The Volume Alterations of the Amygdala in Autism Spectrum Disorder: A Meta-Analysis on MRI Study

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Abstract

Background: Due to the unclear etiology and pathogenesis of autism spectrum disorder (ASD), there is still a lack of effective drugs for prevention and treatment of ASD, which can improve the prognosis of autism through early intervention. However, the current diagnostic methods are mainly based on qualitative indicators such as behavioral standards, which cannot timely and accurately diagnose autism. A large number of studies have found abnormal amygdala volume in autism patients. This study aimed to evaluate amygdala volume in patients with ASD and elucidate the potential relationship between amygdala volume and ASD by using systematic review and meta-analysis, with a view to providing a new approach for early diagnosis of ASD.

Methods: Comprehensive electronic search in Pubmed, Web of Science, EBSCOhost, Embase, the Cochrane Review Library, CNKI and WanFang data to find original articles about the relationship between amygdala volume and the ASD. Heterogeneity across studies were assessed using I^2 and Q statistics. Random-effects model was used to estimate the odds ratios (ORs) with 95% confidence intervals (CIs). Sensitivity analyses to assess the influence of individual studies on the pooled estimate. Publication bias was investigated using funnel plots and Egger's regression test. If the funnel plot is asymmetry, the reason is distinguished by using the contour-enhanced funnel plots and trim-and-fill method.

Results: The results showed that the volume of the right amygdala significantly increased in patients with ASD (WMD: 0.137, 95% CI: [0.051, 0.222], $Z = 3.132$, $P < 0.001$). Subgroup analysis by age showed that the volume of the left amygdala significantly increased in young child patients with ASD (MD: 0.153, 95% CI: [0.025, 0.281], $Z = 2.341$, $P < 0.05$), but not change in child (MD: 0.153, 95% CI: [-0.026, 0.332], $Z = 1.672$, $P > 0.05$), adolescent (MD: 0.095, 95% CI: [-0.189, 0.379], $Z = 0.654$, $P > 0.05$) and adult (MD: 0.068, 95% CI: [-0.103, 0.240], $Z = 0.781$, $P > 0.05$) ASD patient. The volume of the right amygdala significantly increased in young child (MD: 0.174, 95% CI: [0.043, 0.304], $Z = 2.60$, $P < 0.05$) and child patients (MD: 0.192, 95% CI: [0.040, 0.343], $Z = 2.480$, $P < 0.05$) with ASD, but not change in adolescent (MD: 0.208, 95% CI: [-0.201, 0.618], $Z = 0.998$, $P > 0.05$) and adulthood patients (MD: 0.126, 95% CI: [-0.040, 0.291], $Z = 1.488$, $P > 0.05$). Subgroup analysis by gender showed that the volume of the left amygdala not change in male (MD: 0.101, 95% CI: [-0.031, 0.233], $Z = 1.498$, $P > 0.05$) and female group (MD: 0.067, 95% CI: [-0.023, 0.157], $Z = 1.452$, $P > 0.05$). The volume of the right amygdala significantly increased in female group (MD: 0.099, 95% CI: [0.019, 0.178], $Z = 2.439$, $P < 0.05$), but not change in male group (MD: 0.117, 95% CI: [-0.014, 0.248], $Z = 1.755$, $P > 0.05$).

Conclusions: The volume of the amygdala significantly increased in young children with ASD. These findings suggest that the volume of the amygdala in young children might be a potential early auxiliary imaging diagnosis method of ASD.

Lay Summary

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1 Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and communication as well as repetitive behaviors. ASD affects 14.7 per 1,000 children in the United States[1] and 4.1 per 1,000 in China[2]. Besides, ASD is more prevalence in males than in females, with reported ratios ranging from 2:1 to 5:1[3, 4]. Early diagnosis of ASD is of paramount importance as it opens the road to early intervention, which is associated with better prognosis. However, most children with ASD are not diagnosed until preschool or school age, which means they are missing the most opportune time to be getting treatment. Therefore, it is very important to find a simple and non-invasive diagnostic method.

Although the precise neurobiological mechanism of behavioral social problems in autism is not yet fully understood, one influential hypothesis is that abnormal in the structures and/or functions of the "social brain area", particularly the prefrontal cortex, middle temporal gyrus and amygdala, underlie social malfunctioning in individuals with ASD[5–7]. As a hub in the "social brain area", the amygdala, which was located within the anterior medial portion of the brain's temporal lobe and included in the limbic system, maintains diverse connections with the neocortex, basal ganglia, hippocampus, thalamus and other brain cortical areas via a network of white matter (WM) tracts[8], responsible for information processing that subserve emotional learning, social cognition, and social interaction[9]. So, the emotional, behavioral, and social impairments in autism may be associated with the structural and/or functional abnormalities of the amygdala. MRI study of the amygdala in children with social interaction problems has found that social interaction problems are associated with the enlargement of the amygdala[10–12]. The size of the amygdala in autistic children increases during young childhood and does not change significantly in older children. In adults it shrinks. This is different from the amygdala development in healthy children[13, 14]. Many studies have shown that structural and/or functional abnormalities in the amygdala contribute to social dysfunction in ASD[8, 12, 13, 15–17]. The magnetic resonance imaging (MRI) technique, with its advantages of noninvasiveness, high spatial resolution, and improved contrast for soft tissues, has been widely applied for studying the brain diseases. Compare the volume change of the amygdala by MRI may provide a novel approach for the early diagnosis of autism, which is the key for early behavioral interference and individualized therapy. A considerable body of MRI studies have been conducted and found volume abnormal of amygdala in autism, but the results were not consistent. Some studies have found decreased volumes of amygdala in autism[18, 19], while others have found increased volumes in autism[2, 20]; and some studies didn't find differences[21, 22]. To evaluate more precisely the potential relationship between amygdala volume and the autism, further compare the differences of amygdala volume between different ages and genders, we hereby report on a meta-analysis using all available published data.

2 Materials And Methods

Search Strategies

A computerized search of Pubmed, Web of Science, EBSCOhost, Embase, the Cochrane Review Library, China National Knowledge Infrastructure (CNKI) and WanFangdata up to Nov 2020 was conducted using the following search strategy: ("autism" or "ASD" or "autism spectrum disorder"), and ("amygdala"), and ("MRI" or "Magnetic Resonance Imaging"). The search was restricted to English and Chinese language publications. A manual search of the references in the retrieved articles and relevant reviews was also conducted. A flowchart of information pertaining to identification, screening, eligibility, and the final selected datasets was constructed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[23].

Inclusion and Exclusion Criteria

Studies comparing the volume of the amygdala between patients with autism and control subjects were included. The inclusion criteria were (1) Case-control study design; (2) demonstrated specific diagnostic criteria of autism; and (3) The means and standard deviations of amygdala volume (left or right) which derived from structural MRI was available in the report. The major criteria for exclusion were: (1) duplication of earlier publications (for studies using the same sample in different publications, only the most complete information was included following careful examination), (2) Animal studies, postmortem and voxel-based morphometry analyses were excluded. (3) The data of amygdala volume comes from a public database. (4) Unpublished papers, dissertations, editorials, conference articles, reviews and book chapters.

Data Extraction

The full texts of potentially relevant studies were then retrieved and assessed for eligibility by established criteria detailed above. The following data were also collected: author, year of publication, diagnostic criteria, country, sample size, mean age, gender, measuring method, and the mean, standard deviation of amygdala volume. All data were evaluated independently by two authors. Any disagreement about literature search, study selection, and data extraction was resolved by consensus under the guidance of the senior authors.

Data Analysis

All statistical analyses were performed using Weighted Mean Differences (WMD) methodology in STATA 15.0 (StataCorp, College Station, TX, United States). We used 95% confidence interval (CI) to gauge the precision of the summary estimates. Heterogeneity among the included studies was assessed using the I^2 and Q statistic. A random-effects model or fixed-effects model was used to calculate the pooled WMD in the presence or absence of heterogeneity, respectively. The significance of the pooled MD was determined through a Z-test, and $p < 0.05$ was considered to be statistically significant. Publication bias was investigated using funnel plots and Egger's regression test. The principle of Egger's regression test is the effect value that calculates each research, variance and standard error, with standard independent variable, effect value is linear regression. Its intercept represents the degree of asymmetry, and the greater the deviation from 0, the more pronounced the degree of asymmetry. Egger's regression test and funnel plot were used to judge the publication bias from both quantitative and qualitative aspects. If the funnel plot is asymmetry, the reason for the asymmetry is distinguish by using the contour-enhanced funnel plots [24, 25] and trim-and-fill method[26, 27]. We also conducted sensitivity analysis to test the robustness of associations by sequentially omitting each of the included studies one at a time. To further explore the potential relationship between amygdala volume and ages and genders of autism, subgroup analyses were performed.

3 Results

3.1 Literature Search and Study Characteristics

We used several search criteria to include or exclude reported studies on the relationship between the volume of the amygdala and autism (Fig. 1). A total of 28 studies[2, 10, 13, 18–22, 28–47] (1,011 cases and 823 controls) concerning the volume of the amygdala were included in the final evaluation (Table 1).

Table 1
Main characteristics of datasets included in this meta-analysis

No.	First Author	Year	Country	Diagnostic criteria	Sample size	Gender	Age (year)	MRI techniques/ Segmentation	Total brain (cm3)	Amygdala volume (cm3)	
										Left	right
1	Haznedar	2000	American	DSM-IV	ASD (n = 17,M/F:15/2)	MIX	27.7 ± 11.3	1.5 T GE Signa/Manual	1314 ± 122	1.21 ± 0.22	1.217 ± 0.267
					TDC (n = 31,M/F:15/2)		28.8 ± 9.4		1304 ± 178	1.22 ± 0.22	1.215 ± 0.258
2	Pierce	2001	American	DSM-IV	ASD (n = 7)	M	21–41	1.5 T GE Signa/Manual	Not report	0.92 ± 0.13	0.87 ± 0.12
					TDC (n = 8)		20–42		Not reportNot report	1.09 ± 0.13	1.01 ± 0.11
3	Sparks	2002	American	DSM-IV, ADOS-G	All ASD (n = 45)	MIX	3.17–4.50	1.5 T GE Signa/Automated	1191.87 ± 94.71	1.25 ± 0.23	1.19 ± 0.26
					All TDC (n = 26)	MIX	3.0–4.67		1085.87 ± 109.2	1.10 ± 0.20	1.02 ± 0.23
					ASD(n = 38)	M				1.25 ± 0.23	1.20 ± 0.25
					TDC (n = 18)					1.08 ± 0.20	0.94 ± 0.19
					ASD (n = 7)	F				1.20 ± 0.22	1.14 ± 0.29
					TDC (n = 8)					1.16 ± 0.21	1.18 ± 0.22
4	Rojas	2004	American	DSM-IV	ASD (n = 15)	MIX	19–47	1.5 T GE Signa/Manual	1237.57 ± 166.27	2.46 ± 0.41	2.57 ± 0.43
					TDC (n = 17)		37–51		1257.87 ± 87.69	2.57 ± 0.24	2.60 ± 0.30
5	*Schumann	2004	American	ADI-R and ADOS-G	All ASD (n = 63)	M	12.7 ± 3.5	1.5 T and 3.0 T GE Signa/Manual	1214 ± 119.3	2.05 ± 0.22	2.13 ± 0.23
					All TDC (n = 22)	M	13.1 ± 3.1		1190 ± 77	1.94 ± 0.30	1.96 ± 0.30
					ASD (n = 30)	M	7.5–12.5			2.04 ± 0.25	2.10 ± 0.21
					TDC (n = 11)	M	7.5–12.5			1.77 ± 0.18	1.81 ± 0.18
					ASD (n = 33)	M	12.75–18.5			2.05 ± 0.23	2.16 ± 0.25
					TDC (n = 11)	M	12.75–18.5			2.11 ± 0.25	2.10 ± 0.22
6	Boucher	2005	UK	WADIC and DSM-IV	ASD (n = 10)	M	23 ± 9	1.5 T GE Signa/Automated	1215.75 ± 37.55	2.82 ± 0.14	2.98 ± 0.21
					TDC (n = 10)		24 ± 2		1127.25 ± 18.41	2.34 ± 0.1	2.41 ± 0.12
7	Nacewicz	2006	American	ADI-R	ASD (n = 16)	M	14.3 ± 4.7	3.0-T GE Signa/Automated	Not report	1.78 ±	1.770 ± 0.123

										0.13	
					TDC (n = 14)		13.7 ± 3.9		Not report	1.92 ± 0.17	1.921 ± 0.186
8	Palmen	2006	Netherlands	DSM-IV	ASD (n = 42)	MIX	15.6 ± 5.25	1.5 T GE Signa/Manual	1408.36 ± 99.32	1.32 ± 0.38	1.51 ± 0.27
					TDC (n = 42)		15.33 ± 5.40		1345.59 ± 78.77	1.29 ± 0.30	1.53 ± 0.29
9	Corbett	2009	American	DSM-IV, ADOS	ASD (n = 12)	MIX	9.63 ± 1.48	1.5 T GE Signa/Manual	1299.78 ± 47.15	1.76 ± 0.31	1797.38 ± 356.30
					TDC (n = 15)		9.63 ± 1.47		1247.05 ± 79.91	1.81 ± 0.22	1811.62 ± 201.91
10	Hazlett	2009	American	ADI-R and ADOS-G	ASD (n = 63)	M	2.8 ± 0.4	1.5 T GE Signa/Manual	Not report	1.92 ± 0.03	2.03 ± 0.03
					TDC (n = 31)		2.6 ± 0.6		Not report	1.58 ± 0.05	1.67 ± 0.05
11	*Schumann	2009	American	ADI-R and DSM-IV	All ASD (n = 50)	MIX		1.5 T GE Signa/Manual	Not report	1.66 ± 0.24	1.72 ± 0.23
					All TDC (n = 39)	MIX			Not report	1.57 ± 0.24	1.61 ± 0.24
					ASD (n = 38)	M	3.0 ± 0.76			1.75 ± 0.20	1.81 ± 0.19
					TDC(n = 28)	M	2.83 ± 0.59			1.69 ± 0.15	1.73 ± 0.16
					ASD (n = 12)	F	4.67 ± 0.51			1.40 ± 0.14	1.47 ± 0.10
					TDC(n = 11)	F	3.08 ± 0.53			1.26 ± 0.07	1.31 ± 0.07
12	Dziobek	2010	Germany	ADI-R and DSM-IV	ASD (n = 27)	MIX	42.0 ± 11.3	not report/Automated	Not report	1.00 ± 0.15	1.04 ± 0.19
					TDC (n = 29)		44.9 ± 14.6		Not report	1.04 ± 0.15	1.04 ± 0.22
13	Groen	2010	Netherlands	DSM-IV	ASD (n = 23)	MIX	15.15 ± 1.86	1.5-T Siemens/Automated	1683.26 ± 210.87	1.69 ± 0.20	1.756 ± 0.200
					TDC (n = 29)		15.65 ± 1.66		1637.9 ± 185.14	1.59 ± 0.16	1.629 ± 0.144
14	kim	2010	Korea	DSM-IV	ASD (n = 31,M/F:24/7)	MIX	6–7	1.5 T GE Signa/Manual	Not report	1.82 ± 0.20	1.68 ± 0.25
					TDC (n = 20,M/F:12/8)		6–7		Not report	1.60 ± 0.30	1.45 ± 0.27
15	O'Brien	2010	UK	DSM-IV	All ASD (n = 22)	MIX		1.5 T GE Signa/Manual	Not report	2.74 ± 0.47	2.64 ± 0.44
					All TDC (n = 22)				Not report	2.7 ± 0.3	2.65 ± 0.30
					ASD (n = 12)		13 ± 2			2.6 ± 0.5	2.5 ± 0.5
					TDC (n = 10)		13 ± 2			2.7	2.7 ± 0.3

									± 0.3		
					ASD (n = 10)		35 ± 10		2.9 ± 0.4	2.8 ± 0.3	
					TDC (n = 12)		32 ± 8		2.7 ± 0.3	2.6 ± 0.3	
16	Cheung	2011	China	ADI-R and DSM-IV	ASD (n = 36,M/F:30/6)	MIX	11.4 ± 2.7	1.5 Tesla system/Automated	1450 ± 105	2.1 ± 0.3	3.4 ± 0.4
					TDC (n = 55,M/F:47/8)		10.7 ± 2.7		1440 ± 108	2.1 ± 0.2	3.4 ± 0.4
17	Murphy	2011	UK	ICD-10 and ADI-R	ASD (n = 32,M/F:30/2)	MIX	23 ± 11	1.5 Tesla system/Manual	1117.5 ± 134.12	2.80 ± 0.34	2.78 ± 0.36
					TDC (n = 32,M/F:31/1)		23 ± 11		1095.83 ± 104.8	2.64 ± 0.30	2.52 ± 0.26
18	Semrud	2013	US and Canada	DSM-IV	ASD (n = 29)	MIX	12.8 ± 2.6	3T GE Signa/Automated	973 ± 0.16	1.42 ± 0.04	1.84 ± 0.30
					TDC (n = 31)		13.1 ± 2.7		968.8 ± 0.13	0.94 ± 0.07	0.83 ± 0.06
19	Barnea	2014	US	ADI-R and ADOS	ASD (n = 15)	M	$10.6 (8-12)$	1.5T MR/Manual	Not report	2.65 ± 0.23	2.43 ± 0.12
					TDC (n = 22)		$10.6 (7-13)$		Not report	2.66 ± 0.20	2.44 ± 0.10
20	Maier	2015	Germany	ICD-10 and DSM-IV	ASD (n = 30)	MIX	35.4 ± 9.1	3T Tim-trio magnetom/Manual	Not report	1.31 ± 0.13	1.36 ± 0.17
					TDC (n = 30)		35.5 ± 8.3		Not report	1.27 ± 0.18	1.28 ± 0.14
21	*Trontel	2015	American	ADI-R, ADOS-G, DSM-IV	ASD (n = 56)	M	10.4 ± 4.1	Siemens Trio 3.0 T/Automated	Not report	1.8 ± 0.27	1.77 ± 0.27
					TDC (n = 31)		12.0 ± 4.2		Not report	1.7 ± 0.2	1.7 ± 0.2
22	Chen	2016	China	DSM-IV and CCMD-3	ASD (n = 16,M/F:11/5)	MIX	2.81 ± 0.91	1.5-T GE Signa/Automated	Not report	1.68 ± 0.14	1.82 ± 0.15
					TDC (n = 18,M/F:11/7)		2.51 ± 0.50		Not report	1.58 ± 0.11	1.73 ± 0.10
23	Gibbard	2017	UK	ADOS	ASD (n = 25)	MIX	23.22 ± 4.05	1.5 T Siemens/Automated	1320.3 ± 104.95	1.87 ± 0.30	1.81 ± 0.32
					TDC (n = 26)		24.73 ± 4.10		1304.76 ± 121.68	1.79 ± 0.26	1.60 ± 0.29
24	Herrington	2017	USA	ADOS-2, ADI-R	ASD (n = 24,M/F:10/14)	MIX	11.9 ± 2.7	Not report/Automated	1232.09 ± 124.69	1.06 ± 0.27	1.104 ± 0.259
					TDC (n = 37,M/F:15/22)		11.6 ± 2.8		1198.12 ± 154.82	1.03 ± 0.17	1.041 ± 0.210
25	Shou	2017	China	ICD- 10	ASD (n = 14,M/F:12/2)	MIX	4.1 ± 0.72	GE Discovery MR750 3.0T/Manual	1244.47 ± 164.14	1.39 ± 0.18	Not report
					TDC (n = 14,M/F:10/4)		4.5 ± 0.74		1273.30 ± 88.34	1.27 ± 0.11	Not report
26	Lucibello	2018	Italy	ADI-R, ADOS-G	ASD (n = 25,M/F:22/3)	MIX	4.0 ± 0.92	1.5 T PHILIPS/Automated	Not report	1.33 ± 0.17	1.542 ± 0.214

					TDC (n = 28,M/F:21/7)		4.42 ± 0.75		Not report	1.31 ± 0.19	1.490 ± 0.227
27	Zhu	2018	China	DSM IV	ASD (n = 39,M/F:35/4)	MIX	2.15 ± 0.70	3.0T MR/Manual	Not report	1.04 ± 0.41	1.09 ± 0.38
					TDC (n = 24,M/F:18/6)		3.64 ± 1.08		Not report	0.67 ± 0.25	0.75 ± 0.19
28	*Nordahl	2020	American	ADI-R, ADOS-G	All ASD (n = 226)	MIX		3T Siemens Trio/Manual	Not report	1.56 ± 0.18	1.73 ± 0.19
					All TDC (n = 120)	MIX			Not report	1.51 ± 0.15	1.64 ± 0.16
					ASD (n = 73)	F	3.25 ± 0.53			1.47 ± 0.17	1.64 ± 0.19
					TDC (n = 57)	F	3.16 ± 0.5			1.45 ± 0.13	1.57 ± 0.16
					ASD (n = 153)	M	3.24 ± 0.57			1.61 ± 0.16	1.78 ± 0.17
					TDC (n = 63)	M	3.07 ± 0.49			1.56 ± 0.15	1.70 ± 0.14

3.2 The volume of amygdala in autism versus control group

3.2.1 The volume of left amygdala

28 studies (included 1011 ASD and 823 controls) were used in this analysis. These studies had significant heterogeneity ($I^2 = 96.8\%$, 95% CI: [82.3%, 98.7%]; $H = 5.582$, 95% CI: [2.374, 8.836], $\tau^2 = 0.0406$), so a random-effect model was used to calculate pooled WMD. Forest plot (Fig. 2A) showed that the diamond was on the right side of the vertical line and did not intersect with the line, which demonstrates a significantly increase the volume of the left amygdala in patients with ASD compared to control (WMD: 0.095, 95% CI: [0.017, 0.174], $Z = 2.379$, $P < 0.05$). The funnel plot (Fig. 2B) was asymmetrical, as assessed by visual inspection and Egger's meta-regression analysis ($p < 0.001$, 95% CI: [-7.79, -2.63], Fig. 2C). To differentiating asymmetry due to publication bias from that due to other factors, the contour-enhanced funnel plot (Fig. 2D) was used. The missing data were found distributed in left side (shaded area, statistical significance), and no additional studies were found by the application of the trim-and-fill method, hence asymmetry might have been caused by several factors (such as true heterogeneity) and not by publication bias. In addition, we found that the asymmetry of funnel plot was caused by 4 articles[28, 37, 39, 43]. When these articles were removed, the heterogeneity was significantly reduced ($I^2 = 54.1\%$) and the diamond was extremely close to the vertical line (WMD: 0.042, 95% CI: [0.008, 0.075]). Sensitivity analysis suggested that the results were affected by Hazlett's study, when removed the article, the diamond was intersect with the vertical line.

3.2.2 The volume of right amygdala

27 studies (included 996 ASD and 809 controls) were used in this analysis. These studies had significant heterogeneity ($I^2 = 96.2\%$, 95% CI: [79.7%, 98.5%]; $H = 5.127$, 95% CI: [2.218, 8.075], $\tau^2 = 0.0469$), so a random-effect model was used to calculate pooled WMD. Forest plot (Fig. 3A) showed that the diamond was on the right side of the vertical line and did not intersect with the line, which demonstrates a significantly increase the volume of the right amygdala in patients with ASD compared to control (WMD: 0.137, 95% CI: [0.051, 0.222], $Z = 3.132$, $P < 0.001$). The funnel plot (Fig. 3B) was asymmetrical, as assessed by visual inspection of the plot and by Egger's meta-regression analysis ($p = 0.016 < 0.05$, 95% CI: [-6.30, -0.75], Fig. 3C). To differentiating asymmetry due to publication bias from that due to other factors, the contour-enhanced funnel plot (Fig. 3D) was used. The missing data were found distributed in left side (shaded area, statistical significance), and no additional studies were found by the application of the trim-and-fill method, hence asymmetry might have been caused by several factors (such as true heterogeneity) and not by publication bias. We also found that the asymmetry of funnel plot was caused by 4 articles[28, 37, 39, 43]. When these articles were removed, the heterogeneity was significantly reduced ($I^2 = 63.0\%$) and the diamond was still on the right side of the vertical line and did not intersect with the line (WMD: 0.061, 95% CI: [0.022, 0.099]). Sensitivity analysis suggested that the results were robust and reliable.

3.3 subgroup analysis

3.3.1 subgroup analysis by age

To explore the relationship between age and amygdala volume, a subgroup analysis by age was conducted. We divided all studies into five groups according to age: (1) young children (0–6 years), (2) children (6–12 years), (3) adolescent (12–18 years), (4) adult (> 18 years) and (5) other group. Our results show that the volume of the left amygdala (Fig. 4A) significantly increase in young child patients with ASD (MD: 0.153, 95% CI: [0.025, 0.281], $Z = 2.341$, $P < 0.05$), but not change in child (MD: 0.153, 95% CI: [-0.026, 0.332], $Z = 1.672$, $P > 0.05$), adolescent (MD: 0.095, 95% CI: [-0.189, 0.379], $Z = 0.654$, $P > 0.05$) and adult (MD:

0.068, 95% CI: [-0.103, 0.240], $Z = 0.781$, $P > 0.05$) ASD patient. The volume of the right amygdala (Fig. 4B) significantly increased in young child (MD: 0.174, 95% CI: [0.043, 0.304], $Z = 2.60$, $P < 0.05$) and child patients (MD: 0.192, 95% CI: [0.040, 0.343], $Z = 2.480$, $P < 0.05$) with ASD, but not change in adolescent (MD: 0.208, 95% CI: [-0.201, 0.618], $Z = 0.998$, $P > 0.05$) and adult patients (MD: 0.126, 95% CI: [-0.040, 0.291], $Z = 1.488$, $P > 0.05$).

3.3.2 subgroup analysis by gender

To explore the relationship between sex and amygdala volume, a subgroup analysis by gender was conducted. We divided the patients into three groups according to sex: (1) male, (2) female and (3) other unclassified group. Our results show that the volume of the left amygdala not change in male (MD: 0.101, 95% CI: [-0.031, 0.233], $Z = 1.498$, $P > 0.05$) and female (MD: 0.067, 95% CI: [-0.023, 0.157], $Z = 1.452$, $P > 0.05$) group (Fig. 5A). The volume of the right amygdala significantly increased in female group (MD: 0.099, 95% CI: [0.019, 0.178], $Z = 2.439$, $P < 0.05$), but not change in male group (MD: 0.117, 95% CI: [-0.014, 0.248], $Z = 1.755$, $P > 0.05$). (Fig. 5B)

4 Discussion

The present meta-analysis demonstrates that the volume of the right amygdala significantly increased in patients with ASD. The structural abnormality of the right amygdala may lead to less microstructural integrity in the right amygdala-cortical connections, which are associated with an increased severity of the autism phenotype [44]. The same results were found on the left side, but the results were not robust and greatly affected by heterogeneity.

Further subgroup analysis by age showed that the volume of the left and right amygdala in patients with ASD significantly increased in young child[34], but not change in adolescence and adulthood compare to control. The amygdala in children with autism is initially larger than normal but does not undergo the age-related increase in volume that takes place in typically developing children[48]. The development trajectory of amygdala in ASD drastically deviated from the typical developmental. Anomalous enlargement of the amygdala may be caused by an excessive increase in the number of neurons. Avino et al.'s[15] study found that individuals with autism initially have excess numbers of mature neurons in the amygdala during early childhood, followed by a marked decline beginning in adolescence. Schumann et al.'s [11] research found that the autistic amygdala appears to undergo an abnormal pattern of postnatal development that includes early enlargement and ultimately a reduced number of neurons. Subgroup analysis by gender showed that the volume of the right amygdala was only significantly increased in female of ASD, not in the male. This may be because female with ASD have higher rates of mood disorders [11] and internalizing problems[51] than male counterparts, so that females with ASD may exhibit more severe social [13, 46, 52, 53]. However, due to female individuals being diagnosed less frequently than male individuals at a roughly 1 to 4 rates, female patients are less common, only 3 studies were included in female analysis (14 studies were not reported the volume of amygdala by gender), the results need to be further strengthened by including more literature.

Our results did not entirely consistent with previous analysis[54], which not found significant difference in size of the amygdala between ASD and control. Compared to Stanfield's reports[54], our study had greater statistical power, 28 studies were including in our study and 6 studies in Stanfield et al. Additionally, we performed a sensitivity analysis to ensure the robustness and reliability of the results. However, our research also has some limitations: (1) The number of original studies and the sample size included in the meta-analysis are relatively small, especially in the subgroup analysis. Future studies on gender and age are needed to further corroborate our findings. (2) Heterogeneity, which can greatly affect the conclusions of meta-analysis, was high in our analysis. In addition to age and gender mentioned above, the other influencing factors such as clinical subtypes of ASD, co-occurring other psychopathology disorder and pharmacological interventions are also contributing to the high heterogeneity of ASD[55, 56]. First, ASD is a heterogeneous neurodevelopmental disorder, including autism, Asperger's Syndrome (AS), Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS), and other subtypes[57]. Both phenotypic heterogeneity and variability in clinical presentation of symptoms of each subtype may contribute to the high heterogeneity[58]. Second, co-occurring other psychopathology disorder is also the source of heterogeneity. Across childhood and adolescence, an estimated 70–80% of individuals with ASD have at least one co-occurring psychiatric condition, and approximately 40% have 2 or more[59, 60]. Co-occurring other psychopathology disorder such as anxiety and attention-deficit/hyperactivity disorder (ADHD) may affect the patterns of amygdala development [40, 61]. Third, pharmacological interventions are also the reasons for the increase in heterogeneity. Despite a lack of pharmacological treatment options for ASD core symptoms, the prevalence of psychopharmacotherapy and polypharmacy in ASD patients is considerable, which is probably due to the treatment of non-core ASD symptoms and psychiatric comorbidities. Prior to pharmacological interventions likely altering neural circuitry and possibly masking the true underlying neural basis of ASD. However, there are simply not enough studies to carry out the corresponding subgroup analysis. (3) Asymmetric funnel plots were found in our analysis. Contour-enhanced funnel plots were used to identify sources of asymmetry. Our study might suggest that the asymmetry of funnel plot was caused by significant heterogeneity which derived from 4 articles[28, 37, 39, 43], rather than publication bias. The heterogeneity of these studies is closely related to the effect size, and these studies have larger effect size (0.334–1.015) than other studies (-0.17-0.26).

5 Conclusion

In conclusion, our results show that the volume of the amygdala significantly increased in young children with ASD. These findings suggest that the volume of the amygdala in young children might be a potential early auxiliary imaging diagnosis method of ASD.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors. No informed consent was required as this article is a review and no individual participants have identifying information.

Consent for publication

Not applicable

Competing interests

The authors declare that there are no competing interests.

Availability of data and materials

The data that support the findings of this study are available from the first author upon reasonable request.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Contributions

Yunhua Chen and Xiaoli Zhen independently searched the literature, extracted the data and analyzed the data. Yunhua Chen completed the first draft of the paper, and Professor Min Wen and Professor Bo Zhou revised and polished the paper. Xue Wang, Ling Yao, Jinggang Peng, Wanxia Liu, Yibu Liu, Xuehui Yan, Yi Zhang assisted. All authors read and approved the final manuscript.

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Figures

Figure 1

PRISMA 2009 Flow Diagram

Figure 2

28 studies (included 1011 ASD and 823 controls) were used in this analysis. These studies had significant heterogeneity ($I^2 = 96.8\%$, 95% CI: [82.3%, 98.7%]; $H = 5.582$, 95% CI: [2.374, 8.836], $\tau^2 = 0.0406$), so a random-effect model was used to calculate pooled WMD. Forest plot (Fig 2A) showed that the diamond was on the right side of the vertical line and did not intersect with the line, which demonstrates a significantly increase the volume of the left amygdala in patients with ASD compared to control (WMD: 0.095, 95% CI: [0.017, 0.174], $Z = 2.379$, $P < 0.05$). The funnel plot (fig 2B) was asymmetrical, as assessed by visual inspection and Egger's meta-regression analysis ($p < 0.001$, 95% CI: [-7.79, -2.63], fig 2C). To differentiating asymmetry due to publication bias from that due to other factors, the contour-enhanced funnel plot (fig 2D) was used.

Figure 3

27 studies (included 996 ASD and 809 controls) were used in this analysis. These studies had significant heterogeneity ($I^2 = 96.2\%$, 95% CI: [79.7%, 98.5%]; $H = 5.127$, 95% CI: [2.218, 8.075], $\tau^2 = 0.0469$), so a random-effect model was used to calculate pooled WMD. Forest plot (Fig 3A) showed that the diamond was on the right side of the vertical line and did not intersect with the line, which demonstrates a significantly increase the volume of the right amygdala in patients with ASD compared to control (WMD: 0.137, 95% CI: [0.051, 0.222], $Z = 3.132$, $P < 0.001$). The funnel plot (fig 3B) was asymmetrical, as assessed by visual inspection of the plot and by Egger's meta-regression analysis ($p = 0.016 < 0.05$, 95% CI: [-6.30, -0.75], fig 3C). To differentiating asymmetry due to publication bias from that due to other factors, the contour-enhanced funnel plot (fig 3D) was used.

Figure 4

To explore the relationship between age and amygdala volume, a subgroup analysis by age was conducted. We divided all studies into five groups according to age: (1) young children (0-6 years), (2) children (6-12 years), (3) adolescent (12-18 years), (4) adult (>18 years) and (5) other group. Our results show that the volume of the left amygdala (fig 4A) significantly increase in young child patients with ASD (MD: 0.153, 95% CI: [0.025, 0.281], $Z = 2.341$, $P < 0.05$), but not change in child (MD: 0.153, 95% CI: [-0.026, 0.332], $Z = 1.672$, $P > 0.05$), adolescent (MD: 0.095, 95% CI: [-0.189, 0.379], $Z = 0.654$, $P > 0.05$) and adult (MD: 0.068, 95% CI: [-0.103, 0.240], $Z = 0.781$, $P > 0.05$) ASD patient. The volume of the right amygdala (fig 4B) significantly increased in young child (MD: 0.174, 95% CI: [0.043, 0.304], $Z = 2.60$, $P < 0.05$) and child patients (MD: 0.192, 95% CI: [0.040, 0.343], $Z = 2.480$, $P < 0.05$) with ASD, but not change in adolescent (MD: 0.208, 95% CI: [-0.201, 0.618], $Z = 0.998$, $P > 0.05$) and adult patients (MD: 0.126, 95% CI: [-0.040, 0.291], $Z = 1.488$, $P > 0.05$).

Figure 5

To explore the relationship between sex and amygdala volume, a subgroup analysis by gender was conducted. We divided the patients into three groups according to sex: (1) male, (2) female and (3) other unclassified group. Our results show that the volume of the left amygdala not change in male (MD: 0.101, 95% CI: [-0.031, 0.233], $Z = 1.498$, $P > 0.05$) and female (MD: 0.067, 95% CI: [-0.023, 0.157], $Z = 1.452$, $P > 0.05$) group (fig 5A). The volume of the right amygdala significantly increased in female group (MD: 0.099, 95% CI: [0.019, 0.178], $Z = 2.439$, $P < 0.05$), but not change in male group (MD: 0.117, 95% CI: [-0.014, 0.248], $Z = 1.755$, $P > 0.05$). (fig 5B)