

Abnormalities of Gray Matter Volume and Its Correlation with Clinical Symptoms in Adolescents with High-Functioning Autism Spectrum Disorder

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Background: Previous studies have indicated abnormal gray matter volume (GMV) in individuals with autism spectrum disorder (ASD); however, there is little consistency across the findings within these studies, partly due to small sample size and great heterogeneity among participants between studies. Additionally, few studies have explored the correlation between clinical symptoms and GMV abnormalities in individuals with ASD. Here, the current study examined GMV alterations in whole brain and their correlations with clinical symptoms in a relatively large and homogeneous sample of participants with ASD matched typically developing (TD) controls.

Methods: Forty-eight adolescents with high-functioning ASD and 29 group-matched TD controls underwent structural magnetic resonance images. Voxel-based morphometry was applied to investigate regional GMV alterations. The participants with ASD were examined for the severity of clinical symptoms with Autism Behavior Checklist (ABC). The relationship between GMV abnormalities and clinical symptoms was explored in ASD group using voxel-wise correlation analysis within brain regions that showed significant GMV alterations in individuals with ASD compared with TD controls.

Results: We found increased GMV in multiple brain regions, including the inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus, superior temporal gyrus, occipital pole, anterior cingulate, cerebellum anterior lobe, cerebellum posterior lobe, and midbrain, as well as decreased GMV in cerebellum posterior lobe in individuals with ASD. The correlation analysis showed the GMV in the left fusiform was negatively associated with the scores of sensory factor, and the GMV in the right cerebellum anterior lobe was positively associated with the scores of social self-help factor.

Conclusion: Our results indicated that widespread GMV abnormalities of brain regions occurred in individuals with ASD, suggesting a potential neural basis for the pathogenesis and symptomatology of ASD.

Keywords: autism spectrum disorder, symptoms severity, Autism Behavior Checklist, structural magnetic resonance imaging, gray matter volume

Background

Autism spectrum disorder (ASD), which is characterized by persistent deficits in social interaction and communication, repetitive behaviors and restricted interests, is a severe neurodevelopmental disorder and a leading cause of mental disability among Children worldwide. In 2018, the prevalence of ASD is reported to be 1 in 44 children aged 8 years and is on the rise.¹ Besides, low self-care ability and increased unemployment or underemployment are commonly present among patients with ASD when they reach adulthood.² Consequently, high prevalence and disability bring about enormous social and economic burden.³

As early diagnosis of ASD is known to improve long-term functioning of affected children and enhance the quality of life of ASD individuals when they achieve adulthood, there is urgent requirement for timely and accurate diagnosis of ASD so as to provide efficient services and prevent the patient's condition from worsening. However, early identification and diagnosis of ASD is difficult on account of the heterogeneity in severity and types of ASD symptoms, changes in diagnostic criteria, co-occurrence with other mental disorders, and the absence of biological diagnostic markers. Unfortunately, the pathophysiological mechanism of ASD remains poorly understood and controversial.

Over the last few decades, multiple studies have demonstrated that brain abnormalities are associated with the disease.⁴ There is one prominent theory that ASD involves the rapid enlargement of total brain volume in the first few years of life,^{5,6} while the picture in adolescents or adults is murkier.⁷ In contrast, several studies reported that the total brain volume of ASD was enlarged in adolescents.^{8,9} Increasing evidence from morphological studies emerged that this increase in total brain volume might prominently come from gray matter, but not white matter.^{10–12} The patterns of gray matter volume (GMV) abnormalities have become of significance and may provide further insights into understanding the neuropathology of ASD. Previous postmortem studies have revealed structural and morphometric changes of gray matter in ASD patients.^{13,14} During the past decade, magnetic resonance imaging (MRI) has made astounding advances and various MRI-based methods are applied to characterize morphological differences in ASD. Studies using region of interest (ROI) analysis have reported specific regions with a relatively greater enlargement of GMV, such as the temporal lobe,¹⁵ some regions with a combination of increases and reduction of GMV.¹⁶ However, Haar et al¹⁷ failed to find any volumetric differences in regional gray matter using an ROI approach. An earlier study¹⁸ in ASD children 3 to 4 years of age revealed cerebral enlargement in cerebellum and amygdala in children with ASD compared to TD. Voxel-based morphometry (VBM) studies, which, unlike the ROI approach, has the ability to detect differences in regional GMV throughout the whole brain without any a priori regional assumptions, have also produced variable findings. The most prevalent results were GMV abnormalities in the cerebellum. Cerebellar GMV reductions of ASD patients were detected widely in vermis, anterior and posterior lobules while increased cerebellar GMV were also revealed.^{16,19–21} In addition, the GMV abnormalities were reported in various brain regions located in frontal lobe, temporal lobe, parietal lobe, anterior cingulate cortex, insula, caudate nucleus, lingual gyrus and so on,^{19,22,23} which provided evidence supporting that atypical cerebello-thalamo-cortical network in ASD.^{24,25} However, there were more than a few studies reported no significant difference of GMV alterations between ASD individuals and TD controls.^{17,26–28} These inconsistent findings may be partially attributable to small sample sizes or differences in imaging methodology and demographic and clinical characteristics of the samples. A recent meta-analysis study used coordinate-based anatomical likelihood estimation (ALE) analysis of VBM studies examining high-functioning autism spectrum disorder (HFASD), showed that just 6 out of 21 studies recruited more than 25 individuals with ASD.²⁹ Small sample size limits the statistical power for investigation of comparison during study data analysis, especially for VBM method, as it requires correction for multiple comparisons. Methodological differences may also have an effect on the measurement of GMV and lead to variable results, such as image acquisition and image analysis. As ASD is a heterogeneous developmental disorder,³⁰ there is an inherent variability between affected individuals, with diverse clinical manifestations and different levels of intelligence, which is most likely associated with variations in neuroanatomical abnormalities.^{31,32} Therefore, the picture emerging is that GMV abnormalities deserve further examination in individuals with ASD through the recruitment of relatively large-size and homogeneous samples of patients, reducing the influence from potential confounding factors.

Many of previous studies investigating GMV alterations in ASD have recruited only young children or adult cohorts, even mixed groups of participants at different age levels. However, relatively few attempts have been made to investigate adolescents with ASD. The results have also been inconsistent. For example, some studies have found increased GMV in the medial frontal gyrus (MFG) in adolescents with ASD,^{33–35} but other studies have not.^{36–38} Moreover, decreased GMV has been reported in the cerebellum in adolescents with ASD,^{33,38} However, some authors failed to replicate the finding,^{34,36,37} or even found increased GMV.³⁵ A previous meta-analysis has explored GMV alterations in pediatric patients with ASD, but only five VBM studies of adolescent populations were included.³⁸ Therefore, the central question of how the brain GMV alterations manifest in adolescent ASD remains unaddressed and deserves further examination.

Several pioneering studies have examined the relationships between GMV alterations and autistic symptom severity in individuals with ASD. For instance, altered GMV was reported to be negatively associated with symptom severity in

several regions.³⁹ Recently, Supekar et al⁴⁰ reported GMV in the motor cortex, supplementary motor area, and cerebellum was related to repetitive/restricted behaviors in ASD girls whereas GMV in the right putamen was related to repetitive/restricted behaviors in ASD boys, with some sex-specific effects. A more recent study observed that GMV of the inferior frontal gyrus (IFG), rectus, and caudate were negatively correlated with the subscale scores or total score on the Scale for the Autism Behavior Checklist (ABC) in Chinese boys with low functioning ASD.⁴¹ The inconsistency of the studies above could be due, in part, to the relatively small sample size, or differences in sample characteristics and methodological approaches. In the current study, we used VBM approach⁴² to investigate alterations in regional GMV of individuals with ASD. We also tried to examine correlations between GMV alterations and the severity of autistic symptoms in individuals with ASD, using the subscales of the ABC. To address issues of sample variability and the inconsistency in neuroanatomical findings, we recruited a relatively larger sample and used strict inclusion criteria for individuals with ASD according to age, gender, intelligence quotient (IQ), and diagnosis, and age, gender, and IQ-matched TD controls.

Methods

Participants

We recruited 58 adolescents with HFASD and 66 typically developing (TD) controls at Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine from February, 2017 to May, 2020. Seven ASD participants and one control subject were excluded because their MRI images were of substandard quality such as excessive movements or technical issues. Additionally, three other ASD and two TD participants were excluded to restore group matching on age, gender, and full-scale intelligence quotient (FSIQ), resulting in a final sample of 48 ASD (39 males, 9 females) and 63 TD (43 males, 20 females) participants (Table 1). The ASD participants were diagnosed according to DSM-5,⁴³ and met the criteria for ASD. ASD participants also completed a clinical diagnostic interview with a trained and board-certified psychiatrist experienced in evaluating ASD and comorbid psychiatric conditions. All ASD participants were medication naive and did not have any comorbid psychiatric disorders (eg, attention deficit hyperactivity disorder, oppositional defiant disorder, anxiety disorders, and mood disorders). Children with ASD-related disorders (eg, tuberous sclerosis, Fragile-X syndrome) or other neurological disorders (eg, epilepsy, Tourette's syndrome) were excluded. TD controls were enrolled from Shanghai by advertisements posted in the local school and community. They were interviewed for recruitment and had no self-reported history of ASD, or any current or previous psychiatric or neurological condition. TD controls with first-degree family history of psychotic episodes were also excluded. IQ was assessed using the Wechsler intelligence Scale for Children 4th edition (WISC-IV).⁴⁴ Every participant with ASD scored above the common cutoff

Table 1 Demographic Data and Abnormal Behavioral Performance in Individuals with ASD and TD Controls

	ASD (n=48) ^a		TD (n=63) ^a		Statistics	
	Mean	S.D.	Mean	S.D.	t/x ²	P value
Age, years	13.0	1.90	12.9	1.8	0.33	0.74 ^b
Gender (male/female)	39/9		43/20		2.384	0.123 ^c
Handedness (right/left)	48/0		63/0		–	–
FSIQ	106.9	19.2	111.0	14.3	–1.26	0.211 ^b
ABC						
Sensory	11.3	5.8	NA		–	–
Relating	19.9	7.3	NA		–	–
Body concept	13.0	8.7	NA		–	–
Language	13.2	8.1	NA		–	–
Social self-help	14.1	5.6	NA		–	–
Total ABC score	71.42	28.3	NA		–	–

Notes: There was no significant difference between ASD and TD control groups in age, gender, and FSIQ (all p values >0.05). ^aSeven ASD patients and one TD control were excluded due to excessive head motion. Three other ASD and two TD participants were excluded to restore group matching on age, gender and FSIQ. ^bTwo-tailed t-tests. ^cTwo-tailed chi-square tests.

Abbreviations: ASD, autism spectrum disorder; TD, typically developing; FSIQ, full-scale intelligence quotient; ABC, Autism Behavior Checklist; NA, not applicable.

for the distinction of “low” and “high” functioning ASD (FSIQ > 80).⁴⁵ All participants were Han Chinese, and classified as right-handers according to the Annett Handedness Scale.⁴⁶ The patients had a mean $\pm$ SD age of 13.0 ± 1.9 years (range, 10–18) and a mean $\pm$ SD FSIQ scores of 106.9 ± 19.2 (range, 80–145). The controls had a mean $\pm$ SD age of 12.9 ± 1.8 years (range, 10–18) and a mean $\pm$ SD FSIQ scores of 106.9 ± 19.2 (range, 80–143).

General inclusion criteria for both groups included as follows: (1) aged 10–18 years, (2) right-handed, (3) an ability to possess a full comprehension of the survey instructions and contents. All research procedures employed in this study were in strict conformity with the guidelines of the Declaration of Helsinki. The study protocol was approved by the Medical Research Ethics Committee of Shanghai Mental Health Center. Written informed consents were obtained from each participant and his/her legally authorize guardians prior to inclusion in the study.

Assessment of Autistic Symptoms

The ABC is a checklist of non-adaptive behaviors⁴⁷ that consists of 57 items in 5 areas of categories, including problems related to Sensory (sensation and perception; 9 items), Relating (relation and connection; 12 items), Body concept (physical activity and rigid use of objects; 12 items), Language (communication and interaction; 13 items) and Social self-help (adaptability and self-care; 11 items).⁴⁸ ABC items were rated as “yes” (rated as 1, with symptom) or “no” (rated as 0, without symptom) for each question during the assessment. ABC was well-established instruments for the screening and diagnosis of childhood autism.⁴⁹ It has been widely used in clinical and scientific research, now being one of the most mature rating scales for domestic use.⁵⁰

Imaging Acquisition

All magnetic resonance imaging (MRI) data were collected at Shanghai Mental Health Center using a 3-Tesla Siemens Verio scanner. A standard head coil was padded with foam to reduce head motion and scanner noise. T1-weighted anatomical MRI were acquired using a 3D-MPRAGE sequence: repetition time (TR) = 2530 ms; echo time (TE) = 2980 ms; inversion time = 1100 ms; flip angle (FA) = 7°; field of view (FOV) = 256 mm $\times$ 256 mm; matrix = 256 $\times$ 256; slice thickness = 1 mm, no gap; 192 sagittal slices; and acquisition time = 363 s. All brain scans were examined by an experienced neuroimaging physician and were found to be free from organic brain pathology (for example, tumors, cerebrovascular malformation, and hydrocephalus).

Data Preprocessing and Processing

GMV alterations were examined on T1 images using VBM toolbox in Statistical Parametric Mapping software (SPM, <http://www.fil.ion.ucl.ac.uk/spm>) and the diffeomorphic anatomical registration through an exponentiated Lie algebra (DARTEL) algorithm was taken to achieve more precise segmentation and normalization.⁵¹ Individual MR images were segmented to gray matter, white matter and cerebrospinal fluid sections. The mean images of the individual gray matter were then created. Individual gray matter images were aligned to the Montreal Neurological Institute (MNI) space. Finally, all GMV images were smoothed with a 8-mm full-width at half-maximum isotropic Gaussian kernel.

Statistical Analysis

The demographic characteristics were analyzed with SPSS software (PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc). Two-sample *t*-test was used for testing the differences in age and FSIQ between adolescents with HFASD and TD controls. Gender difference was tested with the Pearson Chi-Square test. The height threshold of statistical significance was set at $p < 0.05$.

Group-level analyses were carried out to examine brain regions with significant detectable GMV abnormalities in adolescents with HFASD. Group-level analyses were carried out to examine GMV abnormalities in adolescents with HFASD. The GMV over the whole-brain structures were compared between the ASD group and TD control group applying permutation-based statistical analysis with 5000 permutations, with age, gender, FSIQ, and total intracranial volume (TIV) as covariates. Statistical significance was defined as $p < 0.001$, correcting for family-wise error (FWE) correction using threshold-free cluster enhancement (TFCE).⁵² The altered GMV brain areas in ASD group were used as inclusion masks to perform the following voxel-wise correlation analysis.

Voxel-wise correlation analyses performed to explore the brain regions that correlated with the severity of autistic symptoms including the total score and each component of ABC (Sensory, Relating, Body concept, Language and Social self-help), respectively. The covariates age, gender, FSIQ, and the TIV were considered as covariates of no interest and were entered into the model to adjust for their potential confounding effects on relation between GMV and symptom characteristics. The above-mentioned clusters, survived thresholding at $p < 0.001$ with FWE-TFCE correction, were applied to include only those voxels that showed significant GMV differences between adolescents with HFASD and TD controls. Correlations were undertaken for significance using the randomized permutation-based nonparametric inference with 5000 permutations and TFCE multiple comparison-corrected. The correlations were considered significant at a p-value of 0.01 corrected for TFCE owing to an exploratory nature of this analysis.

Results

Participants' Demographic Characteristics

Table 1 showed the demographic characteristics and abnormal behavioral performance of adolescents with HFASD and TD controls in the current study. There were no significant differences in age ($p = 0.74$), gender ($p = 0.123$), and FSIQ ($p = 0.211$) between adolescents with HFASD and TD controls.

Regional GMV Abnormalities in ASD Compared with TD Controls

Compared with TD controls, increased GMV values were observed in adolescents with HFASD in the right IFG, right MFG, left superior frontal gyrus (SFG), left superior temporal gyrus (STG), right occipital pole, anterior cingulate, right cerebellum anterior lobe (CAL), right cerebellum posterior lobe (CPL), and right midbrain ($P < 0.001$ for all, FWE-TFCE-corrected; Figure 1 and Table 2). In contrast, decreased GMV values were found mainly in the left CPL in the HFASD group relative to TD ($P < 0.001$ for all, FWE-TFCE-corrected; Figure 1 and Table 2). Individual age, gender, FSIQ scores and TIV were used as covariates during the group comparisons. Subsequently, the correlation analysis in HFASD group was performed within the regions of GMV abnormalities.

Relationship Between GMV Values and Autistic Symptoms

In the HFASD group, there were significantly negative correlations between the GMV value in the left fusiform and the scores of Sensory factor ($r = -0.48$, $P < 0.01$, TFCE-corrected; Figure 2A), and positive correlations between the GMV values in the right CAL and the Social self-help factor ($r = 0.45$, $p < 0.01$; TFCE-corrected; Figure 2B). The ABC total score, Relating, Body concept, and Language showed no significant correlations with the GMV values within the regions that showed significant group differences. The results of above correlation analysis of the adolescents with HFASD are summarized in Table 3.

Discussion

In the current neuromorphometric study, an automated and unbiased voxel-based approach was used to investigate the whole-brain GMV abnormalities in the adolescents with HFASD, as well as its relationship to the severity of their clinical symptoms. Based on the present study, the GMV in the adolescents with HFASD was widely increased in numerous regions (ie, the right IFG, left superior frontal gyrus, left STG, right occipital pole, left ventral anterior cingulate (VAC), right dorsal anterior cingulate (DAC), right CAL, right CPL, and right midbrain). In contrast, the GMV of left CPL in the HFASD group was decreased compared to the TD group. Moreover, the GMV in the left fusiform was negatively associated with the scores of Sensory factor, and the GMV in the right CAL was positively associated with the Social self-help factor. These findings demonstrated that the GMV alterations are present in individuals with ASD, suggesting that the abnormalities of GMV, as the primary neuropathology of ASD, might play a fundamental role in the nature of clinical symptoms of this disorder. It's worth to mention that these significant correlations between altered GMV in these regions (left fusiform and right CAL) and autistic symptoms were corrected for multiple comparisons using TFCE, but unfortunately they did not pass FWE-correction in the multiple testing. We speculate that the small effect size of GMV

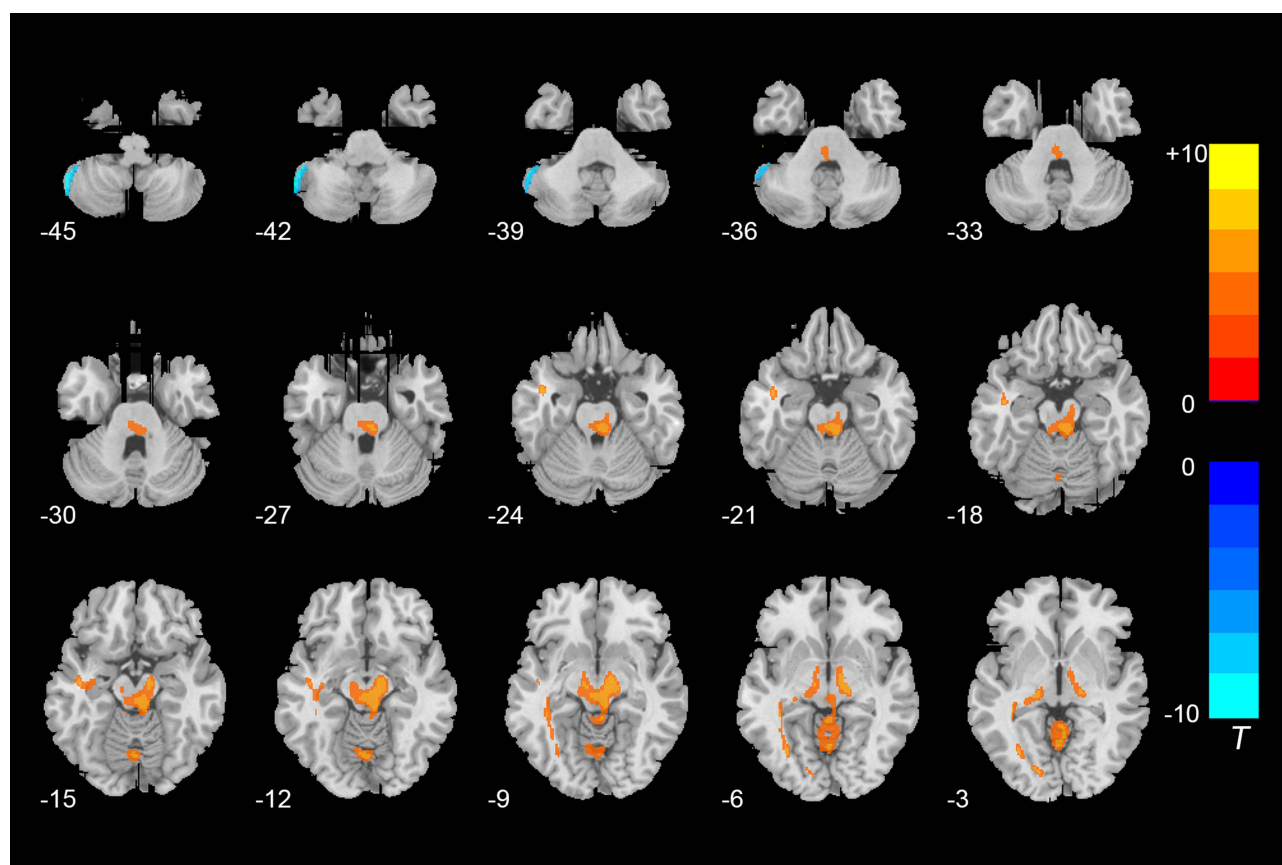


Figure 1 Brain regions with significantly altered GMV in individuals with ASD compared to TD controls. Statistically significant differences in GMV were defined as $p < 0.001$, corrected by TFCE and FWE after adjusting for age, gender, FSIQ scores and TIV. Warm color indicates that GMV is higher in the ASD group than in the TD control group, and vice versa.

abnormalities on psychopathology is likely a matter of location of the gray matter impairment rather than a matter of the intensity of the impairment.

In the current study, the results of widespread GMV alterations in several regions in individuals with ASD compared with that of TD controls are consistent with most of the studies examining GMV values in patients with ASD,^{19,39,53–55} suggesting that the disruption of GMV might contribute to the psychopathology of ASD. However, some other studies failed to report any difference in GMV values between patients with ASD and TD controls,^{17,26–28} or even most of the brain regions with decreased GMV in Chinese boys with low functioning ASD.⁴¹ The discrepancy of the studies above could be partly due to the relatively small sample size, different sample characteristics, limited brain regions investigated, and differences in GMV analysis (voxel-based approach vs ROI-based approach) in these previous studies.

Our current results showed a general pattern of increased GMV in numerous brain regions in the ASD group, compared with TD group, except in the part of the cerebellum. A few studies have emerged accounting for the patterns of neuroanatomical abnormalities in ASD across development, and shed light on alterations in GMV reported in our research. These studies have described a distinct neurodevelopmental trajectories in ASD individuals across the lifespan, which is characterized by an early brain overgrowth,^{56,57} followed by developmental arrest in late childhood and early adolescence,⁵⁸ and accelerated neuroatrophy in adulthood.^{59,60} According to the theory, the brains of individuals with ASD should be larger than those of TD controls during adolescence, even though there is a lag in brain development in this period. Our results showed both increases and decreases in cerebellar GMV in adolescents with ASD with VBM analysis, which is consistent with some previous studies.^{16,20,21} However, some previous studies failed to find any significant difference in cerebellar GMV between patients with ASD and TD controls,^{28,61} even only increased^{39,62} or decreased^{41,63,64} cerebellar GMV in individuals with ASD. There may be several reasons for this discrepancy, such as the

Table 2 Brain Regions with Significant GMV Alterations Between Individuals with ASD and TD Controls

Region	Hemisphere	Cluster Size (Voxel)	MNI Coordinates (mm)			t value
			x	y	z	
ASD>TD						
Frontal lobe						
IFG	Right	124	38	−3	32	11.20
SFG	Right	132	17	30	32	9.74
MFG	Left	214	−18	42	26	8.91
Temporal lobe						
STG	Left	71	−65	−60	24	7.57
Occipital lobe						
Occipital pole	Right	2384	6	−99	−8	5.83
Lingual gyrus	Left	953	−10	−83	−4	4.40
Fusiform gyrus	Left	615	−29	−66	−6	4.30
Limbic lobe						
VAC	Left	226	−2	25	−5	6.32
DAC	Right	132	17	30	32	9.74
Cerebellum						
CAL	Right	3023	2	−56	−5	5.31
CPL	Right	1202	9	−65	−34	5.07
CPL	Right	340	18	−35	−53	5.17
Brainstem						
Midbrain	Right	3586	6	−32	−20	6.50
ASD<TD						
Cerebellum						
CPL	Left	831	−54	−57	−47	−12.27

Note: Statistically significant differences in GMV were defined as $p < 0.001$, corrected by TFCE and FWE after adjusting for age, gender, FSIQ scores and TIV.

Abbreviations: IFG, inferior frontal gyrus; SFG, superior frontal gyrus; MFG, medial frontal gyrus; STG, superior temporal gyrus; VAC, ventral anterior cingulate; DAC, dorsal anterior cingulate; CPL, cerebellum posterior lobe; CAL, cerebellum anterior lobe; TIV, total intracranial volume; MNI, Montreal Neurological Institute.

small sample size, differences in sample characteristics (eg, different developmental ages, gender, and IQ), differences in scanner techniques, including field strengths and sequence parameters, and differences in GMV analysis (postmortem autopsy vs region of interest analysis vs voxel-based approach) in these previous studies.

ASD is a complex disorder that is characterized by multiple symptoms ranging from low-level (eg, sensory processing) to high-level (eg, language, socio-emotional processing, self-referential processing) functions. Consequently, it is not surprising that the extent of neuroanatomical changes reported in our research and in previous studies, involves regions and neural networks throughout the whole brain. Sensory processing is a primary concern for ASD patients. Sensory processing relies on several brain regions, including STG, postcentral gyrus, precuneus, superior parietal cortex, prefrontal cortex, occipital pole, fusiform gyrus, basal ganglia and cerebellum.^{65–69} A recent study has reported that the larger GMV in early sensory regions (eg, lingual gyrus, STG, postcentral gyrus, rolandic operculum, temporal pole, IFG, middle frontal gyrus) significantly correlate with atypical sensory processing of visual, auditory, tactile, and taste/smell modalities.⁷⁰ In our study we found GMV alterations in the IFG, STG, occipital pole and cerebellum. We also found significant correlations between GMV in the fusiform and the scores of Sensory factor on the ABC. Therefore, these neuroanatomical abnormalities may be related to the commonly seen sensory processing deficits in individuals with ASD.

A defining feature of ASD is abnormal social cognition, including deficits in facial emotion perception, theory of mind and empathy.^{71–75} Neural underpinnings of the social behavioral abilities have been investigated extensively, and consists of the amygdala, inferior frontal cortex, medial prefrontal cortex, anterior cingulate cortex, insula, STG, and fusiform gyrus, known collectively as “social brain”.^{71,72,76,77} Indeed, a previous VBM study also demonstrated the

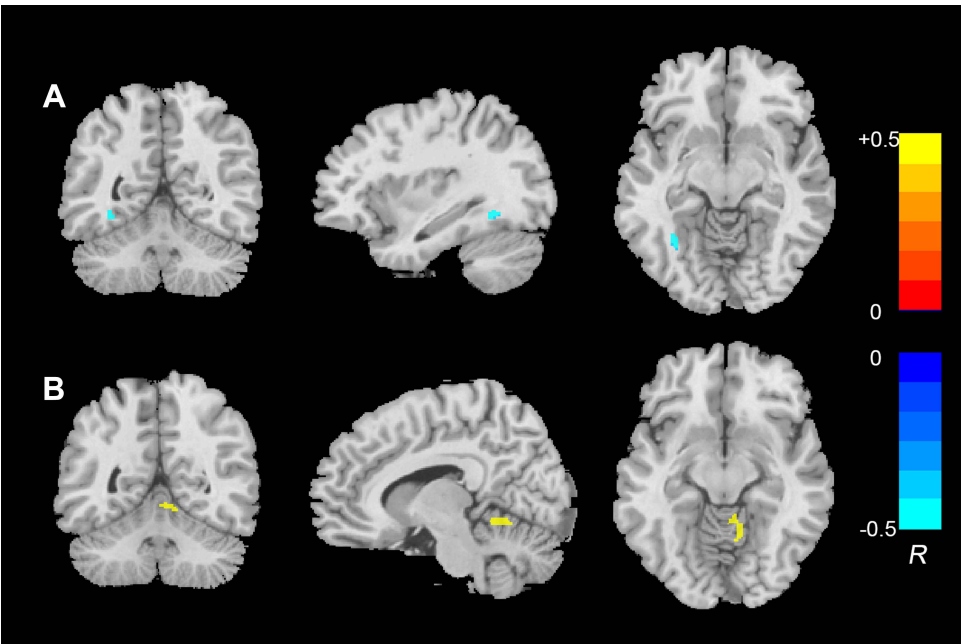


Figure 2 The correlation analysis showed the GMV in the left fusiform was negatively associated with the scores of sensory factor (A), and the GMV in the right CAL was positively associated with the social self-help factor (B).Significant correlations between ABC and GMV were defined as $p < 0.01$, corrected by TFCE after adjusting for age, gender, FSIQ scores and TIV. Warm color indicate positive correlation, and vice versa.

GMV in male adolescents with ASD was increased in those regions associated with social cognition, such as fusiform gyrus, anterior cingulate cortex, superior temporal sulcus, and STG.³⁶ Brain imaging studies have observed hypoactivation in the fusiform face area during the perception of emotional facial expressions in patients with ASD.^{78–81} Studies that investigated the neural basis of theory of mind in ASD found that the deficits of these processes were associated with atypicalities in a set of regions,^{39,82–84} commonly termed theory of mind network, including the medial prefrontal cortex, precuneus, lateral orbitofrontal cortex, middle frontal gyrus, STG, and temporoparietal junction. Impairment in empathy has been implicated in ASD.^{85,86} Indeed, a previous lesion study has indicated that the IFG may be critical for emotional empathy.⁸⁷ Additionally, in an anatomical MRI study investigating the associations between brain regions and empathy for emotion, Eilam-Stock et al revealed that GMV alterations in the IFG may be associated with deficits of emotional empathy.³⁹ The results of our study also revealed GMV abnormalities in the IFG, fusiform gyrus, STG, and anterior cingulate cortex (VAC and DAC). These neuroanatomical abnormalities may be associated, therefore, with social cognition deficits commonly seen in ASD patients. The general picture may reflect an abnormal social cognitive neuroanatomic network.

Our results also suggest GMV abnormalities in several brain regions in ASD that may be connected with altered self-referential processing^{88,89} and autobiographical memory^{90,91} in the disease. The neural basis of self-referential processing has been explored in typically developing samples⁹² and point to a network of cortical midline structures including MFG, anterior cingulate cortex, posterior cingulate cortex, middle cingulate cortex and precuneus,^{89,92,93} and it's worth noting

Table 3 Significant Correlations Between ABC Scores and GMV in ASD

	Correlation Coefficient r	P	Anatomical Region	MNI Coordinate			Cluster Size (Voxel)
				X	Y	Z	
Sensory	−0.48	<0.01	Left fusiform	−35	−54	−9	45
Social self-help	0.45	<0.01	Right CAL	9	−53	−11	158

Notes: Significant correlations between ABC scores and GMV were defined as $p < 0.01$, corrected by TFCE after adjusting for age, gender, FSIQ scores and TIV.
Abbreviations: CAL, cerebellum anterior lobe; TIV, total intracranial volume; ABC, Autism Behavior Checklist; MNI, Montreal Neurological Institute.

that the MFG is regarded as an important hub of the network.⁹⁴ Koush et al⁹⁵ revealed that the SFG play a crucial role in the modulation of self-referential processing in the temporal parietal junction. Other study has also indicated that the IFG is involved in the self-related judgments.⁹⁶ Our results of increased GMV in the IFG, SFG and MFG may be connected, therefore, with abnormal self-referential processing in individuals with ASD.

The increased GMV in the right midbrain in the ASD group in the current study may be involved in the structural aberrations in the mesolimbic reward pathway which was reported to be related to social interaction impairments in children with ASD, especially in the ventral tegmental area.⁹⁷ The mesolimbic reward pathway, which consists of the ventral tegmental area of the midbrain, the nucleus accumbens of the striatum, and the white matter tracts that reciprocally connects them, is a core brain circuit for processing reward value.⁹⁸ A well-known ASD theory assumes that individuals with ASD find social stimuli less rewarding than their typical developmental peers, resulting in impaired social interaction.⁹⁹ Preclinical animal models of ASD also showed a significant link between abnormal mesolimbic reward pathway and aberrancies in reciprocal social interactions.^{100,101} Additionally, Rodier and Arndt revealed an anatomical dissociation between autistic behaviors, such as limited expressive movements of the face, eyes and vocal productions, and the malformation in the midbrain in the embryo.¹⁰² In our study, the midbrain was identified as an area of increased GMV in ASD, which may be the neuroanatomical basis of abnormal reward processing and social information processing in individuals with ASD.

The cerebellum is one of the most common sites of aberrance in ASD, which have been associated with ASD for more than two decades. The concept that the cerebellum is only concerned with fine motor function has been outdated; There are a lot of evidences that the cerebellum is related to higher cognitive functions such as language. Although a recent consensus paper emphasizes the neuroanatomical changes of the cerebellum in individuals with ASD,¹⁰³ previous studies have yielded conflicting results. Indeed increased,^{9,18} decreased^{104,105} and preserved GMV¹⁰⁶ have been reported in studies on cerebellar structures in individuals with ASD compared to TD controls. Consistent with previous studies, our results indicated both increased and decreased GMV in various brain regions of cerebellum. We found altered GMV located in the CPL, a region associated with cognitive and language tasks.¹⁰⁷ Additionally, we observed increased GMV in the CAL and a significant positive correlation between the GMV in the right CAL and abnormal self-care ability in social life in individuals with ASD. As is well known, accumulated evidence has shown that deficits in sensorimotor integration and control in ASD are closely related to self-care performance in social life.^{108,109} Our results of GMV aberrance in the cerebellum anterior and posterior lobes may be related to abnormal sensorimotor function and cognitive function, respectively. Therefore, the topography of sensorimotor and cognitive subregions of the cerebellum emerge because the cerebellum forms closed-loop circuits with sensorimotor and cognitive areas of the cerebral cortex.¹¹⁰

Limitations

Several limitations should be noted when interpreting the results of our study. First, the sample size in our study was still relatively small on account of recruitment difficulties of adolescents with HFASD. The current study strictly limited the inclusion criteria (ie, adolescents with HFASD) to increase statistical power and reduce variability. However, as ASD is a heterogeneous condition with multiple risk factors and etiologies, our sample may not be sufficiently homogeneous. For that reason, future studies with larger samples of individuals falling on different sub-groups of the ASD spectrum are desirable to promote a better description of neuroanatomical changes that contribute to the symptomatology of ASD. On the other hand, our study used strict inclusion criteria and control for different variables, such as age and IQ, and hence, the generalizability of our findings is inevitably reduced. Moreover, one limitation to classification of ASD in current study is the use of only DSM-5 criteria, rather than combining with the systematic method such as Autism Diagnostic Observation Schedule Second Edition (ADOS-2), which is widely used instrument in the diagnosis of ASD. Therefore, the ASD subjects included in current study may have an overestimated risk of ASD diagnosis. Furthermore, owing to the cross-sectional design, we cannot affirm valid conclusions by virtue of the process of disease. In other words, it was impossible to tell exactly whether the autistic symptoms were present as the result of the altered GMV of the brain regions in ASD. Future longitudinal studies could quite likely provide further insight into a fundamental role of the aberrations of regional GMV in the neurobehavioral manifestations of ASD. Lastly, we measured regional GMV of brain

using VBM, which is one of the most commonly used approaches in the study of neuroanatomical aberrations in clinical populations. However, other neuroanatomical methods, such as cortical folding and sulcal depth, cortical surface area, cortical thickness, as well as tract-based spatial statistics for white-matter tract, would be valuable to produce more results about other structural measures as well.

Conclusions

In summary, with fewer confounders, our findings indicate that individuals with ASD have altered GMV values in the numerous regions, suggesting the involvement of GMV abnormalities of ASD. Moreover, the GMV abnormalities of the fusiform and CAL were associated with the clinical symptoms, suggesting that GMV abnormalities may be associated with the psychopathology of ASD. The findings from this study seem to provide an empirical and theoretical basis for exploration for biological markers and further targeted therapy of ASD. While we speculated that the GMV abnormalities of brain regions may be the neuropathological mechanism underlying the symptomatology of ASD, the mechanisms still remain unknown. Thus, the picture that emerges is that GMV alterations require replication in larger samples in individuals with ASD.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

Xiaoxin Zhao, Shuyi Zhu, Yang Cao, Peipei Cheng, Yuxiong Lin, Zhixin Sun, Wenqing Jiang, and Yasong Du declare that they have no conflicts of interest for this work.

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