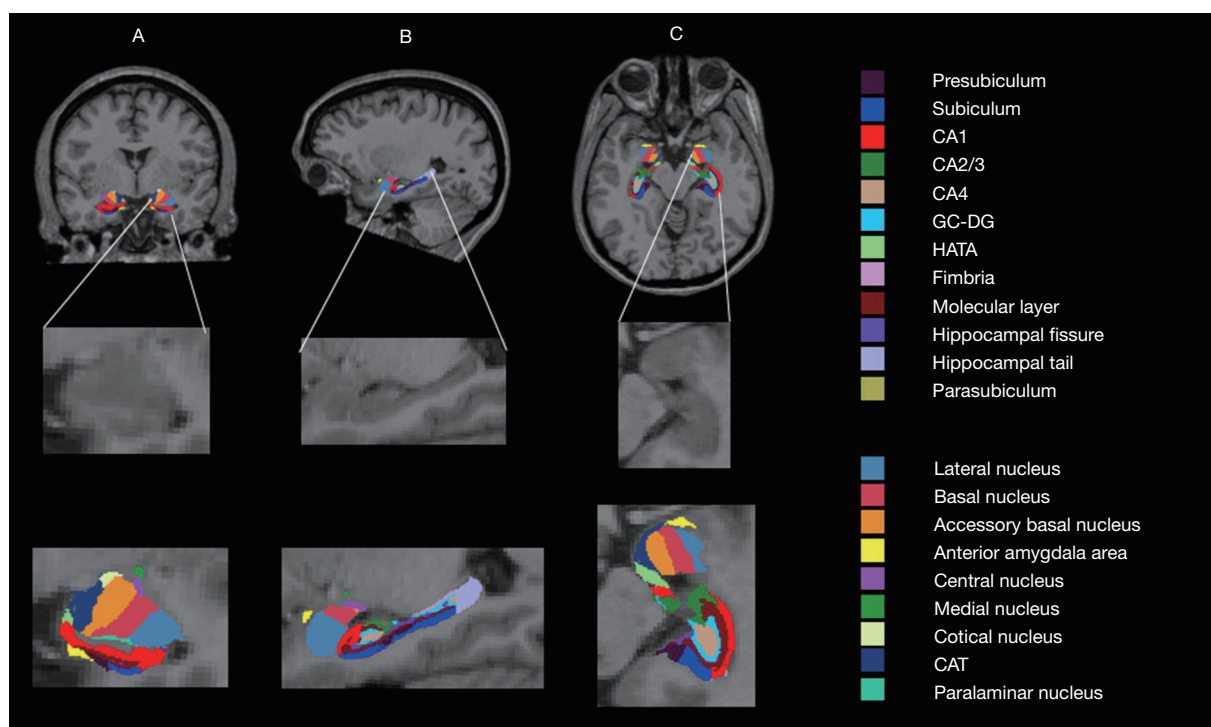
Figure 1 Sub-regions of hippocampus and amygdala on one of the subjects: The column of A, B, C represent the image view of coronal, sagittal and axial, respectively. The second row represents the hippocampus and amygdala without any labels as reference. Moreover, the third row shows the enlarged images on the left.

Image processing

The reconstructions of the cortical surface were carried out on T1-weighted images in FreeSurfer 6.0 software (http://surfer.nmr.mgh.harvard.edu/). Images were preprocessed by motion correction and brain extraction (26). Talairach transformation and intensity correction were also performed for cortical surface reconstruction. Subsequently, brain tissue was segmented into gray matter, white matter and cerebrospinal fluid. Moreover, the tessellation of the boundary between gray matter and white matter was performed. Subsequently, the segmentation of subcortical structures was examined by a nonlinear warping atlas (27), and the volumes of whole hippocampus and amygdala were obtained. All of the above steps could be implemented using the standard "recon-all" pipeline in FreeSurfer.

Furthermore, the hippocampal/amygdala module, which is only present in the FreeSurfer dev version (ftp://surfer.nmr.mgh.harvard.edu/pub/dist/freesurfer/dev) for the time being, was used to parcellate hippocampus and amygdala further. A probabilistic atlas and a modified version of Van Leemput's algorithm were applied on the segmentation of these two structures (28). The atlas was proposed by Iglesias *et al.* (29) and Saygin *et al.* (28). Similarly, both hippocampus atlas and amygdala atlas were constructed through combining the segmentation of the *ex vivo* data and *in vivo* data. The *ex vivo* data provide the internal structures, and the *in vivo* data informs the outer contour of the nuclei. The underlying model of the atlas is based on a tetrahedral mesh. In the tetrahedral mesh, each vertex has a related vector of label probabilities for subfields. At the location of each vertex, the labels are sampled to segment the nuclei. Compared with direct registration to a reference space, more accurate label posterior probabilities using a high-density tetrahedral mesh were produced. A prior distribution of Gaussian parameters on each vertex and an affine, sum of squares-based registration algorithm was also used in the segmentation of these two nuclei. More detailed information on the segmentation method could be found in the literature of Saygin *et al.* (28), Iglesias *et al.* (29) and Van Leemput *et al.* (30). Finally, Freeview, a package software in Freesurfer, was used to show the segmentation of these two structures, as shown in *Figure 1*.

Table 1 The demographic information of each group

Index	Patients (n=69)	Controls (n=72)	t value/χ^2	P value
Age	37.739±13.733	35.857±11.738	0.389[&]	0.046*
Gender (F: M)	11:58	21:51	3.512**	0.061
Handedness (L: R: B)	10:57:2	1:69:2	8.446**	0.015*

[&], t-test, **, chi-square test, *, P<0.05, F: M, female: male; L: R: B, left: right: both.

Hippocampus sub-regions segmentation

Thirteen subfields were obtained for hippocampus: cornus ammonis (CA)1, CA2/3, CA4, molecular layer, alveus, GC-DG, HATA, subiculum, presubiculum, parasubiculum, fimbria, hippocampal tail, and fissure.

According to the location and pyramidal layer thickness, subiculum, CA1, CA2, CA3 were defined: the widest region is subiculum, the thinner is CA1, and then is CA2, and CA3 is thinner than CA2. Since the contrast is not clear, the CA2 and CA3 were combined, and because of the thin shape and unreliable division removed alveus volume in this study (29). The presubiculum lies between the subiculum (laterally) and the parasubiculum (medially). CA4 sub-regions locates within the dentate gyrus and fills the inside of the GC-DG label. The GC-DG consists of a polymorphic layer, a molecular layer, and a granule cell layer. The molecular layer lies above the subiculum and underneath the hippocampal fissure. The hippocampal fissure opens medially and extends laterally until there is residual space between the molecular layer of hippocampus and dentate gyrus. The fimbria, which is a white matter structure, lies in the mid-body of the hippocampus. HATA is superior to the other subfield and locates in the median region. More detailed information about the segmentation method could be found in the literature of Iglesias *et al.* (29).

Amygdala sub-regions segmentation

In total 9 nuclei were segmented for the amygdala, including lateral, basal, accessory-basal, anterior-amygdaloid-area (AAA), central, medial, cortical, corticoamygdaloid-transition (CAT), and paralaminar nucleus. The lateral nucleus is the largest nucleus and the first to appear in the anterior portion of the amygdala. Following the lateral nucleus, the basal nucleus appears. The medial border of the amygdala is CAT, laterally bordering AAA, accessory-basal, basal, paralaminar, and central nucleus along with the anterior-posterior extent. The AAA lies the anterior end of the amygdala, bordering CAT anteriorly and laterally. The central nucleus is between basal nucleus laterally and

CAT medially, which appears circular and dasal to accessory basal. The medial nucleus covered nearly all of the lateral-dorsal boundary of CAT. The Cortical nucleus appears as a small circular nucleus, which borders accessary-basal. The paralaminar nucleus borders the basal and lateral nucleus, which is a small, light band. More detailed information about the segmentation method could be found in the literature of Saygin *et al.* (28).

Statistical analysis

The general linear model (GLM) was performed to analyze the changes in the volume of the hippocampus and amygdala areas in schizophrenia patients compared with healthy people. *t*-test was performed for statistical analysis of age and handedness, as well as Chi-square test for gender. Regarding the estimated total intracranial volume (eTIV), gender, handedness, and age, we used these variables as covariates for the volume changes between patients and controls. False discovery rate (FDR) correction was performed using Matlab (MathWorks Inc., Natick, MA, USA). Moreover, the significant level was set at 0.05. All steps of imaging processing and statistical were performed by ourselves.

Results

Demographics

Table 1 illustrates the demographic information of each group. There is no significant difference in gender between schizophrenia patients and healthy controls. But age (t=0.389, P=0.046) and handedness (χ^2=8.846, P=0.015) show significant differences between two groups.

Hippocampal volume differences in schizophrenia

Table 2 shows the statistical analysis of hippocampal sub-regions volumes between two groups. The bilateral

Table 2 The difference between the two groups in the hippocampus

Sub-regions	Patients (n=69)	Controls (n=72)	F	FDR P value
Right_Whole_hippocampus	3,555.600±401.266	3,635.494±330.309	7.488	0.023*
Right_subiculum	442.333±53.473	450.758±47.200	5.194	0.052
Right_CA1	677.725±95.796	696.364±79.776	4.895	0.052
Right_fissure	151.867±27.767	143.311±22.849	0.900	0.39
Right_presubiculum	285.176±40.256	294.943±33.649	7.939	0.022*
Right_parasubiculum	57.013±11.200	60.509±10.161	7.170	0.023*
Right_molecular_layer	578.458±71.094	593.151±59.247	6.209	0.036*
Right_GC-DG	304.139±37.450	309.093±34.378	3.219	0.108
Right_CA3	236.028±33.510	235.878±35.875	0.557	0.495
Right_CA4	262.559±33.408	265.849±30.199	2.319	0.169
Right_fimbria	78.248±17.019	80.176±17.911	1.253	0.313
Right_HATA	61.812±11.060	63.214±10.055	2.092	0.186
Right_Hippocampal_tail	572.109±76.614	585.560±63.418	4.412	0.062
Left_Whole_hippocampus	3,421.036±379.999	3,562.187±320.962	16.080	<0.001**
Left_subiculum	447.002±52.121	463.461±49.086	10.800	0.005*
Left_CA1	634.639±87.845	663.584±80.657	11.040	0.005*
Left_fissure	149.884±27.707	143.269±24.933	0.164	0.686
Left_presubiculum	302.624±44.0009	317.232±42.265	10.220	0.009*
Left_parasubiculum	59.929±12.802	63.040±12.512	4.823	0.052
Left_molecular_layer	557.072±66.309	578.757±56.167	11.590	0.005*
Left_GC-DG	289.939±35.510	297.688±31.138	4.972	0.052
Left_CA3	212.040±29.911	210.761±31.123	0.165	0.686
Left_CA4	249.603±29.655	255.051±26.114	3.931	0.075
Left_fimbria	83.563±22.968	88.358±20.409	3.122	0.11
Left_HATA	58.801±9.933	61.610±11.795	5.446	0.05
Left_Hippocampal_tail	525.823±67.951	562.647±61.964	16.580	<0.001**

The data in the second and third columns of the table represent the mean volume ± standard deviation. Unit: mm^3; *, $P<0.05$; **, $P<0.001$.

hippocampus in patients appear to shrinker volume compared with controls (R: F=7.488, P=0.023; L: F=16.080, P<0.001). When the hippocampus were divided into sub-regions, we found that several areas showed smaller volume in patients, including left hippocampal tail (F=16.580, P<0.001), left subiculum (F=10.800, P=0.005), left CA1 (F=11.040, P=0.005), right parasubiculum (F=7.170, P=0.023), bilateral presubiculum (R: F=7.939, P=0.022; L: F=10.220, P=0.009), and molecular layer (R: F=6.209, P=0.036; L: F=11.590, P=0.005). In other areas of the hippocampus, the difference does not reach a statistically significant level (P>0.05). *Figure 2* shows the volume of hippocampal subfields with significant differences in two groups, which indicates the volume of these sub-regions decreased in patients group compared with controls.

Amygdala volume differences in schizophrenia

As shown in *Table 3*, we find a significant reduction in left amygdala volume in schizophrenic patients (F=11.164,
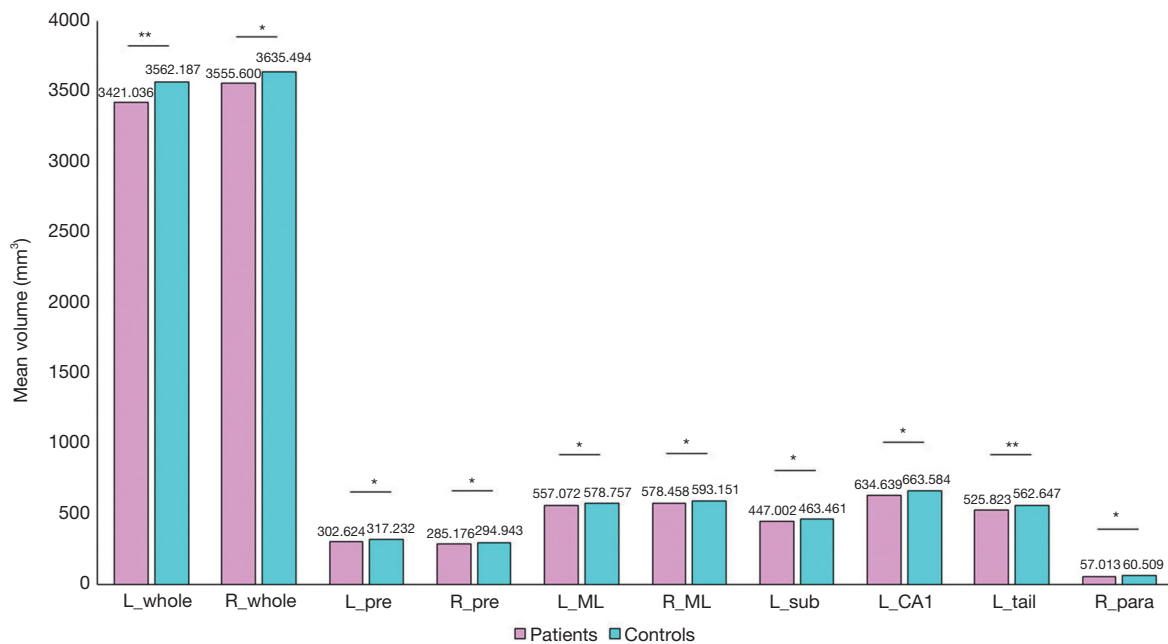
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Figure 2 Histogram of the hippocampal sub-region between the two groups. *, P<0.05; **, P<0.001. Note horizontal axis: sub-region; vertical axis: mean volume. L, left; R, right; Whole, the whole hippocampus; pre, presubiculum; ML, the molecular layer; sub, subiculum; CA, cornus ammonis; tail, hippocampal tail; para, parasubiculum.

P=0.005). *Figure 3* describes the raw mean volume of amygdala sub-regions with significant decline in patients, including basal nucleus (R: F=7.278, P=0.023; L: F=18.930, P<0.001), AAA (R: F=5.701, P=0.045; L: F=16.062, P<0.001), paralaminar nucleus (R: F=8.510, P=0.016; L: F=13.604, P<0.001) and left lateral nucleus (F=8.184, P=0.017). In the remaining regions, the difference is not statistically significant (P>0.05).

Discussion

In this study, we comprehensively compared the volume changes in the subfields of the hippocampus and amygdala between schizophrenia patients and healthy people. The results showed that the whole volume of bilateral hippocampus in patients group was smaller than the control group, as well as several sub-regions including the left hippocampal tail, left subiculum, left CA1, right parasubiculum, bilateral presubiculum and molecular layer. Regarding the amygdala, the main findings were smaller volume in the bilateral basal nucleus, AAA, paralaminar nucleus and left the lateral nucleus, and especially the left side was more significant.

Hippocampal structure

Previous result found in left anterior and midbody of CA1 and CA2, and mid- to anterolateral hippocampal regions showed significant volume changes in schizophrenia patients (31). Also, recently, a review focused on the changes of hippocampal sub-regions in schizophrenia reported that the most prominent volume alteration is CA1 (32). These findings were partly consistent with our results. Perhaps the individual specificity among different dataset and methods resulted in different results. Also, there was evidence showed that CA1 could encode the temporal order of events (33). To a certain degree, this finding indicates that the atrophy of CA1 may lead to thought disorder, which is the symptom of disorganized type. Furthermore, we find that there are more sub-regions on the left hippocampus with volume changes than the right. This is in some way compatible with the hyperactivity of the left hippocampus proposed by Hanlo and his colleagues (34) in schizophrenia. We suppose that patients with schizophrenia due to over-active on the left hippocampus which led to the atrophy in advance of schizophrenia, these hippocampal sub-regions may be more susceptible to disease processes. Besides, there

Table 3 The difference between the two groups in the amygdala

Sub-regions	Patients (n=69)	Controls (n=72)	F	FDR P value
Right_Whole_amygdala	1,812.465±176.288	1,844.695±176.288	5.288	0.053
Right_Basal_nucleus	451.230±57.323	463.065±46.632	7.278	0.023*
Right_Accessory_Basal_nucleus	280.836±40.908	284.635±31.888	2.250	0.194
Right_AAA	58.776±9.293	61.444±8.341	5.701	0.045*
Right_Central_nucleus	51.896±9.854	51.929±8.544	0.423	0.679
Right_Medial_nucleus	28.054±8.009	27.896±7.23	0.042	0.880
Right_Cortical_nucleus	30.351±5.887	30.377±4.82	0.023	0.880
Right_Corticoamygdaloid_transitio	181.023±27.053	186.205±21.356	3.953	0.075
Right_Paralaminar_nucleus	48.776±5.986	50.076±5.266	8.510	0.016*
Right_Lateral_nucleus	681.522±82.229	689.068±61.739	4.503	0.060
Left_ Whole_amygdala	1,747.688±211.624	1,805.059±188.163	11.164	0.005*
Left_Basal_nucleus	435.223±55.324	458.967±51.747	18.930	<0.001**
Left_Accessory_Basal_nucleus	264.078±36.314	270.568±32.884	4.470	0.060
Left_AAA	53.827±8.179	58.361±8.195	16.062	<0.001**
Left_Central_nucleus	48.990±9.154	48.894±8.966	0.373	0.679
Left_Medial_nucleus	24.417±6.740	24.047±6.890	0.251	0.686
Left_Cortical_nucleus	27.257±5.505	26.786±5.096	0.290	0.686
Left_Corticoamygdaloid_transitio	173.244±24.109	178.285±22.830	4.779	0.060
Left_Paralaminar_nucleus	48.531±6.497	50.716±6.124	13.604	<0.001**
Left_Lateral_nucleus	672.121±83.233	688.433±72.343	8.184	0.017*

The data in the second and third columns of the table represent the mean volume ± standard deviation. Unit: mm^3; *, $P<0.05$; **, $P<0.001$.

is a pathophysiological process of psychosis discovered by previous researchers. The process involves the increase of synaptic glutamate levels at first, then increase of metabolic demand and blood flow, and down-regulation of hippocampal GABAergic interneurons. Because glutamate receptors exist in the hippocampus, the region may be vulnerable to excitotoxic injury and dysregulation of glutamatergic neurotransmission (35). We speculate whether the volume of specific hippocampal sub-region reduction is related to the number of glutamate receptors.

Volume decrease of these sub-regions is reasonable to some extent in schizophrenia. When we combined the atrophy of hippocampus with schizophrenia subtypes, we found the presubiculum and subiculum shrinking may happen to two types of schizophrenia: paranoid type and catatonic type, because the decreased volumes of these regions have strong associations with bad performance on

several cognitive domains (36). Another study reported that parasubiculum was related to movements and the catatonic patients may exhibit purposeless, agitated movement, or maybe almost immobile (37), so the parasubiculum atrophy may be related to the onset of catatonic schizophrenia.

Mathew *et al.* (18) and Haukvik *et al.* (19) found CA1, CA2/3, CA4/DG, presubiculum and subiculum appear to shrink in schizophrenia patients. Different from their findings, we only found a volume decrease in the left subiculum and left CA1. The difference maybe due to different segmentation methods and software version we used. Though connections between subiculum and memory retrieval have been proven (38), there was another evidence support left subiculum volume was significantly correlated verbal memory function (39). Based on that, we speculate the volume of left subiculum is more susceptible than the right because it has a stronger relation to memory. To a
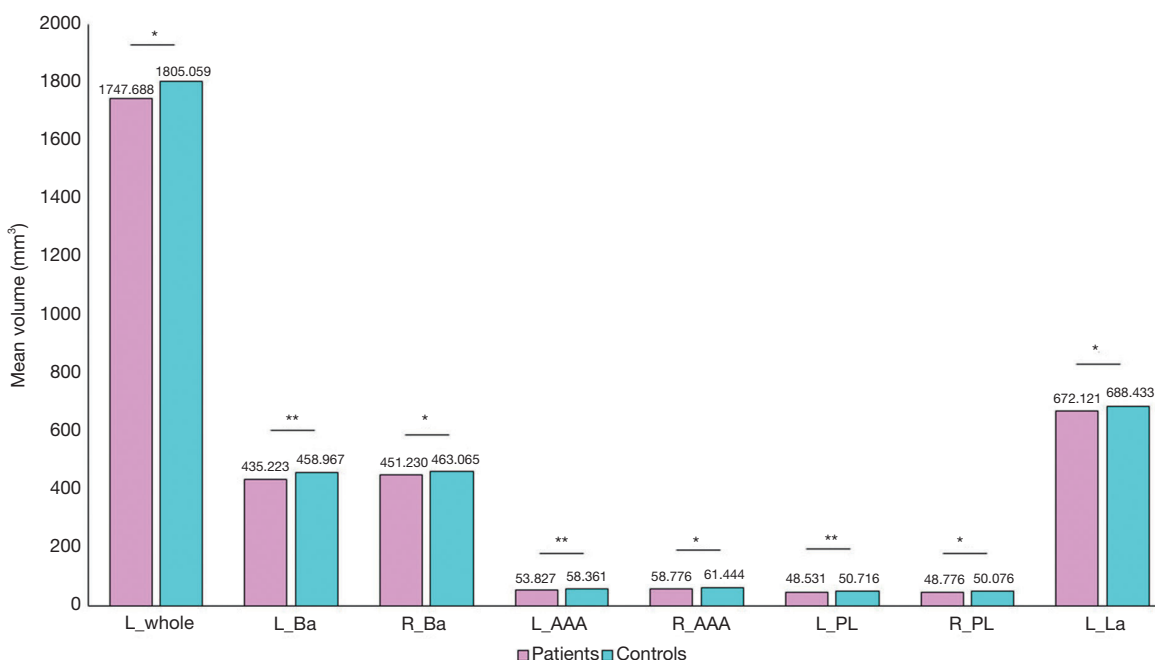
Figure 3 Histogram of difference amygdala sub-regions between the two groups. *, P<0.05; **, P<0.001. Note horizontal axis: sub-region; vertical axis: mean volume. L, left; R, right; Whole, whole amygdala; Ba, basal nucleus; AAA, anterior-amygdaloid-area; PL, paralaminar nucleus; La, lateral nucleus.

certain degree, the degree of volume alteration may depend on the stage of schizophrenia, so that volume reduction may occur on the left earlier than the right.

Interestingly, we found that the bilateral molecular layer and left tail also showed significant shrinkage. There was evidence that proved that the molecular layer was related to cognitive processes (40), and the activation of postsynaptic 5-HT(1A) receptors in the hippocampal tail could prevents learned helplessness (41). These findings indicated that schizophrenia patients might have impairments in learning and memory ability.

What is more, in patients with schizophrenia, the extent of hippocampal volume reduction may be related to treatment. The bilateral GC-DG with increased volume before treatment falls to a healthy level after 6 weeks' treatment, and CA4 reached a close level to a healthy level after treatment (42). This may be due to the high sensitivity of these regions, which will return to normal levels before other hippocampal sub-regions. We did not observe any changes in GC-DG and CA4. Our study did not consider the length of the disease, and the time of treatment and efficacy, this may be one of the reasons why the results differ from previous studies.

Interestingly, there is evidence suggesting that the decreased volume of the hippocampus in patients with schizophrenia is associated with a decrease in the number of cells in the region (43,44). For example, the brain cell density (absolute number of pyramidal cells) of CA1/CA2, CA3, CA4 was significantly decreased, and these sub-regions also showed corresponding volume decrease, which was reported by Falkai *et al.* (44). These findings suggested the correlation between the volume of the hippocampus and the cell number. However, in our study, we did not perform any work about the cell numbers, and it would be performed in the future.

Amygdala structure

The previous study found the negative connection between stereotypes and the volume of the right amygdala. Moreover, during positive emotional processing, there was a significant negative connection between emotional passivation and left amygdala neural activation. As the condition worsens, the volume of the amygdala begins with one side (left or right) and gradually shrinks to the sides. There was also evidence of a significant increase in dopamine content in

the left amygdala in schizophrenia (45). Since the disorder of the dopamine system in schizophrenic patients has been extensively demonstrated (45,46), we speculate that there may be some associations between the disorder of dopamine system and the change of amygdala volume in patients with schizophrenia. In our study, bilateral amygdala volume decreased in the patients' group but no significance in the right. Combined with these studies, maybe left amygdala is more related to emotion in schizophrenia, rather than the right amygdala. However, Malchow and his colleagues (47) suggest that the recent onset of schizophrenia will also have a decrease in bilateral amygdala volume. Compared with the control group, Okada *et al.* also found that the amygdala volume of schizophrenic patients showed bilateral volume reduction (13). This difference may be due to the different samples and whether or not the medicine is taken.

Innovatively, we segmented the amygdala into smaller size on schizophrenia patients than the previous study. In elderly schizophrenia patients and controls, previous studies have found structural differences in the medial amygdala, intrauterine-ventral-medial and accessories substrate significant tissue loss, medial, central, and cortical nuclei outer soft tissue loss (48). When compared with psychotic bipolar disorder, the previous study has found volumes of left basolateral and centromedial, and all sub-regions in the right amygdala were decreased in schizophrenia (49). In our study, compared with the control group, basal, AAA, paralaminar nucleus and left lateral nucleus illustrated declined volume in patients group. Based on the previous study, we discussed the associations between the volume decrease of these sub-regions and clinical classification of schizophrenia. The basal nucleus is connected with emotion, cognition, and it can control voluntary motor movements (50,51). AAA is involved in sustaining attention (52) and memory (53), which is occupied by magnocellular cholinergic neurons that secrete acetylcholine (54). So there was research that showed the paralaminar nucleus is related to mood and anxiety disorder (55,56). With the publication of DSM-5, there are five sub-classifications of schizophrenia include paranoid type (delusions or auditory hallucination), disorganized type (thought disorder and flat affect), catatonic type (immobile, or exhibit purposeless, agitated movement), undifferentiated type and residual type (57). It is possible that different subtypes of schizophrenia will have decreased volume of different amygdala sub-regions, such as paranoid type and basal nucleus, disorganized type and paralaminar nucleus. It is undeniable that the reduction in the volume of these sub-regions found in our study may be caused by one certain subtype of schizophrenia, which requires more research to verify.

The different segmentation methods may affect the results. One recent study reported that across development, the connectivity of central, basal, and lateral nucleus continues to change. Development participants did not be included in our study, which is another potential application. Moreover, the functional study on amygdala sub-regions combined with structural changes is necessary to study.

This study has several limitations. First, the sample size is not large, resulting in the existence of sampling errors. Second, the participant included in this study were aged from 18 to 65 years old. There are no younger and order adults. Third, there is the study shows that volume change is related to the course of schizophrenia (58). However, the distinction between the clinical course of the patients was not taken into consideration in our study. Moreover, our data were acquired from the public database, so the pathological subtypes of the schizophrenia were not taken into consideration in this study. Also, other factors that can affect the outcome, lifestyle habits such as smoking and drinking can cause a reduction in the volume of gray matter (59).

In conclusion, this study suggested some new findings on the volume changes of the hippocampus, such as the molecular layer. It is worth emphasizing that we found volume decrease in the basal nucleus, AAA, paralaminar nucleus and left the lateral nucleus in schizophrenia. The decreased volumes in these sub-regions suggest these sub-regions may play more important roles in the study of schizophrenia. We believe there should be more research of this field in the future, especially considering pathological subtypes of schizophrenia.

Acknowledgments

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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