Developmental brain structural atypicalities in autism: A voxel-based morphometry analysis

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Abstract

Background

Accumulating structural Magnetic Resonance Imaging (sMRI) studies have showed atypicalities in developmental changes of structural regional brain in autism, with largely inconsistent results.

Methods

The current study investigated the brain structural abnormal features of autistic individuals aged 6~30 years. We included 52 autism individuals and 50 age, gender, and IQ matched typically developing individuals (TD), who were divided into three groups: childhood (6-12 years old), adolescent (13-18 years old) and adulthood (19-30 years old). Whole brain volume and Voxel-Based Morphometry (VBM) analyses were employed on the sMRI data collected from our participants.

Results

We found no significant difference in the volume of whole brain, gray matter and white matter between autism and TD groups of the three age groups. For VBM analyses, the volumes of gray matter in right superior temporal gyrus and right inferior parietal lobule in children autism group were smaller than those in TD group; the volume of gray matter in left inferior parietal lobule in adolescent autism group was larger than that in TD group; the volume of gray matter in right middle occipital gyrus in adult autism group was larger than that in TD group, and the gray matter in left posterior cingulate gyrus was smaller than that in TD group.

Conclusions

Findings suggest autism individuals showed different atypical brain regions of gray matter volume in childhood, adolescent, and adulthood relative to their normal peers respectively, indicating that it is essential to take developmental perspectives into consideration when exploring brain structural abnormalities in autism.

Background

Autism is a neurodevelopmental disorder that begins before 3 years old. Its main clinical manifestations are social communication and communication impairments, restricted and repetitive behaviors and restricted interests [1]. The prevalence of autism is increasing year by year, it was reported by the Centers for Disease Control and Prevention that the prevalence of autism spectrum disorders, including autism, was as high as 1/54, seriously impairing the social function of patients and imposing a heavy burden on their families and society [2]. Previous studies have suggested that the etiology of autism might be highly

related with the interaction effects between genetic and environmental factors, but its pathological mechanism is still not clear [3, 4]. The brain structural developmental atypicalities caused by genetic and environmental factors might be largely involved in the neuro mechanisms of autism, as shown in previous studies [5, 6].

Structural Magnetic Resonance Imaging (sMRI) studies have reported atypical whole brain volume in autism, with largely inconsistent findings [7]. For example, Aylward, Minshew [8] showed that the whole brain volume of autism children increased by about 5%, but the whole brain volume of adolescents and adults showed no difference relative to TD. However, another study reported that the total brain volume increased by 5-7% during adolescence [5]. Moreover, Riddle, Cascio [7] included participants ranging from children to adults, and found that the whole brain volume of autistic individuals showed no difference compared with TD. Regarding the total brain gray matter volume in autism, Freitag, Luders [9] found that the gray matter volume of adolescents in the autism group increased compared with the TD group. Mitelman, Bralet [10] found that the volume of gray matter in autistic adults also increased relative to TD adults. Some studies also reported autistic symptom correlation of the structural atypicalities in autism. Mitchell, Reiss [11] found that the reduction in the volume of the dorsolateral prefrontal cortex in autism was correlated with social and communication scores of Autism Diagnostic Observation Schedule (ADOS). Hollander, Anagnostou [12] reported that the increase in the volume of the right caudate nucleus in autism adults was positively correlated with the Restricted and Repetitive Behaviors (RRB) score of Autism Diagnostic Interview (ADI) in autism.

The inconsistencies in results of sMRI studies in autism might be correlated with several factors: first, the age ranges of the participants included in those studies were inconsistent, including individuals covering childhood, adolescence and adulthood [13]. These inconsistencies made it more difficult to summarize the atypical structural brain areas at different developmental stages. Second, these inconsistencies in brain structure atypicalities in autism were also related to gender and IQ of the subjects [14].

In the current study, we included cross-sectional structural MRI data of autism participants and TD aged 6-30 years old to explore the age-related differences of whole brain volume and the gray matter volume between the two groups. Separate analyses were conducted among three developmental stages: late childhood (6-12 years), adolescence (13-18 years) and adulthood (19-30 years old). We predicted that probably no brain structural abnormalities would be found between autism and TD groups among the whole-age group (i.e. 6-30 years old). However, specific atypical structural regions in childhood, adolescent, and adulthood would be identified in autism relative to TD.

Methods

Participants

Fifty-two high-functioning autism individuals aged 6-30 years old meeting DSM-IV criteria for autism were recruited through the outpatient clinic at the Peking University Sixth Hospital from March 2013 to January

2017. The diagnosis was established by two deputy chief physicians or chief physicians using the Diagnostic and Statistical Manual-IV (DSM-IV). Fifty TD individuals aged 6-30 years old were enrolled through advertising from January 2016 to January 2017. All participants were right-handed and had an intelligence quotient (IQ) greater than 70 measured with either the Chinese-Wechsler Intelligence Scale for Children (C-WISC) or the Wechsler Adult Intelligence Scale-Revised in China (WAIS-RC) [15, 16]. Participants were excluded if they had mental disorders (other than the autistic disorder in autism group), suffered from severe physical diseases, neurological diseases and brain trauma, have used any psychotropic drugs, were unable to cooperate with examination, or had metal implants including non-removable dentures. All participants were divided into three age groups: 6-12, 12-18, and 18-30 years old. Age, gender, and IQ were matched for autism and TD groups in each age group (see Table 1 for Demographic Information). This study is approved by the Ethics Committee of the Sixth Hospital of Peking University. Children and their guardians understand the content and purpose of the study and agree to participate in the study. Guardians have signed the written informed consent. Adult subjects understand the content and purpose of the study, agree to participate in the study and have signed the written informed consent themselves.

Table 1
Demographic information.

Group	ASD (n=52) Mean ± SD	TD (n=50) Mean ± SD	<i>t/x²</i>	<i>P</i>
6-12 years				
Age	9±2.0	9±1.7	-0.278	0.783
Full IQ	102.4±19.6	109.7±12.9	-1.479	0.147
Gender (male/female)	21/3	11/8	3.451	0.063
13-18 years				
Age	14.1±1.2	14.7±2.1	-1.051	0.301
Full IQ	108.7±13.1	116.5±10.0	-1.996	0.054
Gender (male/female)	15/3	14/4	0.000	1.000
19-30 years				
Age	21.9±3.0	22.6±3.8	-0.487	0.631
Full IQ	115.1±17.9	121.5±5.3	-1.098	0.297
Gender (male/female)	9/1	12/1	0.000	1.000

MRI Data Collection

All MRI data were collected by GE Discovery 750 3.0T magnetic resonance scanner in the Third Hospital of Peking University, using 8-channel phased array head coil. Subjects were supine and fixed with foam pad during scanning. 3D T1 SPGR sequence sagittal scanning was used with the following parameters: TR (repetition time) = 4.78ms, TE (echo time) = 2.02ms, Flip angle = 15°, FOV (field of view) = 24mm * 24mm, matrix size = 240 * 240, slice thickness = 1.0mm, voxel size = 1.0 mm * 1.0 mm * 1.0 mm. 166 slices of images were collected from the whole brain.

MRI Data Processing

All MRI data processing software runs on MatLab R2009a platform. Image preprocessing is based on the VBM8-DARTEL toolbox (<http://dbm.neuro.uni-jena.de/vbm>) of statistical parameter software SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>). Each time, only one age group of autism participants and the normal controls were processed. The three age groups were processed in turn as follow procedures: a. AC-PC correction for MRI images; b. anatomical segmentation of T1 weighted structural images using segmentation template of 'New Segment' to extract the original image and volume of gray matter, white matter and cerebrospinal fluid; c. using DARTEL toolbox to average each part of the image, getting initial registration template, and then try to match the images and templates according to white matter, gray matter and cerebrospinal fluid to obtain the re-averaged images and generate the optimal template of DARTEL through six iterations; d. non-linear transformation is used to match the initial segmentation image to the optimal template of DARTEL; e. the deformable field obtained by DARTEL registration process is used to register the images into MNI space (Montreal Neurological Institute) and to generate volume modulation maps. All image positions and individual voxel sizes (1.5mm*1.5mm*1.5mm) are aligned to achieve spatial volume comparability; f. Gauss smoothing of standardized images is performed (FWHM = 6mm) to improve the image SNR (signal-to-noise ratio).

Statistical Analyses

For whole brain volume analyses, single variable covariance analysis was employed in each age group separately, with whole brain volume, whole brain white matter volume and whole brain gray matter volume as dependent variables, gender and diagnostic grouping as fixed factors, age and IQ as covariates.

For VBM analysis in SPM8, using generalized linear model, the smoothed gray matter images of autism group and TD were tested by voxel-based double-sample *t*-test. Age, gender, IQ and intracranial volume (=white matter volume+gray matter volume+cerebrospinal fluid volume) were taken as covariates, and the whole brain statistical analysis was carried out voxel by voxel. Gauss random field theory was used for multiple comparison correction. Threshold of voxel level was set as $P < 0.001$, and the cluster number of voxels was considered significant if it was more than 50 [17].

Results

Whole brain volume

For whole brain volume size comparison analyses, no significant difference was found in between autism and TD group in the three age groups separately (see supplementary Table 1-3).

Regional Grey Matter Volume in ASD: Voxel-based Morphometry

6-12 years old: In the older childhood age cohort, two regions showed significant smaller grey volume in autism than TD group: clusters of right superior temporal gyrus and right inferior parietal lobule ($P < 0.001$, uncorrected, cluster number > 50 , voxel size = 3.375). No region was found where autism demonstrated greater volume than TD (see Figure 1 and Table 2).

Table 2

Regions showing significant differences of grey matter volume between ASD and TD groups based on VBM analyses in three age groups (uncorrected).

Regions	BA	Voxel Number	Peak MNI			Peak Intensity
			X	Y	Z	
6-12 years old						
ASD↔TD	No significant results					
TD↔ASD						
Right superior temporal gyrus	22	102	39	-18	-3	-4.088
Right inferior parietal lobule	40	90	48	-51	49.5	
13-18 years old						
ASD↔TD						
Left inferior parietal lobule	40	357	-42	-57	48	5.966
TD↔ASD	No significant results					
19-30 years old						
ASD↔TD						
Right middle occipital gyrus	19	86	33	-75	22.5	4.281
TD↔ASD						
Left anterior cingulate gyrus	31	80	-9	-27	37.5	-4.905
<i>Note:</i> Within-cluster peaks were identified based on DPABI (http://rfmri.org/dpabi) and CUI Xu's xjview (http://www.alivelearn.net/xjview/). Cluster size is reported in number of voxels (2×2×2mm). BA, Broca's area.						

13-18 years old: In the adolescent age cohort, one region showed significant greater grey volume in autism than TD group: left inferior parietal lobule ($P < 0.001$, uncorrected, cluster number > 50 , voxel

size=3.375). No region was found where autism showed smaller volume than TD (see Figure 1 and Table 2).

19-30 years old: In the young adult cohort, one region showed significant greater grey volume in autism than TD group: right middle occipital gyrus ($P < 0.001$, uncorrected, cluster number > 50 , voxel size=3.375). One region demonstrated significant smaller grey volume in autism than TD group: left anterior cingulate gyrus ($P < 0.001$, uncorrected, cluster number > 50 , voxel size=3.375) (see Figure 1 and Table 2).

Discussion

In the current study, we included 52 autism individuals and 50 normal controls, who were matched for age, gender and IQ. We found no significant difference in the volume of whole brain, whole gray matter and whole white matter between the two groups in distinct developmental stages (6-12, 13-18 and 19-30 years old). However, using VBM analyses, we observed different grey matter regions showed significant differences in volume between autism and TD group in different age cohorts, involving parietal lobe, occipital lobe, temporal lobe and cingulate gyrus.

Whole Brain Volume In Autism

In our study, the whole brain volume, whole gray matter volume, and whole white matter volume of subjects in autism group and TD were compared among three age groups (6-12 years old, 13-18 years old and 19-30 years old), and no significant volume difference was found between the two groups in each age cohort. Our result was consistent with many previous studies. For the whole brain volume comparison, Jou, Minshew [18] recruited 22 autism children and 22 normal controls aged 8-12 years, and they found no difference in the whole brain volume between the two groups. [19] included 29 autism adults and 29 normal controls, and also found no difference in whole brain volume between two groups. Riddle, Cascio [7] used sMRI data from a large database including 539 autistic individuals and 573 controls, and they found that no difference in the whole brain volume between childhood (6-12.6 years), early adolescence (12.7-16.1 years), late adolescence (16.2-22 years) and adult (older than 22 years) autistic individuals and normal controls.

For the whole brain gray matter volume analyses, one study recruited 86 autism individuals and 90 normal controls aged 7-29 years, and results showed that there was no difference in the whole brain gray matter volume between two groups [20]. Another study also suggested that the differences in gray matter volume between autism and TD adolescents and adults were more reflected in the imbalance of gray matter volume in local brain regions than in whole brain gray matter volume [20]. For the whole brain white matter comparison, Radua, Via [21] conducted a meta-analysis of the study on the white matter VBM of autistic individuals in Pubmed database from 2002 to 2010, and they found no significant difference in the whole brain white matter volume between autism and TD groups.

A few previous studies also showed that the whole brain volume of autism group was larger than that of TD group, which was inconsistent with our results. The reason for the inconsistency may largely be related with different IQ ranges in the two groups. Freitag, Luders [9] included 15 autistic individuals and 15 normal controls aged 14-22 years old, whose IQ showed significant differences between the two groups, and they found that the whole brain volume, whole brain gray matter volume and whole brain white matter volume of the autism group were all larger than those of the TD group. Additionally, for Asperger's syndrome without mental intelligence impairment, no previous study has reported that Asperger's syndrome individuals exhibited enlarged whole brain gray matter volume compared with normal controls. The reason may be that Asperger's syndrome individuals usually have higher IQ than autism individuals in general [22], which supported the view that IQ affected the whole brain volume of autism. To better investigate the relationship between IQ and whole brain volume in autism, autistic participants with different IQ ranges need to be included in the study in further research.

Brain Regions With Atypical Gray Matter Volume In Autism

Right Superior Temporal Gyrus

It is found in the current study that the gray matter in right superior temporal gyrus of 6-12-year-old autism group was smaller than that of TD group, while there was no difference between autism and control groups in age groups of 13-18 and 19-30 years old. Previous studies have shown that the superior temporal gyrus is closely related to language [23], visual function [24], auditory function [25] and social cognition [26]. Social cognition refers to the processing of facial expression, eye gaze, physical movement and other information by individuals in social communication. The overall goal is to recognize and understand the mental state of others [27]. The posterior part of superior temporal gyrus, which involves advanced cortical integration function, integrates sensory information and limbic system information, is the core cortical area of social brain [28]. [29] recruited 21 autistic children and 12 controls aged 7-11 years old, and they found that the density of gray matter in superior temporal sulcus of autistic individuals decreased compared with normal people, which supported the results of the current study. Kates, Mostofsky [30] analyzed brain sMRI data of five 7-year-old autistic twins and found that the volumes of their superior temporal gyrus were smaller than those of normal children. From twin studies, structural atypicalities of superior temporal gyrus were considered correlated with heredity in autism.

Compared with left superior temporal gyrus, right superior temporal gyrus has more important functional significance for autistic individuals. Previous studies have found that the right superior temporal gyrus of autism played a dual role in language and social cognition. Boddaert, Belin [31] found that the activation of left superior temporal gyrus was more obvious than that of the right side in control group when recognizing and understanding speech, while the activation of the right superior temporal gyrus was more obvious in autistic adults. [32] found that delayed development of the integrated function of design action and language in autistic children was related to the development of right superior temporal gyrus.

The above studies may enlighten us that the right superior temporal gyrus atypicalities are closely related to autistic symptoms, and have important pathological significance for autistic individuals.

In this study, we observed no difference in the right superior temporal gyrus gray matter volume between autism and TD groups in 13-18-year-old and 19-30-year-old groups. The atypicality of right superior temporal gyrus gray matter volume was considered age-related as shown in many previous studies. A prospective study of gray matter development included 100 autistic individuals and 117 normal controls aged 3-34 years, and they found that the gray matter volume in temporal lobe decreased with age in both groups. The development trajectory analyses showed that the gray matter volume in temporal lobe of autism was smaller than that in TD group before 14 years old, but there was no significant difference between the two groups after 14 years old [33]. Dickstein, Pescosolido [34] conducted a meta-analysis of the task-based MRI study of autism (535 autistic children and 604 autistic adults) and found that during social tasks, the right superior temporal gyrus of autistic children was less activated than that of autistic adolescents. Therefore, it is necessary to include longitudinal data to observe the volume of this brain area in autism from different developmental stages, which is the gold standard of developmental studies.

In addition, some studies have found that changes in cell volume in superior temporal gyrus were associated with autism [26], which further explained the pathology of the superior temporal gyrus in autism. [35] found that the superior temporal gyrus of autistic individuals showed increased transcript levels of many immune system-related genes with huge variations, which appeared to be associated with the characteristic innate immune response of neurodevelopmental diseases. It is helpful to further identify the susceptibility genes and pathological mechanism.

Although the results of this study are consistent with most previous studies, there are still inconsistencies. For example, one study included 18 autism individuals and 19 normal controls aged 10-16 years, and found that the right superior temporal gyrus volume increased significantly in autism group. The reason may be that the comparison in that study was only about the right superior temporal gyrus volume without distinguishing white matter from gray matter [26, 36]. Other studies did not find atypical volume of left superior temporal gyrus in autistic individuals, or reported that the left superior temporal gyrus volume decreased in autistic individuals but not in the right side. The inconsistencies of these results may be due to many factors including methodological differences, differences in clinical data of subjects, ect.

Inferior Parietal Lobule

We found in the current study that the gray matter volume of right inferior parietal lobule was smaller in autism group than in TD group for children (6-12 years old), and the grey matter volume of left inferior parietal lobule was larger in autism group than in TD group for adolescents (13-18 years old). No difference was observed in the gray matter volume of bilateral inferior parietal lobule between autism group and TD group for young adults (19-30 years old). The inferior parietal lobule is involved in sensory input, especially visual and spatial localization [37]. It is also a part of human mirror nervous system [38] involving image thinking, imitative action [39], eye contact [40] and semantic processing [41], and was

considered as one of the most highly connected hubs in brain [42]. Venkataraman, Duncan [43] found that the left inferior parietal lobule of autism was involved in the formation of social pathological networks. A meta-analysis of fMRI studies found that the anterior inferior parietal lobule of autism was abnormally activated during observation and imitation, and mirror neuron dysfunction existed [38]. Many previous studies have found that the right inferior parietal lobule gray matter volume of autistic children was smaller than that of the TD group, and the reduction of gray matter volume was positively correlated with the severity of social disorders [44]. Mengotti, D'Agostini [45] recruited 20 autistic children and 22 normal controls (4-14 years old), and they found that the left parietal lobule gray matter volume was larger in autistic children than in TD children. The above findings all supported the results of the current study. Piven, Arndt [46] enrolled 35 autistic individuals and 36 normal controls (12-29 years old) and found that the parietal lobe volume of autistic individuals was enlarged compared with that of the normal controls, which was partly consistent with the results of this study.

The current study has found that the left inferior parietal lobule of autism group was larger in adolescence than that of normal group, but there was no difference between autism adults and TD adults. It is speculated that the gray matter volume of left inferior parietal lobule of autism may gradually decrease from adolescence to adulthood, and similar results have been observed in previous studies. A study on the brain structure of autism adolescents included 25 autistic individuals and 25 normal controls (10-18 years old). The results showed that the volume of bilateral inferior parietal lobule gray matter decreased with age in autism group, but increased with age in normal group [44], which accorded with the conclusion in the current study. Christian et al. recruited 28 autism adults and 28 normal controls (20-55 years old), and found that the left inferior parietal lobule of autism individuals was thinner than that of the normal controls and tended to decrease with age in autism [47].

The results of this study showed that the volume atypicalities of bilateral inferior parietal lobules in autism individuals of different age stages were different. The reason for this finding may also involved the lateralization of brain structure besides the influence of the age factors on the development of inferior parietal lobules in autism. Previous studies have found that the left inferior parietal lobule of autism adolescents was larger than the right lobule [44]. Other studies have also found an increase in left cerebral asymmetry in autistic individuals [48], which supported the results in this study.

Based on those studies above, despite the differences in sample age and clinical characteristics in those studies examining parietal lobules of autistic individuals or the inconsistency of previous research results, many studies have shown that bilateral inferior parietal lobules of autistic individuals were significantly different in structure and function from those of normal people, which fully illustrated the pathological significance of bilateral inferior parietal lobules for autism. The results of this study also provided evidence for bilateral inferior parietal lobule atypicalities in autism.

Right Middle Occipital Gyrus

This study has found that the right middle occipital gyrus gray matter volume of 19-30 years old autism group was larger than that of normal group, and there was no difference between autism and normal

groups in age groups of 6-12 years and 13-18 years. The current results were partly consistent with those of previous studies. One study included 38 autism individuals and 46 normal controls aged 6-17 years old. No significant difference was found in gray matter volume of middle occipital lobe [49]. Ecker, Marquand [50] recruited autistic adults and normal controls aged 20-68 years old and found that the occipital lobe cortex of autistic individuals was thicker than TD. The above results were consistent with the results of this study. Piven, Arndt [46] included 35 autistic individuals and 36 normal controls (12-29 years old, 18 years old on average). It was found that the occipital lobe volume of autistic individuals was enlarged compared with the normal group, which partly supported the results of this study. However, there have been inconsistent reports with our results. A meta-analysis of gray matter abnormalities examining autistic individuals aged 6-14 found that the gray matter volume in left anterior occipital gyrus and left inferior occipital gyrus of autistic individuals were enlarged [51] compared with normal people, while there was no difference in occipital lobe volume between 6-18-year-old autism group and control group in the current study. Another study included autism individuals with an average age of 26 years and normal controls, and they found that the gray matter volume in occipital lobe of autism group was smaller [52] compared with normal control group. Because some studies found that the size of occipital lobe was related to IQ and the severity of autism. Therefore, the reasons for the inconsistencies between those results may be related to a variety of factors, including different sample size, age, IQ, different symptom severity and lateralization anomaly of occipital lobe. Despite of inconsistencies of previous studies, one meta-analysis on gray matter atypicalities in autism revealed that most studies showed structural abnormalities in the occipital lobe of autistic individuals [13].

The occipital lobe is responsible for visual spatial information processing as well as the processing of body language and emotional regulation [53]. Previous functional magnetic resonance studies have shown that autism individuals relied more on occipital primary visual function to encode external information in social and non-social tasks, while normal people relied more on language [54]. Autistic individuals atypically activated the occipital gyrus rather than the traditional spindle facial area during facial processing tasks [55]. Functional magnetic resonance studies also found that there were atypical developmental patterns in the middle occipital gyrus of autistic children and adolescents compared with normal people [56]. Besides, the atypical development of the occipital lobe may also be related with altered gene expression or neurometabolism. Ginsberg, Rubin [57] found atypical gene expression in occipital lobe of autism adults: mitochondrial oxidative phosphorylation and down-regulation of protein translation genes. Levitt, O'Neill [58] found atypical neurometabolites in the occipital cortex of autistic individuals aged 5-16 using proton magnetic resonance spectroscopy. Therefore, both molecular and imaging studies suggested that occipital lobe and middle occipital gyrus played an important role in the pathogenesis of autism. The results of this study provided more evidence for occipital lobe atypicalities in autism.

Left Posterior Cingulate Gyrus

It is found in this study that the left posterior cingulate gyrus gray matter volume of 19-30 years old autism group was smaller than that of normal group, and there was no difference in the left posterior

cingulate gyrus gray matter volume between 6-12 years old and 13-18 years old autism group and normal group. Chandley, Crawford [59] found that pyramidal neurons in cingulate cortex of autistic adults were less than those of normal adults, and the gene expression was abnormal, which supported the results of this study. Sussman, Leung [60] studied 72 autistic individuals and 138 normal controls aged 4-18, and found that the left cingulate gyrus of autistic individuals gradually thinned with age, while the posterior cingulate gyrus of normal people increased with age [44]. This may explain that left posterior cingulate gyrus in this study did not show any difference between autism group and normal group at the ages of 6-12, 13-18 years old, while left posterior cingulate gyrus of autism group was smaller than that of normal group at the ages of 19-30 years old. The autopsy study of adult autistic individuals found that the cellular structure of posterior cingulate gyrus changed including irregularly distributed neurons and the boundary between layer IV and V was difficult to distinguish, suggesting that there were atypical patterns of development and migration of neurons in the posterior cingulate gyrus of autistic individuals [61]. Geurts, Ridderinkhof [62] found that the severity of autistic communication symptom score and left posterior cingulate gyrus gray matter volume were correlated in adults. It is suggested that the gray matter volume in left posterior cingulate gyrus has important pathological significance for autism.

Previous studies have also found atypical levels of neurotransmitters in the left posterior cingulate gyrus of autistic individuals: serotonin 5-HT receptors in the autistic adult's posterior cingulate cortex decreased, and 5-HT played an important role in synaptogenesis, nerve growth and neuronal migration [63]. Using proton magnetic resonance spectroscopy, Nakamura, Sekine [64] found that 5-HT decreased in the cingulate gyrus of autism individuals and was associated with their social cognitive deficits. Levitt et al. found abnormal neurometabolites in the left cingulate gyrus of autistic individuals [65].

The cingulate cortex involves various functions, including motor control [66], cognitive control [66], conflict monitoring [67], and social cognition [68]. These functions are partly neuronal function of cingulate cortex itself and partly functional connections with other brain regions. The cingulate cortex was considered one of the abnormal brain areas closely related to the pathology of autism, and posterior cingulate cortex is part of the human facial expression processing neural network [69] and an important area of marginal-cortical network responsible for social emotional behavior, closely related to social deficits in autism. A meta-analysis of functional magnetic resonance studies on autism found that the activation of cingulate gyrus in autistic adults was significantly weaker than that in normal adults [70]. These findings fully demonstrated the functional abnormalities of left posterior cingulate gyrus in autism, which may be due to the local atypical structure of left posterior cingulate gyrus or the atypical connection of neural network in autism. Other studies have found that in non-social tasks, the left cingulate gyrus of autistic adults was weaker than that of autistic children [34]. In normal population, the functional connectivity between posterior cingulate gyrus and medial prefrontal cortex increased with age, while it decreased with age in autism group [71]. It is suggested that left cingulate gyrus and the posterior cingulate gyrus of autistic individuals had different functional levels at different age stages, which may be related to the change of gray matter volume in left posterior cingulate gyrus of autistic individuals at different age stages.

There are also some inconsistencies in previous results with this study. For example, Cauda, Geda [72] found that the cingulate gyrus gray matter volume of autistic adults increased compared with that of normal adults in a meta-analysis of VBM studies. A meta-analysis did not find any difference in gray matter volume of cingulate cortex between autistic adults and normal adults [13]. The heterogeneity of the results among previous may be related to the differences of sample size, sample age, disease severity, and research methods [73].

Conclusion

In conclusion, the current study showed the whole brain volume, whole brain white matter volume and whole brain gray matter volume of autism individuals aged 6-12, 13-18 and 19-30 showed no significant difference relative to TD. The brain areas with atypical gray matter volume of autism individuals at the three age stages were different, involving right superior temporal gyrus, inferior parietal lobule, right middle occipital gyrus, and left posterior cingulate gyrus. These brain areas were of great significance for us to further understand the neuropathological mechanism of autism. However, the results of this study only involved autism individuals aged 6-30 years and can not be extended to autistic individuals in all age ranges. Secondly, except for the left inferior parietal lobule, other abnormal brain areas were only obtained at the uncorrected level ($P < 0.001$). The future study needs to increase the sample size and include more autistic individuals with different levels of IQ and further conduct a rigorous statistical correction to verify the results in a larger sample size.

Abbreviations

sMRI: structural Magnetic Resonance Imaging; TD: typically developing individuals; VBM: Voxel-Based Morphometry; ADOS: Autism Diagnostic Observation Schedule; RRB: Restricted and Repetitive Behaviors; ADI: Autism Diagnostic Interview; DSM-IV: Diagnostic and Statistical Manual-IV; IQ: intelligence quotient; C-WISC: the Chinese-Wechsler Intelligence Scale for Children; WAIS-RC: the Wechsler Adult Intelligence Scale-Revised in China; TR: repetition time; TE: echo time; FOV: field of view; SPM: statistical parameter software.

Declarations

Ethics approval and consent to participate

This study was conducted under the approval of the Ethics Committee of Peking University Sixth Hospital. This article does not contain any studies with animals performed by any of the authors. The participants and their parents were asked to sign an informed consent prior to their participation in the study.

Consent for publication

All authors agreed the possible publication of our article on Child and Adolescent Psychiatry and Mental Health. The participant has consented to the submission of the article to the journal.

Availability of data and materials

All the clinical data used to support the findings of this study may be released upon application to the data access manager, who can be contacted at ljyuch@bjmu.edu.cn.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

JL, QJC and XL conceived and designed the experiment. HW, ZHM, LZX, ZZJ, XZT JRL and XL conducted the experiment. HW performed the data analyses. QJC and JL supervised the data analyses. HW and ZHM co-wrote the paper. HW, ZHM and LZX revised the manuscript. All authors contributed to the discussion of the manuscript. All authors read and approved the final manuscript.

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References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed: Washington, DC: American Psychiatric Association; 2013.
2. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR Surveillance Summaries*. 2018;67(6):1.
3. Mezzelani A, Landini M, Facchiano F, Raggi ME, Villa L, Molteni M, et al. Environment, dysbiosis, immunity and sex-specific susceptibility: a translational hypothesis for regressive autism pathogenesis. *Nutr Neurosci*. 2015;18(4):145-61.
4. LaSalle JM, Powell WT, Yasui DH. Epigenetic layers and players underlying neurodevelopment. *Trends Neurosci*. 2013;36(8):460-70.

5. Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, et al. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. *Brain*. 2003;126(Pt 5):1182-92.
6. Brambilla P, Hardan A, di Nemi SU, Perez J, Soares JC, Barale F. Brain anatomy and development in autism: review of structural MRI studies. *Brain Res Bull*. 2003;61(6):557-69.
7. Riddle K, Cascio CJ, Woodward ND. Brain structure in autism: a voxel-based morphometry analysis of the Autism Brain Imaging Database Exchange (ABIDE). *Brain Imaging Behav*. 2017;11(2):541-51.
8. Aylward EH, Minshew NJ, Field K, Sparks B, Singh N. Effects of age on brain volume and head circumference in autism. *Neurology*. 2002;59(2):175-83.
9. Freitag CM, Luders E, Hulst HE, Narr KL, Thompson PM, Toga AW, et al. Total brain volume and corpus callosum size in medication-naïve adolescents and young adults with autism spectrum disorder. *Biol Psychiatry*. 2009;66(4):316-9.
10. Mitelman SA, Bralet M-C, Haznedar MM, Hollander E, Shihabuddin L, Hazlett EA, et al. Diametrical relationship between gray and white matter volumes in autism spectrum disorder and schizophrenia. *Brain imaging and behavior*. 2017;11(6):1823-35.
11. Mitchell SR, Reiss AL, Tatusko DH, Ikuta I, Kazmerski DB, Botti JA, et al. Neuroanatomic alterations and social and communication deficits in monozygotic twins discordant for autism disorder. *Am J Psychiatry*. 2009;166(8):917-25.
12. Hollander E, Anagnostou E, Chaplin W, Esposito K, Haznedar MM, Licalzi E, et al. Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. *Biol Psychiatry*. 2005;58(3):226-32.
13. Nickl-Jockschat T, Habel U, Maria Michel T, Manning J, Laird AR, Fox PT, et al. Brain structure anomalies in autism spectrum disorder—a meta-analysis of VBM studies using anatomic likelihood estimation. *Human brain mapping*. 2012;33(6):1470-89.
14. Yang X, Si T, Gong Q, Qiu L, Jia Z, Zhou M, et al. Brain gray matter alterations and associated demographic profiles in adults with autism spectrum disorder: A meta-analysis of voxel-based morphometry studies. *Aust N Z J Psychiatry*. 2016;50(8):741-53.
15. Gong Y. The manual of Wechsler adult intelligence scale revised in China. Changsha Hunan Medical University Press, China. 1992.
16. Gong Y, Cai T. Manual of Chinese revised Wechsler intelligence scale for children. Changsha: Hunan Atlas Publishing House. 1993.
17. D'Mello AM, Crocetti D, Mostofsky SH, Stoodley CJ. Cerebellar gray matter and lobular volumes correlate with core autism symptoms. *Neuroimage Clin*. 2015;7:631-9.

18. Jou RJ, Minshew NJ, Melhem NM, Keshavan MS, Hardan AY. Brainstem volumetric alterations in children with autism. *Psychol Med*. 2009;39(8):1347-54.
19. Tepest R, Jacobi E, Gawronski A, Krug B, Moller-Hartmann W, Lehnhardt FG, et al. Corpus callosum size in adults with high-functioning autism and the relevance of gender. *Psychiatry Res*. 2010;183(1):38-43.
20. Lin H-Y, Ni H-C, Lai M-C, Tseng W-YI, Gau SS-F. Regional brain volume differences between males with and without autism spectrum disorder are highly age-dependent. *Molecular autism*. 2015;6(1):29.
21. Radua J, Via E, Catani M, Mataix-Cols D. Voxel-based meta-analysis of regional white-matter volume differences in autism spectrum disorder versus healthy controls. *Psychol Med*. 2011;41(7):1539-50.
22. Lotspeich LJ, Kwon H, Schumann CM, Fryer SL, Goodlin-Jones BL, Buonocore MH, et al. Investigation of neuroanatomical differences between autism and aspergersyndrome. *Archives of general psychiatry*. 2004;61(3):291-8.
23. Makris N, Pandya DN. The extreme capsule in humans and rethinking of the language circuitry. *Brain Struct Funct*. 2009;213(3):343-58.
24. Grecucci A, Rubicondo D, Siugzdaite R, Surian L, Job R. Uncovering the Social Deficits in the Autistic Brain. A Source-Based Morphometric Study. *Front Neurosci*. 2016;10:388.
25. Edgar JC, Fisk Iv CL, Berman JI, Chudnovskaya D, Liu S, Pandey J, et al. Auditory encoding abnormalities in children with autism spectrum disorder suggest delayed development of auditory cortex. *Mol Autism*. 2015;6:69.
26. Bigler ED, Mortensen S, Neeley ES, Ozonoff S, Krasny L, Johnson M, et al. Superior temporal gyrus, language function, and autism. *Dev Neuropsychol*. 2007;31(2):217-38.
27. Allison T, Puce A, McCarthy G. Social perception from visual cues: role of the STS region. *Trends Cogn Sci*. 2000;4(7):267-78.
28. Boddaert N, Chabane N, Barthelemy C, Bourgeois M, Poline JB, Brunelle F, et al. [Bitemporal lobe dysfonction in infantile autism: positron emission tomography study]. *J Radiol*. 2002;83(12 Pt 1):1829-33.
29. Boddaert N, Chabane N, Gervais H, Good CD, Bourgeois M, Plumet MH, et al. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. *Neuroimage*. 2004;23(1):364-9.
30. Kates WR, Mostofsky SH, Zimmerman AW, Mazzocco MM, Landa R, Warsofsky IS, et al. Neuroanatomical and neurocognitive differences in a pair of monozygous twins discordant for strictly

defined autism. *Ann Neurol*. 1998;43(6):782-91.

31. Boddaert N, Belin P, Chabane N, Poline JB, Barthelemy C, Mouren-Simeoni MC, et al. Perception of complex sounds: abnormal pattern of cortical activation in autism. *Am J Psychiatry*. 2003;160(11):2057-60.
32. Hubbard AL, McNealy K, Scott-Van Zeeland AA, Callan DE, Bookheimer SY, Dapretto M. Altered integration of speech and gesture in children with autism spectrum disorders. *Brain Behav*. 2012;2(5):606-19.
33. Wallace GL, Eisenberg IW, Robustelli B, Dankner N, Kenworthy L, Giedd JN, et al. Longitudinal cortical development during adolescence and young adulthood in autism spectrum disorder: increased cortical thinning but comparable surface area changes. *J Am Acad Child Adolesc Psychiatry*. 2015;54(6):464-9.
34. Dickstein DP, Pescosolido MF, Reidy BL, Galvan T, Kim KL, Seymour KE, et al. Developmental meta-analysis of the functional neural correlates of autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(3):279-89 e16.
35. Garbett K, Ebert PJ, Mitchell A, Lintas C, Manzi B, Mirnics K, et al. Immune transcriptome alterations in the temporal cortex of subjects with autism. *Neurobiol Dis*. 2008;30(3):303-11.
36. Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A. Structural white matter deficits in high-functioning individuals with autistic spectrum disorder: a voxel-based investigation. *Neuroimage*. 2005;24(2):455-61.
37. Bremner F, Schlack A, Duhamel JR, Graf W, Fink GR. Space coding in primate posterior parietal cortex. *Neuroimage*. 2001;14(1 Pt 2):S46-51.
38. Yang J, Hofmann J. Action observation and imitation in autism spectrum disorders: an ALE meta-analysis of fMRI studies. *Brain Imaging Behav*. 2016;10(4):960-9.
39. Rizzolatti G, Sinigaglia C. The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. *Nat Rev Neurosci*. 2010;11(4):264-74.
40. Calder AJ, Beaver JD, Winston JS, Dolan RJ, Jenkins R, Eger E, et al. Separate coding of different gaze directions in the superior temporal sulcus and inferior parietal lobule. *Curr Biol*. 2007;17(1):20-5.
41. Wang J, Conder JA, Blitzer DN, Shinkareva SV. Neural representation of abstract and concrete concepts: a meta-analysis of neuroimaging studies. *Hum Brain Mapp*. 2010;31(10):1459-68.
42. Tomasi D, Volkow ND. Association between functional connectivity hubs and brain networks. *Cerebral cortex*. 2011;21(9):2003-13.

43. Venkataraman A, Duncan JS, Yang DY, Pelphrey KA. An unbiased Bayesian approach to functional connectomics implicates social-communication networks in autism. *Neuroimage Clin.* 2015;8:356-66.
44. Cheng Y, Chou KH, Fan YT, Lin CP. ANS: aberrant neurodevelopment of the social cognition network in adolescents with autism spectrum disorders. *PLoS One.* 2011;6(4):e18905.
45. Mengotti P, D'Agostini S, Terlevic R, De Colle C, Biasizzo E, Londero D, et al. Altered white matter integrity and development in children with autism: a combined voxel-based morphometry and diffusion imaging study. *Brain Res Bull.* 2011;84(2):189-95.
46. Piven J, Arndt S, Bailey J, Andreasen N. Regional brain enlargement in autism: a magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry.* 1996;35(4):530-6.
47. Scheel C, Rotarska-Jagiela A, Schilbach L, Lehnhardt FG, Krug B, Vogeley K, et al. Imaging derived cortical thickness reduction in high-functioning autism: key regions and temporal slope. *Neuroimage.* 2011;58(2):391-400.
48. Herbert MR, Harris GJ, Adrien KT, Ziegler DA, Makris N, Kennedy DN, et al. Abnormal asymmetry in language association cortex in autism. *Ann Neurol.* 2002;52(5):588-96.
49. Foster NE, Doyle-Thomas KA, Tryfon A, Ouimet T, Anagnostou E, Evans AC, et al. Structural Gray Matter Differences During Childhood Development in Autism Spectrum Disorder: A Multimetric Approach. *Pediatr Neurol.* 2015;53(4):350-9.
50. Ecker C, Marquand A, Mourão-Miranda J, Johnston P, Daly EM, Brammer MJ, et al. Describing the brain in autism in five dimensions—magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach. *Journal of Neuroscience.* 2010;30(32):10612-23.
51. Liu J, Yao L, Zhang W, Xiao Y, Liu L, Gao X, et al. Gray matter abnormalities in pediatric autism spectrum disorder: a meta-analysis with signed differential mapping. *Eur Child Adolesc Psychiatry.* 2017;26(8):933-45.
52. Ecker C, Suckling J, Deoni SC, Lombardo MV, Bullmore ET, Baron-Cohen S, et al. Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: a multicenter magnetic resonance imaging study. *Arch Gen Psychiatry.* 2012;69(2):195-209.
53. Libero LE, Stevens CE, Jr., Kana RK. Attribution of emotions to body postures: an independent component analysis study of functional connectivity in autism. *Hum Brain Mapp.* 2014;35(10):5204-18.
54. Sahyoun CP, Belliveau JW, Soulieres I, Schwartz S, Mody M. Neuroimaging of the functional and structural networks underlying visuospatial vs. linguistic reasoning in high-functioning autism. *Neuropsychologia.* 2010;48(1):86-95.

55. Pierce K, Müller R-A, Ambrose J, Allen G, Courchesne E. Face processing occurs outside the fusiform face area in autism: evidence from functional MRI. *Brain*. 2001;124(10):2059-73.
56. Gadgil M, Peterson E, Tregellas J, Hepburn S, Rojas DC. Differences in global and local level information processing in autism: an fMRI investigation. *Psychiatry Res*. 2013;213(2):115-21.
57. Ginsberg MR, Rubin RA, Falcone T, Ting AH, Natowicz MR. Brain transcriptional and epigenetic associations with autism. *PLoS One*. 2012;7(9):e44736.
58. Levitt JG, O'Neill J, Blanton RE, Smalley S, Fadale D, McCracken JT, et al. Proton magnetic resonance spectroscopic imaging of the brain in childhood autism. *Biol Psychiatry*. 2003;54(12):1355-66.
59. Chandley MJ, Crawford JD, Szebeni A, Szebeni K, Ordway GA. NTRK2 expression levels are reduced in laser captured pyramidal neurons from the anterior cingulate cortex in males with autism spectrum disorder. *Mol Autism*. 2015;6:28.
60. Sussman D, Leung R, Vogan V, Lee W, Trelle S, Lin S, et al. The autism puzzle: Diffuse but not pervasive neuroanatomical abnormalities in children with ASD. *NeuroImage: Clinical*. 2015;8:170-9.
61. Oblak AL, Rosene DL, Kemper TL, Bauman ML, Blatt GJ. Altered posterior cingulate cortical cytoarchitecture, but normal density of neurons and interneurons in the posterior cingulate cortex and fusiform gyrus in autism. *Autism Res*. 2011;4(3):200-11.
62. Geurts HM, Ridderinkhof KR, Scholte HS. The relationship between grey-matter and ASD and ADHD traits in typical adults. *Journal of autism and developmental disorders*. 2013;43(7):1630-41.
63. Oblak A, Gibbs TT, Blatt GJ. Reduced serotonin receptor subtypes in a limbic and a neocortical region in autism. *Autism Res*. 2013;6(6):571-83.
64. Nakamura K, Sekine Y, Ouchi Y, Tsujii M, Yoshikawa E, Futatsubashi M, et al. Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Arch Gen Psychiatry*. 2010;67(1):59-68.
65. Libero LE, Reid MA, White DM, Salibi N, Lahti AC, Kana RK. Biochemistry of the cingulate cortex in autism: An MR spectroscopy study. *Autism Res*. 2016;9(6):643-57.
66. Amiez C, Petrides M. Neuroimaging evidence of the anatomo-functional organization of the human cingulate motor areas. *Cereb Cortex*. 2014;24(3):563-78.
67. Botvinick MM. Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn Affect Behav Neurosci*. 2007;7(4):356-66.
68. Apps MA, Lesage E, Ramnani N. Vicarious reinforcement learning signals when instructing others. *Journal of Neuroscience*. 2015;35(7):2904-13.

69. Haxby JV, Hoffman EA, Gobbini MI. The distributed human neural system for face perception. *Trends Cogn Sci.* 2000;4(6):223-33.
70. Di Martino A, Ross K, Uddin LQ, Sklar AB, Castellanos FX, Milham MP. Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. *Biol Psychiatry.* 2009;65(1):63-74.
71. Doyle-Thomas KA, Lee W, Foster NE, Tryfon A, Ouimet T, Hyde KL, et al. Atypical functional brain connectivity during rest in autism spectrum disorders. *Ann Neurol.* 2015;77(5):866-76.
72. Cauda F, Geda E, Sacco K, D'Agata F, Duca S, Geminiani G, et al. Grey matter abnormality in autism spectrum disorder: an activation likelihood estimation meta-analysis study. *J Neurol Neurosurg Psychiatry.* 2011;82(12):1304-13.
73. Uddin LQ, Supekar K, Menon V. Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Front Hum Neurosci.* 2013;7:458.

Figures

Figure 1

Regions showing significant differences of grey matter volume between ASD and TD groups based on VBM analyses (uncorrected). A: Right superior temporal gyrus; B: Right inferior parietal lobule; C: Left

inferior parietal lobule; D: Right middle occipital gyrus; E: Left anterior cingulate gyrus.

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