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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Study

Diagnostic value of amygdala volume on structural magnetic resonance imaging in Alzheimer's disease

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Author contributions: Wang P designed the study; Wang DW wrote the paper; Bian XL, Zhou SY, and Yang H drafted the work and collected the data; Ding SL collected and analyzed the data.

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Abstract

BACKGROUND

The main clinical manifestation of Alzheimer's disease (AD) is memory loss, which can be accompanied by neuropsychiatric symptoms at different stages of the disease. Amygdala is closely related to emotion and memory.

AIM

To evaluate the diagnostic value of amygdala on structural magnetic resonance imaging (sMRI) for AD.

METHODS

In this study, 22 patients with AD and 26 controls were enrolled. Their amygdala volumes were measured by sMRI and analyzed using an automatic analysis software.

RESULTS

The bilateral amygdala volumes of AD patients were significantly lower than those of the controls and were positively correlated with the hippocampal volumes. Receiver operating characteristic curve analyses showed that the sensitivity of the left and right amygdala volumes in diagnosing AD was 80.8% and 88.5%, respectively. Subgroup analyses showed that amygdala atrophy was more serious in AD patients with neuropsychiatric symptoms, which mainly included irritability (22.73%), sleep difficulties (22.73%), apathy (18.18%), and

additional data are available.

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hallucination (13.64%).

CONCLUSION
Amygdala volumes measured by sMRI can be used to diagnose AD, and amygdala atrophy is more serious in patients with neuropsychiatric symptoms.

Key Words: Alzheimer's disease; Amygdala; Structural magnetic resonance imaging; Neuropsychiatric symptoms

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Core Tip: Amygdala volume measured by structural magnetic resonance imaging can be used for the diagnosis of Alzheimer's disease, and the degree of amygdala atrophy is more severe in patients with neuropsychiatric symptoms.

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INTRODUCTION

Amygdala, a part of the medial temporal lobe, is closely related to emotion and memory, and is one of the key brain regions in the pathogenesis of Alzheimer's disease (AD)[1,2]. Studies have shown that the dysfunction of amygdala plays an important role in the emotional disorder of AD[3,4]. The pathological changes of AD brain such as senile plaque formation, nerve fiber tangle and neuron loss can appear in the amygdala[5-8]. Clinical studies have shown that injury of the amygdala can lead to agitation, irritability, anxiety, and apathy[9-11]. Patients with anxiety disorder, autism, phobia, and post-traumatic stress disorder can have dysfunction of amygdala[12,13]. Medial temporal lobe is the earliest site of brain atrophy in AD[14]. There have been a lot of studies on MRI to evaluate the degree of atrophy of medial temporal lobe, but fewstudies on amygdala[15,16].

In this study, the amygdala volumes were measured by structural magnetic resonance imaging (sMRI) both in AD patients and controls to evaluate the diagnostic value of amygdala. The correlation between amygdala atrophy and clinical features of AD was also analyzed.

MATERIALS AND METHODS

Participants

Twenty-two patients with AD and twenty-six controls were recruited from the Second Hospital of Shandong University (Shandong, China) between May 2017 and July 2019. The average age of the AD group was 73.9 ± 7.5 years, and the ratio of male to female was 1:1. Among the 22 patients, 4 cases were mild AD, 10 cases were moderate AD, and 8 cases were severe AD (Table 1). The inclusion and exclusion criteria were shown in our published article[17]. The study was approved by the Medical Research Ethics Committee of the Second Hospital of Shandong University and informed consent was obtained from all participants.

Neuropsychological tests

All subjects received a cranial MRI scan and underwent neuropsychological tests including the Chinese version of the Mini Mental State examination[18], the Clinical Dementia Rating (CDR) scale (0: No dementia; 1: Mild dementia; 2: Moderate dementia; and 3: Severe dementia)[19], the Hamilton depression scale, and neuropsychiatric inventory (NPI)[20,21]. The NPI scale was used to evaluate the mental and

Table 1 Demographics characteristics of all participants

Characteristics	AD, *n* = 22	Control, *n* = 26	*P* value
Age (yr)	74.7 ± 8.9	70.8 ± 8.5	0.12[1]
Gender (female/male)	11/11	14/12	0.79[2]
Education (yr)	5.1 (4.6-11.2)	6.2 (3.1-10.9)	0.85[3]
CDR (0/1/2/3)	0/4/10/8	26/0/0/0	-
MMSE	13.6 ± 8.0	27.8 ± 1.5	< 0.001[1]
Onset times (yr)	3.8 (2.5-8.5)	-	-

[1]*P* values were calculated by Student's *t*-test.
[2]*P* values were calculated by χ^2 test.
[3]*P* values were calculated by Mann-Whitney *U* test. $P < 0.05$ was considered statistically significant. AD: Alzheimer's disease; CDR: Clinical Dementia Rating; MMSE: Mini Mental State examination.

behavioral symptoms of all AD patients and the severity of the symptoms was graded. The scale scores included the total scores of patients and psychological distress scores of caregivers. The former was obtained by multiplying the frequency of mental symptoms by the severity[20,21].

Acquisition and processing of images

All subjects received three-dimensional brain volume sequence brain MRI scans. T1-weighted image were analyzed using a set of automated analysis tools, and the steps were described in detail in our previous article[17]. The bilateral amygdala volumes were measured both in AD patients and controls.

Statistical analyses

Categorical variable data are expressed as a frequency and percentage. Numerical data are presented as the mean ± SD or median (interquartile range). Spearman's rank or Pearson correlation coefficient was used for the correlation analyses. Quantitative values were compared using the Student's *t*-test or Mann-Whitney *U* test. One-way analysis of variance or the Kruskal-Wallis test was used to compare the data among three groups. The χ^2 test was used to assess differences in categorical data. Diagnostic values were evaluated by receiver operating characteristic (ROC) curves and the area under the curve (AUC). $P < 0.05$ was considered for a statistically significant difference. Statistical analyses were performed using SPSS Statistics (version 24.0) and GraphPad Prism version 5.0 software.

RESULTS

Amygdala volume

The left amygdala volume of the AD group was 1170.75 ± 402.63 mm^3, and that of the control group was 1559.65 ± 289.02 mm^3. The right amygdala volume of the AD group was 1342.01 ± 307.68 mm^3, and that of the control group was 1629.97 ± 250.24 mm^3. Student's *t*-test showed that the bilateral amygdala volume in the AD group was significantly smaller than that in the control group (Figure 1, $P < 0.01$).

Subgroup analysis

The severity of dementia was graded by CDR score (4 mild AD, 10 moderate AD, 8 severe AD). As shown in Figure 2, the bilateral amygdala volume became smaller with the aggravation of dementia, but there was no significant statistical difference among the three subgroups (Figure 2, $P > 0.05$).

Student's *t*-test was used to compare the bilateral volume of the amygdala. There was no significant difference between the left and right amygdala (Figure 3A, $P > 0.05$). Twenty-five women and twenty-three men were recruited in this study. Student's *t*-test was used to observe the difference in amygdala volume between different genders. As shown in Figure 3B and C, there was no significant difference in amygdala volume between the female and male subjects ($P > 0.05$).

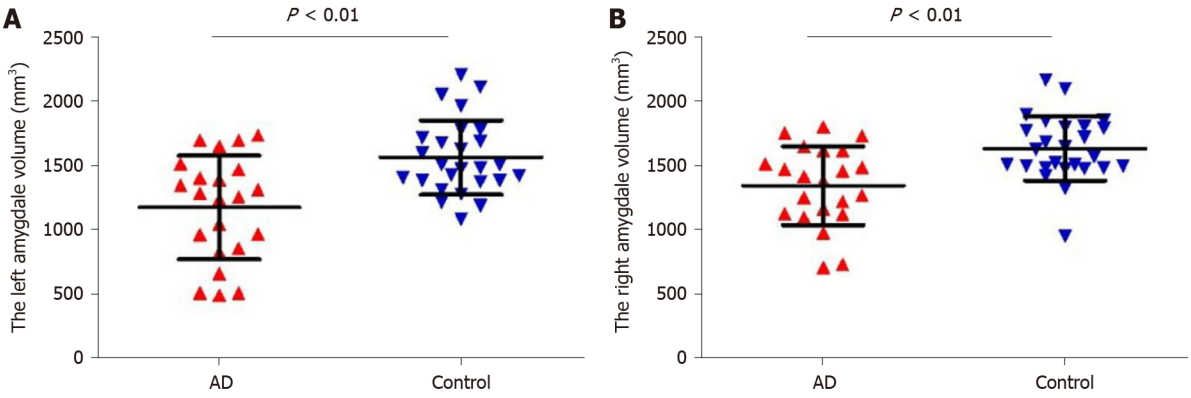

Figure 1 Comparison of amygdala magnetic resonance imaging parameters in two groups. The left and right amygdala volumes of Alzheimer's disease patients were significantly lower than controls. A: Left amygdala volume; B: Right amygdala volume. AD: Alzheimer's disease.

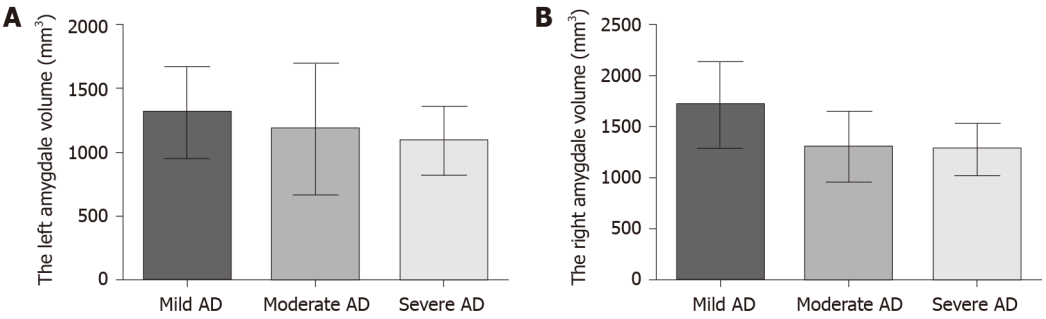

Figure 2 Amygdala volume in different dementia severity. There was no significant difference in the left and right amygdala volume among the three subgroups ($P > 0.05$). A: Left amygdala volume; B: Right amygdale volume. AD: Alzheimer's disease.

Amygdala and neuropsychiatric symptoms

NPI can be used to evaluate the mental symptoms of dementia patients and the psychological distress of caregivers. All AD patients were divided into two groups according to mental symptoms. Thirteen patients had mental symptoms according to NPI scores (Table 2). The volumes of the bilateral amygdala were significantly different between the two groups, and the atrophy of AD patients with mental symptoms was more serious (Figure 4A, $P = 0.0002$; Figure 4B, $P = 0.042$).

As shown in Table 3, 59.1% (13/22) of the AD patients had at least one kind of neuropsychiatric symptom, the most common of which was irritability (22.73%), sleep difficulties (22.73%), apathy (18.18%), and hallucination (13.64%). For mild AD ($n = 4$), one patient (25%) had mental symptoms, manifested as irritability and agitation. Sixty percent (6/10) of moderate AD patients showed abnormal mental behavior, of which irritability and delusion were the most common. Seventy-five percent (6/8) of severe patients had neuropsychiatric symptom, and irritability and delusion were the most common.

Pearson correlation analysis showed that there was no significant correlation between NPI scores and amygdale volumes (Figure 5A and B, $P > 0.05$). In addition, there was no correlation between the psychological distress scores of caregivers and amygdala volumes (Figure 5C and D, $P > 0.05$).

Correlation between amygdala and hippocampal volume

Hippocampal atrophy is a characteristic imaging manifestation of AD, the amygdala attaches to its end, both of them are involved in the pathogenesis of AD. Our previous study measured the volume of hippocampus in all subjects[17]. To further evaluate the relationship between the two brain regions, we analyzed the correlation between the volume of the amygdala and hippocampus.

Pearson correlation analysis showed that there was a significant correlation between left amygdala and hippocampal volumes (Figure 6A, $r = 0.562$, 95%CI: 0.330-0.729, $P < 0.001$). As shown in Figure 6B, there was a significant correlation between the right amygdala volume and hippocampal volume ($r = 0.435$, 95%CI: 0.172-0.640, $P < 0.001$).

Table 2 Neuropsychiatric inventory score and psychological distress scores of caregivers

Case	NPI score, points	Item score, points	Psychological distress scores of caregivers, points
1	27	Hallucination 6, irritability 12, sleep difficulties 9	10
2	24	Hallucination 12, sleep difficulties 12	6
3	14	Agitation 6, irritable 8	6
4	20	Disinhibition 12, sleep difficulties 8	9
5	20	Anxiety 8, indifference 12	6
6	24	Agitation 12, irritable 12	8
7	12	Hallucination 12	5
8	21	Indifference 12, irritable 9	7
9	32	Delusion 12, aggressive 8, sleep difficulties 12	13
10	12	Depression 12	4
11	20	Delusion 12, irritable 8	9
12	18	Indifference 12, sleep difficulties 6	8
13	12	Indifference 12	4

NPI: Neuropsychiatric inventory.

Table 3 Mental symptoms of Alzheimer's disease patients, *n* (%)

Symptoms	Total cases, *n* = 22	Mild AD, *n* = 4	Moderate AD, *n* = 10	Severe AD, *n* = 8
Irritability	5 (22.73)	1 (25)	2 (20)	2 (25)
Sleep difficulties	5 (22.73)	0	4 (40)	1 (12.5)
Indifference	4 (18.18)	0	3 (30)	1 (12.5)
Hallucination	3 (13.64)	0	2 (20)	1 (12.5)
Agitation	2 (9.09)	1 (25)	1 (10)	0
Delusion	2 (9.09)	0	0	2 (25)
Disinhibition	1 (4.55)	0	0	1 (12.5)
Anxiety	1 (4.55)	0	1 (10)	0
Aggressive	1 (4.55)	0	0	1 (12.5)
Depression	1 (4.55)	0	0	1 (12.5)
At least one of the above symptoms	13 (59.1)	1 (25)	6 (60)	6 (75)

AD: Alzheimer's disease.

ROC curve analysis

To evaluate the potential of amygdala volume serving as a novel biomarker for AD, ROC curves were plotted. The AUC was 0.761 for the left amygdala volume, the sensitivity was 80.8%, the specificity was 63.6%, and the cutoff point was 1358 (Figure 7A, P = 0.002). The AUC was 0.771 for the right amygdala volume, the sensitivity was 88.5%, the specificity was 63.6% and the cutoff point was 1472 (Figure 7B, P = 0.001).

DISCUSSION

In this study, the amygdala volumes were measured by sMRI and analyzed using a set of automated analysis tools to evaluate the diagnostic value of amygdala for AD. The

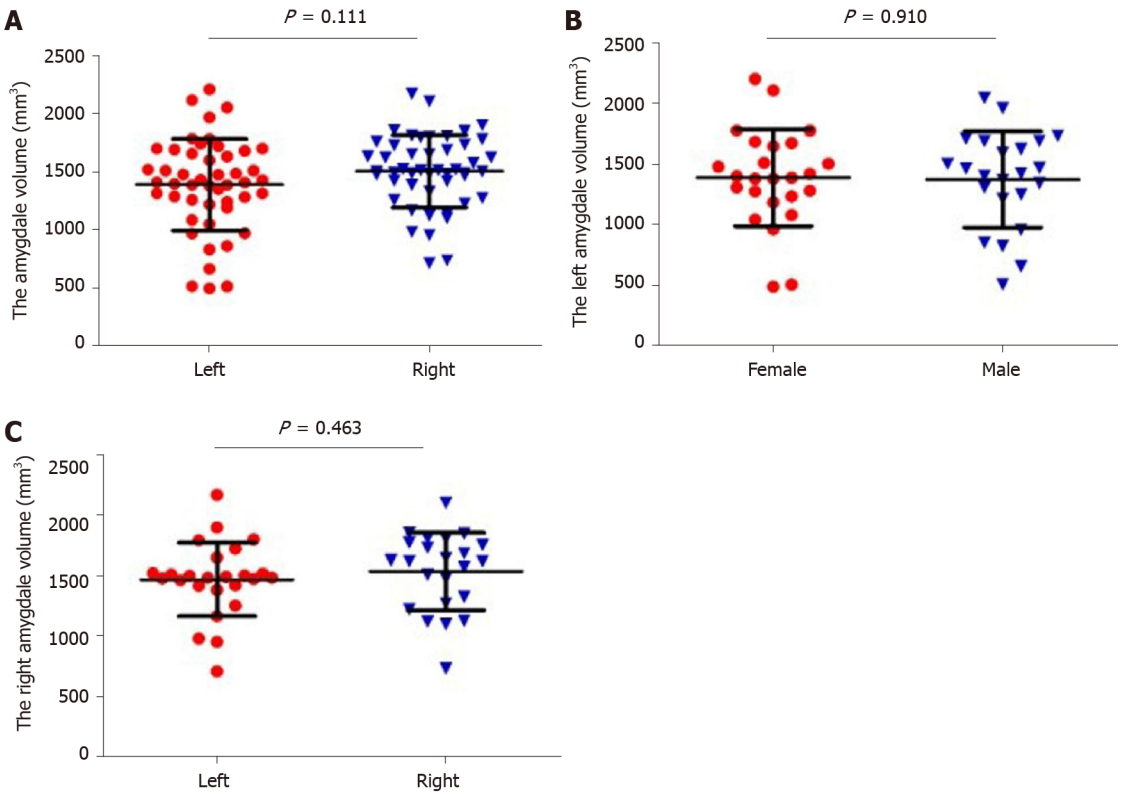

Figure 3 Amygdala volume between different sides and genders. A: There was no significant difference between left and right amygdala ($P > 0.05$); B, C: There was no significant difference in amygdala volume between different genders ($P > 0.05$).

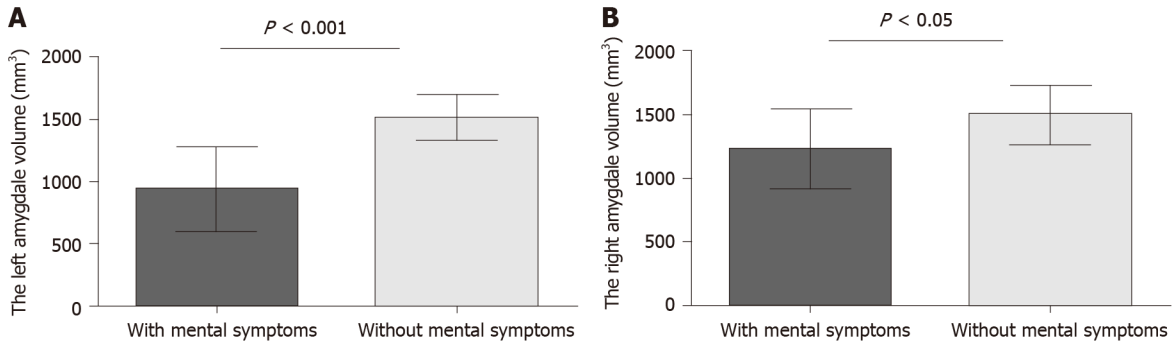

Figure 4 Amygdala volumes between Alzheimer's disease patients with and without mental symptoms. The left and right amygdala volumes of Alzheimer's disease patients with mental symptoms were significantly smaller than patients without mental symptoms. A: Left amygdala volume; B: Right amygdala volume.

results showed that the bilateral amygdala volumes of AD patients were significantly smaller than those of the controls, and were positively correlated with the hippocampal volumes, consistent with previous reports[22,23].

Poulin *et al*[16] found that amygdala atrophy was obvious in early AD and was related to the severity of dementia. Yue *et al*[15] reported that volume of the right amygdala and hippocampus in patients with subjective cognitive decline. However, none of the previous studies evaluated the diagnostic value of amygdala, and there were few studies on the correlation between amygdala atrophy and clinical characteristics. Different from previous studies, we found that the sensitivity of the left and right amygdala volumes in diagnosing AD were 80.8% and 88.5%, respectively, and the cut-off value of the amygdala volume for diagnosis of AD was obtained. Amygdala volume measured by sMRI may be used as a potential imaging marker for the diagnosis of AD. One previous study showed that the degree of amygdala atrophy is correlated with the severity of the dementia[16,24]. We found that the volume of bilateral amygdala became smaller with the aggravation of dementia through subgroup analysis, but there was no significant statistical difference. The reason may

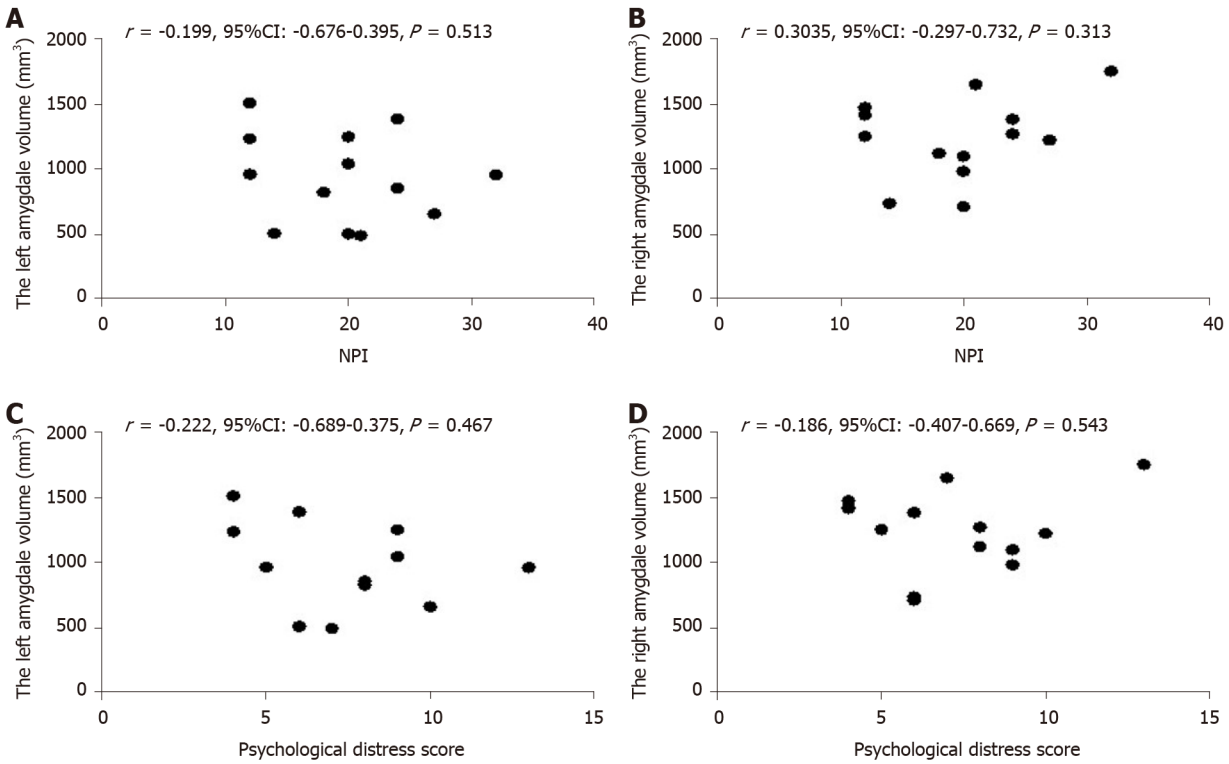

Figure 5 Correlation analyses between neuropsychiatric inventory score and bilateral amygdala. A, B: There was no significant correlation between neuropsychiatric inventory scores and amygdala volumes ($P > 0.05$); C, D: There was no correlation between psychological distress scores of caregivers and amygdala volumes ($P > 0.05$).

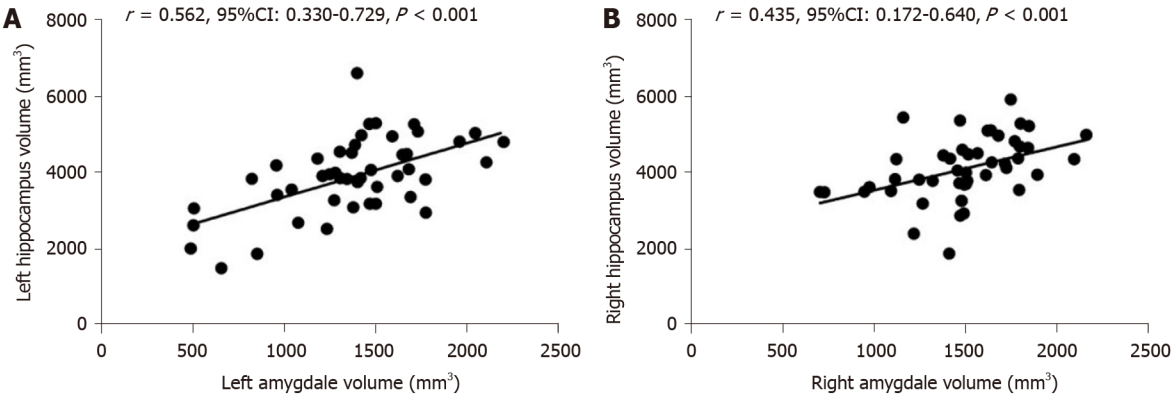

Figure 6 Correlation between amygdala and hippocampus volume. A: There was significant correlation between left amygdala and hippocampal volumes ($P < 0.001$); B: There was a significant correlation between the right amygdala volume and hippocampal volume ($P < 0.001$).

be that the sample size of this study was too small.

The atrophy of the amygdala was more serious in AD patients with mental symptoms in this study, consistent with previous studies[16]. About 80%-90% of patients with AD experience at least one kind of psychobehavioral symptoms, such as anxiety, agitation, irritability, aggression, disinhibition, depression, apathy, which can reduce the quality of life of patients and increase the burden of care[25-28]. The amygdala is attached to the terminal part of the hippocampus and is associated with multiple brain regions to regulate multiple stages of memory formation[1,2]. Some misfolded proteins such as Tau, Aβ, α-synuclein, and TAR DNA-binding protein 43 are present in the amygdala in neurodegenerative diseases[29]. The decreased functional connectivity among the amygdala, inferior frontal gyrus, and medial prefrontal cortex plays an important role in the development of depression in AD patients[30,31]. Previous research has shown that dysfunction of the amygdala plays an important role in the emotional disorder of AD[6-8]. The injury of amygdala can lead to agitation, irritability, anxiety, and apathy[9,10]. Other studies have indicated

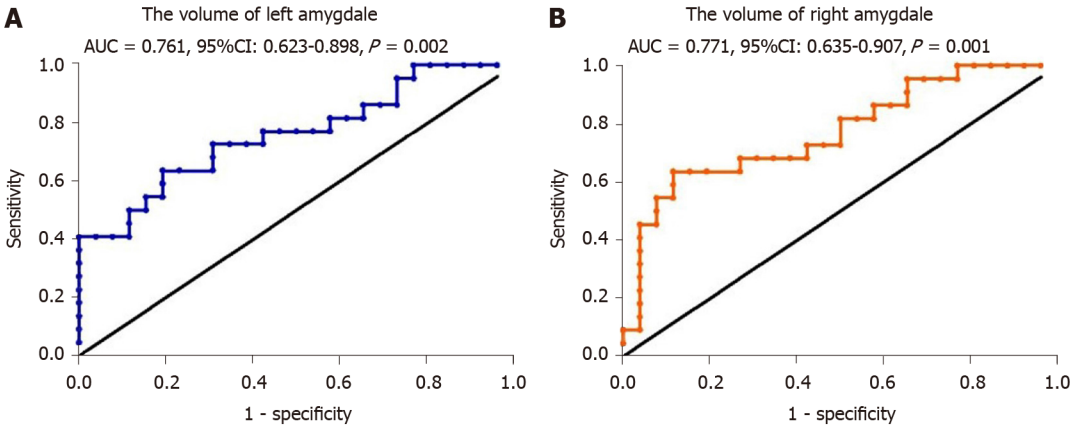

Figure 7 Receiver operating characteristic curve analysis of amygdala volume for diagnosis of Alzheimer's disease. A: Volume of left amygdala; B: Volume of right amygdala. AUC: Area under the curve.

that patients with anxiety disorder, autism, phobia, and post-traumatic stress disorder had dysfunction of amygdala[12,13].

NPI was used to evaluate the severity of mental symptoms of dementia patients and the psychological distress of caregivers in this study. Tanaka *et al*[32] reported a high frequency of apathy, depression, anxiety, and irritability in AD patients. Different from previous studies, we found that 59.1% of AD patients had neuropsychiatric symptoms, the most common of which were irritability, sleep difficulties, apathy, and hallucination. The reason may be that the patients recruited in this study were mostly mild to moderate dementia, leading to a low proportion of mental symptoms. This study also showed that the more serious dementia, the higher the proportion of patients with mental symptoms. This is consistent with previous studies[26].

There were some limitations in this study. Amygdala atrophy has also been seen in other neurodegenerative diseases, such as dementia with Lewy bodies and fronto-temporal dementia[33,34]. It is necessary to compare the amygdala volume in other types of dementia in future in order to improve the specificity of amygdala in the diagnosis of AD.

CONCLUSION

Anyway, the amygdala volumes measured by sMRI can be used for diagnosing of AD and amygdala atrophy was more serious in those with neuropsychiatric symptoms.

ARTICLE HIGHLIGHTS

Research background

Amygdala is closely related to emotion and memory. The dysfunction of amygdala plays an important role in the emotional disorder of Alzheimer's disease (AD). There are few studies evaluating the degree of atrophy of amygdala measured by structural magnetic resonance imaging (sMRI).

Research motivation

The purpose of this study is to evaluate the diagnostic value of amygdala on sMRI for AD.

Research objectives

In this study, the amygdala volumes were measured by sMRI both in AD patients and controls to evaluate the diagnostic value of amygdala. The correlation between amygdala atrophy and clinical features of AD was also analyzed.

Research methods

Twenty-two AD patients and twenty-six controls were enrolled in this study. Their amygdala volumes were measured and analyzed using a set of image analysis

software. All subjects received a cranial MRI scan and underwent neuropsychological tests. The mental and behavioral symptoms of all AD patients and the severity of the symptoms was graded.

Research results

The bilateral amygdala volumes of AD patients were significantly lower than those of the controls. The sensitivity of the left and right amygdala volumes in diagnosing AD was 80.8% and 88.5%, respectively. The amygdala atrophy was more serious in AD patients with neuropsychiatric symptoms including irritability, sleep difficulties, apathy and hallucination.

Research conclusions

In this study, we found that the bilateral amygdala volumes of AD patients were significantly smaller than those of the controls, and were positively correlated with the hippocampal volumes, consistent with previous reports. In addition, the atrophy of the amygdala was more serious in those with neuropsychiatric symptoms. This study confirmed that the amygdala is involved in the mental symptoms of AD.

Research perspectives

It is necessary to compare the amygdala volume in other types of dementia in the future, in order to improve the specificity of amygdala for the diagnosis of AD.

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