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ORIGINAL PAPER

Gray matter asymmetry alterations in children and adolescents with comorbid autism spectrum disorder and attention-deficit/hyperactivity disorder

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Abstract
Despite the high coexistence of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) (ASD + ADHD), the underlying neurobiological basis of this disorder remains unclear. Altered brain structural asymmetries have been verified in ASD and ADHD, respectively, making brain asymmetry a candidate for characterizing this coexisting disorder. Here, we measured the gray matter (GM) volume asymmetry in ASD + ADHD versus ASD without ADHD (ASD-only), ADHD without ASD (ADHD-only), and typically developing controls (TDc). High-resolution T1-weighted data from 48 ASD + ADHD, 63 ASD-only, 32 ADHD-only, and 211 matched TDc were included in our study. We also assessed brain-behavior relationships and the effects of age on GM asymmetry. We found that there were both shared and disorder-specific GM volume asymmetry alterations in ASD + ADHD, ASD-only, and ADHD-only compared with TDc. This finding demonstrates that ASD + ADHD is neither an endophenocopy nor an additive pathology of ASD and ADHD, but an entirely different neuroanatomical pathology. In addition, ASD + ADHD displayed altered GM volume asymmetries in the prefrontal regions responsible for executive function and theory of mind compared with ASD-only. We also found significant effects of age on GM asymmetry. The present study may provide structural insights into the neural basis of ASD + ADHD.

Keywords Autism spectrum disorder · Attention-deficit/hyperactivity disorder · Comorbidity · Gray matter volume asymmetry

Autism spectrum disorder (ASD) manifests with impaired social communication and repetitive behaviors [1]. Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and impulsivity [1]. ASD and ADHD are two genetically complex childhood-onset neurodevelopmental disorders with high prevalence and often co-occur. Approximately 15–25% of ADHD patients show ASD symptoms, and ~ 40–70% of ASD patients have comorbid ADHD symptomatology [2]. Within the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), it is not permitted to diagnose both ASD and ADHD in the same case. In such cases, only a limited number of studies have attempted to examine the co-occurrence of ASD and ADHD. Under the support of DSM-5, concurrent diagnoses are allowed in clinical practice when individuals meet the criteria for both ASD and ADHD (ASD + ADHD) [1]. Existing studies exhibit scarce and inconsistent results in describing the phenotypic variability of patients with ASD + ADHD [3].

Most studies have reported that individuals with ASD + ADHD display deficits associated with both diagnoses and these individuals experience more severe impairments. For example, one study found that ASD + ADHD children expressed more serious attention deficits than

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patients diagnosed with ASD only [4]. Another study found that ASD + ADHD children had greater impairments in adaptive behaviors and a poorer pediatric quality of life in comparison with ASD children or ADHD children [5]. Individuals suffering from ASD + ADHD exhibited more than twice as much cognitive delay as those with ASD only [6]. Moreover, studies demonstrated that comorbid ADHD in ASD was associated with greater impairments in sensory and language processing and social communication, interaction, and awareness [7–9].

Currently, the diagnostic and differential criteria for these mental disorders are solely based on signs and symptoms. More specifically, individuals with ASD + ADHD are usually recognized because they have social communication deficits and repetitive behaviors. However, identifying comorbid ADHD is exceptionally difficult as there are no objective tests to identify such factors. Clinicians are often hampered in their diagnosis and find it tough to decide if one or two diseases could provide the best description of the patient's problem. The comorbid ADHD in ASD is also associated with decreased effectiveness of treatments [10]. Thus, it is urgent to identify objective markers for the diagnosis and differential diagnosis of ADHD + ASD.

The US National Institute of Mental Health has initiated the Research Domain Criteria project to address the problem that symptom-based diagnosis cannot reach effective treatment. One of the main objectives of this proposal is to establish a framework for pathophysiology research, particularly in the areas of neuroscience and genomics [1], and ultimately to use this information to identify new classifications. Neuroimaging studies can contribute to elucidating the underlying neural mechanisms of mental disorders, thus providing valuable information for their classification. Using this model, future studies will undoubtedly improve the efficacy of treatments.

Despite the high coexistence of ASD and ADHD, the greater impairments and poor therapeutic effects in ASD + ADHD, and the substantial value of neuroimaging in identifying ASD + ADHD, neuroimaging studies on ASD + ADHD are limited and the underlying neural basis of this disorder remains unclear. Some brain structural studies on ASD + ADHD have been conducted. For example, research has revealed that children and preadolescents with ASD + ADHD have significantly larger left postcentral gyrus volume than typically developing controls (TDc) [1]. The ASD + ADHD and ASD shared alterations in the striatum (i.e., increased volume in the bilateral caudate and putamen) [11]. ASD + ADHD showed reduced volume in the left inferior frontal gyrus, compared to ASD [12]. Studies aimed at identifying brain structural features shared between ADHD and ASD have shown mixed results [13, 14]. The above findings suggested that the brain structural changes in ASD + ADHD are not a more severe form of ASD or ADHD. Thus, further investigations regarding the unique brain structure alterations in ASD + ADHD are undeniably important. These markers may lead to earlier identification and more accurate treatment, especially at the early developmental stage of the disease, when interventions can lead to the best rehabilitative outcomes.

The human brain exhibits left–right asymmetry in both structure and function [15]. In most TDc, the left hemisphere exerts dominance over verbal cognitive function, and the right hemisphere is specialized for visuospatial attention [15]. The right asymmetry of the frontal region and left asymmetry of the occipital region in TDc have always been described in previous studies [16]. Typical brain asymmetry is perceived to be an evolutionary advantage in improving the efficiency of neural processing and avoiding redundancy in cognitive processing [16].

Altered brain structural asymmetries have been associated with a variety of psychiatric conditions, including ASD and ADHD [16]. In ASD, one study with a large sample size showed that ASD exhibited significantly decreased thickness asymmetries in the orbitofrontal, medial frontal, inferior temporal, and cingulate cortex; altered surface area asymmetries in the medial orbitofrontal and lateral orbitofrontal regions; and increased volume leftward asymmetry in the putamen compared to controls [17]. Meanwhile, Postema et al. performed the largest sample size study to date on brain structural asymmetry of ADHD and reported that ADHD had significantly decreased surface area rightward asymmetries in the total hemisphere and medial orbitofrontal regions compared to controls. The direction and extent of altered surface area asymmetry in the medial orbitofrontal region were the same in ASD and ADHD [18]. However, asymmetric findings about the two disorders are not always consistent. For example, ASD always exhibits deficits in left hemisphere skills, such as language [19], whereas ADHD is particularly related to alterations of the right hemisphere [18]. Individuals with ADHD exhibited increased volume rightward asymmetry in the putamen compared to controls [16], while ASD displayed increased volume leftward asymmetry in the putamen compared to controls [17]. Although many brain structural asymmetry studies on ASD and ADHD have been conducted, as described above, there have been no studies to date on ASD + ADHD. Due to the absence of research, the brain structural asymmetry of ASD + ADHD is still a mystery.

In this study, we attempted to examine the gray matter (GM) volume asymmetry in individuals suffering from ASD + ADHD versus ASD without ADHD (ASD-only), ADHD without ASD (ADHD-only), and TDc. We also explored the brain-behavior relationships and the developmental features of GM volume asymmetry. For this, a modified voxel-based morphometry (VBM) method and large samples (48 ASD + ADHD, 63 ASD-only, 32

ADHD-only, and 211 TDc) were used. We hypothesized that ASD + ADHD may have unique alterations in GM volume asymmetry because these individuals have unique phenotypes. However, we also predicted that there would be shared alterations in GM volume asymmetry between ASD + ADHD and ASD-only and between ASD + ADHD and ADHD-only, as the three groups are partly on the same disease spectrum.

Participants and methods

Participant recruitment

According to previous studies [20], participants were selected based on the following criteria. First, the ASD and TDc were chosen via the diagnostic group coding specification (1 = Autism; 2 = Control) informed by ABIDE II phenotypic data legend, and those suffering from additional psychotic disorders apart from ADHD were excluded. The ASD participants were separated into two subgroups, the ASD + ADHD group, and the ASD-only group, depending on whether the ASD participants comorbid with ADHD. Second, a whole-brain-covered T1-weighted image was required in the dataset for each participant. Third, T1-weighted images of included subjects were of excellent quality to ensure successful pre-processing. Age, gender, and handedness were matched between the ASD + ADHD and ASD-only group, as well as between the ASD and TDc group. After strict inclusion screening, a total of 322 participants, comprising 48 ASD + ADHD, 63 ASD-only, and 211 matched TDc, were aggregated across 6 sites (University of California Davis, Oregon Health and Science University, NYU Langone Medical Center, Kennedy Krieger Institute, Institut Pasteur and Robert Debré Hospital, Erasmus University Medical Center Rotterdam) in ABIDE II: a database containing 521 ASD and 593 TDc (ages 5–64 years) collected from 19 international sites. Autistic traits were assessed by the Social Responsiveness Scale (SRS) and Revised Autism Diagnostic Interview (ADI-R) [20]. In particular, only the diagnosis of comorbidity types was presented in ABIDE II, without relevant questionnaire data or symptom scores.

In addition, we included 32 ADHD-only participants from the Oregon Health and Science University site in the ADHD-200 Sample database (http://fcon_1000.projects.nitrc.org/indi/adhd200/). The ADHD-200 Sample is a grassroots initiative, dedicated to accelerating the scientific community's understanding of the neural basis of ADHD through the implementation of open data-sharing and discovery-based science. T1-weighted images of included subjects were of excellent quality to ensure successful pre-processing. Age and gender were matched between the ADHD-only group and the TDc group.

MRI data acquisition

The T1-weighted anatomical images used in our study were acquired with different MRI scanners, details of sequence parameters, acquisition protocols, and scanner types are available at http://fcon_1000.projects.nitrc.org/indi/abide/ and http://fcon_1000.projects.nitrc.org/indi/adhd200/.

Image analysis

The procedures for data pre-processing and statistical analyses are shown in Fig. 1.

Image preprocessing

Structural image preprocessing was conducted using the Statistical Parametric Mapping 12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), Computational Anatomy Toolbox 12 (CAT12; https://neuro-jena.github.io/cat/), and MATLAB 2022a (https://www.mathworks.com). Before preprocessing, the high-resolution T1-weighted images were visually checked for quality control. Meanwhile, the raw images were manually aligned to the anterior commissure-posterior commissure (AC-PC) axis. The detailed processing steps were as follows. (1) Segment tissues: T1-weighted images were segmented by applying a tissue probability map (downloaded from http://dbm.neuro.uni-jena.de/vbm8/TPM_symmetric.nii) to obtain separate GM segments and white matter (WM) segments. The quality of the segments was then checked. We assessed the segmented images of each subject and excluded subjects with failed tissue segmentations. Kurth et al. provided successful and failed tissue segmentation cases, and we referred to those examples [20]. Meanwhile, we also used the image quality assessment function of CAT12. An overall weighted image quality rating (IQR) was calculated in CAT12 for each participant. The IQR is a single score that summarizes noise, bias, and image resolution for image quality before and after preprocessing. Only subjects with IQR ≥ B in the report were included. Supplementary Fig. 1 provides three successful tissue segmentation examples of our data. (2) Flip tissue segments: the GM and WM segments created in step 1 were horizontally flipped at the midline to generate left–right reversed images. By performing this step, there were both nonflipped and flipped images for each tissue segment. (3) Create a symmetrical template: the analysis-specific Diffeomorphic Anatomical Registration Lie (DARTEL) template was created using all nonflipped and flipped GM and WM segments. (4) Warp images: the nonflipped and flipped GM versions were spatially warped to the

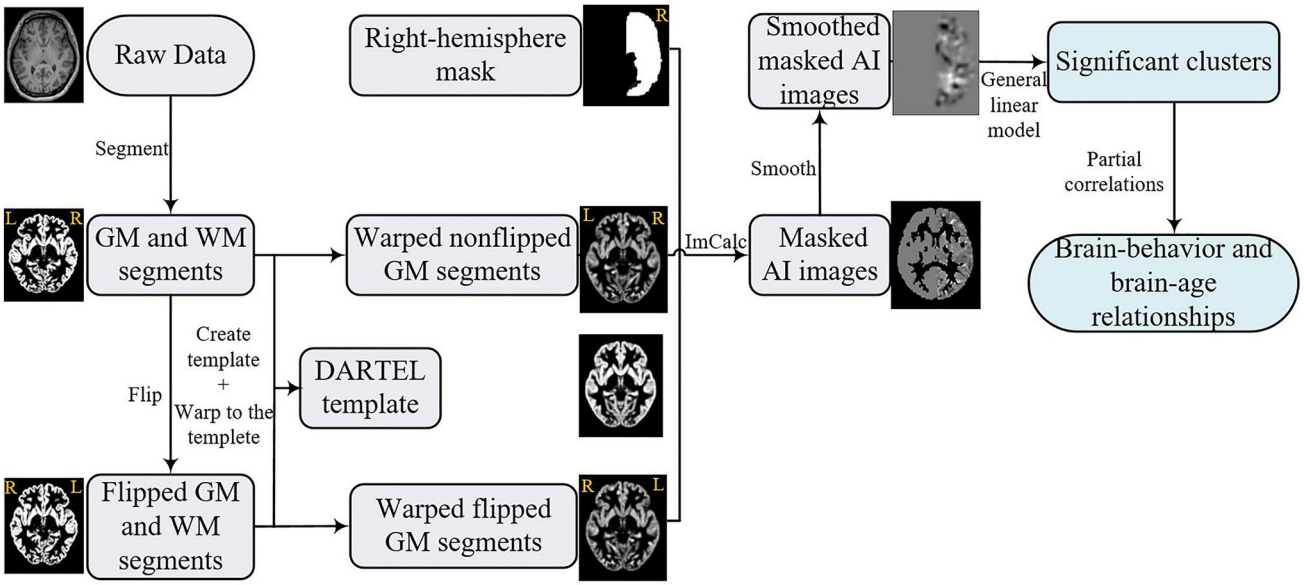

Fig. 1 Processes of data processing and statistical analyses. *GM* gray matter, *WM* white matter, *DARTEL* diffeomorphic anatomical registration lie, *AI* asymmetry index.

abovementioned DARTEL template. (5) Generate a right-hemispheric mask: such a mask was achieved in MRIcron (http://people.cas.edu/rorden/mricron/index.html) in symmetric template space (the DARTEL template) for limiting the statistical analysis in the right hemisphere.

Estimation of the asymmetry index (AI)

The nonflipped and flipped warped GM segments (Created in step 4) were chosen to calculate the GM volume AI images within the abovementioned right-hemispheric mask, under the following formula: $AI = ((i1-i2)/((i1+i2).*0.5)).*i3$ [20], where i1 refers to the nonflipped warped GM segments, i2 refers to the flipped warped GM segments, and i3 refers to the right-hemispheric mask image. In this step, due to the use of the right hemisphere mask, for all nonflipped and flipped warped GM segments, only the right hemisphere is retained for further analysis. Thus, the nonflipped warped GM versions yielded the right hemispheres, and flipped warped GM versions yielded the left hemispheres, respectively. The "i1−i2" in the right hemisphere represents ''right-minus-left'' asymmetry. Therefore, as shown in Supplementary Fig. 2, positive AIs represent rightward GM volume asymmetry and negative AIs represent leftward GM volume asymmetry. Then, the resulting AI maps were spatially smoothed with an 8 mm × 8 mm × 8 mm full-width at a half-maximum Gaussian kernel [6]. To investigate how spatial smoothing may affect the AI images, different Gaussian smooth kernels (6 mm, 10 mm) were used to smooth the AI images.

Statistical analyses

Differences in handedness, gender, and medication between the ASD + ADHD group and ASD-only group, handedness and gender between the ASD and TDc group, and gender between the ADHD-only group and TDc group were analyzed by the chi-square test in the Statistical Package for the Social Sciences 25 (SPSS 25) software (IBM Corp, Armonk, NY), and other variables were compared between groups using the two-tailed t-test. $P < 0.05$ was considered significant.

To test which brain regions showed significant statistical inter-group differences in GM volume asymmetry between the ASD + ADHD group, ASD-only group, ADHD-only group, and TDc group, the general linear models (GLM) were performed in SPM 12, with age, handedness, gender, medication, full intelligence quotient (FIQ), and site as covariates (varying across models). Each site was treated as a separate binary variable in the GLM to covary by site, which can include demographic, clinical and technical heterogeneity. The Gaussian random field (GRF) correction was used for multiple comparisons (two-tailed, voxel-level $p < 0.001$, and cluster level $p < 0.005$) [19]. Brain regions with significant statistical inter-group differences in the GM volume asymmetry were saved as masks using the Data Preprocessing Assistant for rs-fMRI (DPARSF, http://rfmri.org/dpabi; Yan et al. 2016) software.

We repeated the GLM analysis using only the subset of 3 T acquired data (6 out of 7 data sets), to test for possible sensitivity to this technical variable. The sample was reduced from 354 to 334 cases (46 ASD + ADHD, 54

ASD-only, 202 matched TDc, and 32 ADHD-only) in the 3 T-only analysis.

In addition, partial correlations controlling for age, handedness, gender, medication, FIQ, and site were performed in SPSS 25 to probe brain-behavior relationships between autistic traits measured by ADI-R-social subscale and SRS-total scale and AIs showing significant statistical inter-group (ASD + ADHD vs. TDc) differences. The statistical threshold was set at $p < 0.05$ using a Benjamini-Hochberg false discovery rate (FDR) correction with MATLAB to explore the most significant correlations. These analyses were restricted to 41 ASD + ADHD participants whose ADI-R-social subscale was available and 42 ASD + ADHD participants whose SRS-total scale was available.

Similarly, to probe the relationship between AIs showing significant statistical inter-group (ASD + ADHD vs. TDc) differences and age in ASD + ADHD and TDc groups, partial correlations controlling for gender, FIQ, handedness, medication (only in ASD + ADHD group), and site were conducted. The $p < 0.05$ (FDR correction) was considered significant.

Results

Demographic and clinical details

Participants' clinical characteristics and descriptive statistics are summarized in Table 1. ASD and TDc were matched for age, handedness, and gender, but there were significant differences in FIQ and SRS-total scores between the two groups (both $p < 0.001$). Within the ASD group, there were no significant differences between the ASD + ADHD group and ASD-only group in terms of age, handedness, gender, FIQ, and ADI-R-social score (all $p > 0.05$), but there were significant differences in terms of SRS-total score and medication ($p = 0.025$ and $p = 0.031$, respectively). ADHD-only and TDc were matched for age and gender, but there was a significant difference in FIQ between the two groups ($p < 0.001$).

Differences in GM volume asymmetry between ASD + ADHD and TDc.

As showcased in Fig. 2a and Table 2, specific brain regions displayed significant differences between ASD + ADHD and TDc: ASD + ADHD showed significantly increased leftward asymmetry in Cluster A2 (Inferior Frontal/Superior Temporal Gyrus) and decreased rightward asymmetry

Table 1 Participant demographics

	Mean (SD) [range]								
	ASD + ADHD (n = 48)	ASD-only (n = 63)	p	ASD (n = 111)	TDc (n = 211)	p	ADHD-only (n = 32)	TDc (n = 211)	p
Age(years)	10.31(2.79) [6–18]	10.36(3.46) [5–18]	0.883	10.25(3.13) [5–18]	10.53(1.92) [6–18]	0.386	10.88(2.53) [7–18]	10.53(1.92) [6–18]	0.379
Handedness (n, Right/Left/Mixed)	38/2/8	51/4/8	0.760	89/6/16	185/12/14	0.073			
Gender (n, male/female)	40/8	53/10	0.911	93/18	157/54	0.055	20/12	157/54	0.158
FIQ	102.09(17.25) [73–143]	104.00(16.97) [71–136]	0.582	103.15(17.03) [73–143]	115.13(11.79) [73–144]	< 0.001	107.88(12.78) [86–132]	115.13(11.79) [73–144]	< 0.001
Medication (n, on/off)	16/32	10/53	0.031						
ADI-R-social ($N_{ASD+ADHD} = 41$; $N_{ASD-only} = 39$)	19.15(5.96) [0–29]	17.46(6.77) [0–28]	0.240	18.33(6.38) [0–29])					
SRS-total ($N_{ASD+ADHD} = 42$; $N_{ASD-only} = 47$; $N_{TDc} = 189$)	77.10(11.55) [53–101]	71.02(13.31) [42–95])	0.025	73.89(12.81) [42–101]	43.71(5.57) [34–101]	< 0.001			

ASD autism spectrum disorder, *ADHD* attention deficit hyperactivity disorder, *ASD + ADHD* the comorbidity of ASD and ADHD, *ASD-only* ASD without ADHD, *ADHD-only* ADHD without ASD, *TDc* typically developing controls, *SRS* social responsiveness scale, *FIQ* full intelligence quotient, *ADI-R* revised autism diagnostic interview

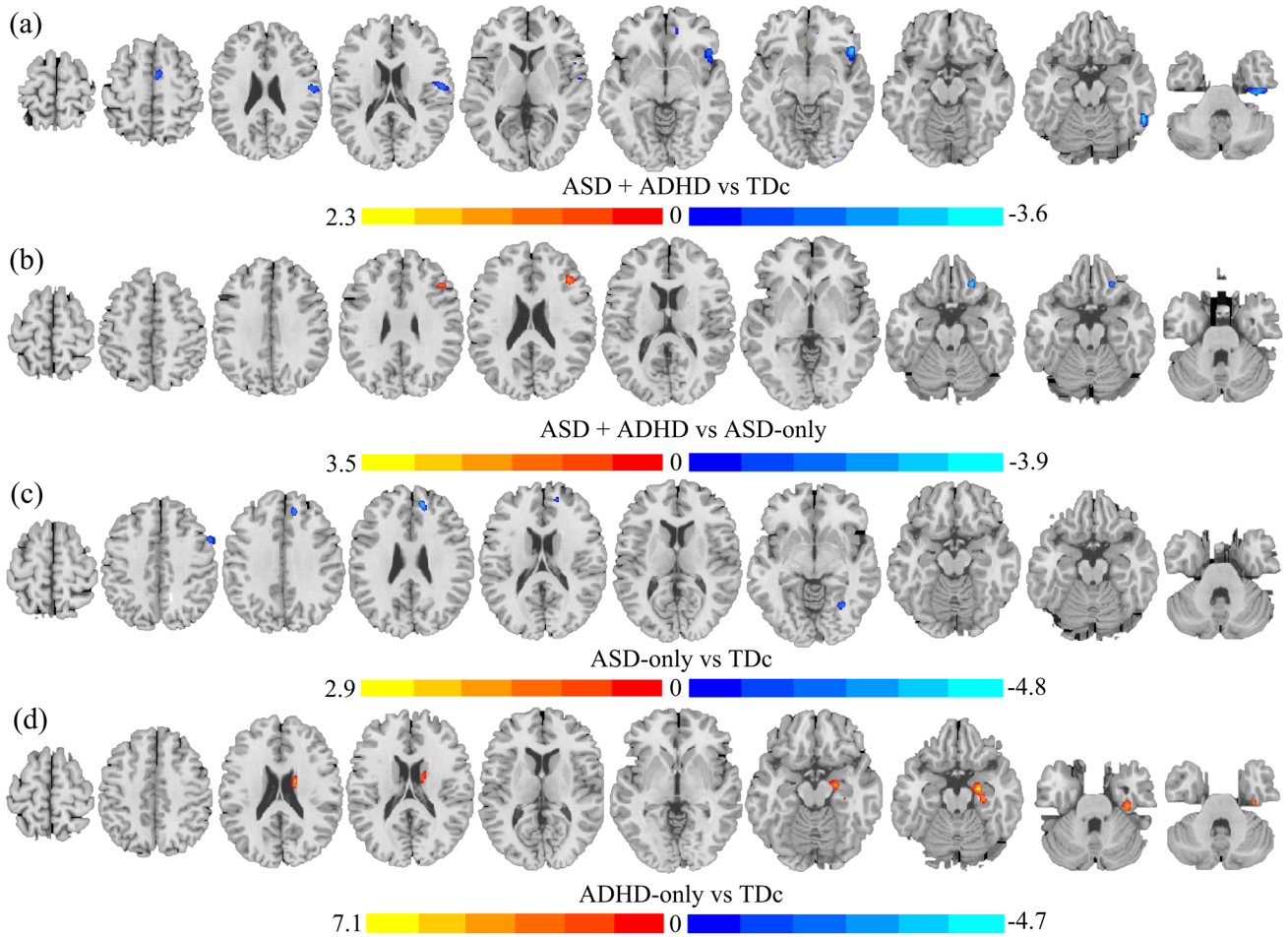

Fig. 2 Differences of GM volume asymmetry in between-group comparisons. **a** ASD + ADHD vs. TDc:5 clusters with significant differences between ASD + ADHD and TDc: **b** ASD + ADHD vs ASD-only.2 clusters with significant differences between ASD + ADHD and TDc. **c** ASD-only vs TDc: 3 clusters with significant differences between ASD-only and TDc. **d** ADHD-only vs TDc: 2 clusters with significant differences between ADHD-only and TDc. Results were corrected for multiple comparisons using the Gaussian random field procedure with the voxel level *P* value < 0.001 and the cluster level of $P < 0.005$. *GM* gray matter, *ASD* autism spectrum disorder, *ADHD* attention deficit hyperactivity disorder, *ASD + ADHD* the comorbidity of ASD and ADHD, *ASD-only* ASD without ADHD, *ADHD-only* ADHD without ASD, *TDc* typically developing controls

in Cluster A1 (Fusiform/Inferior Temporal Gyrus), Cluster A3 (Medial Frontal Gyrus), Cluster A4 (Medial Orbitofrontal Gyrus), and Cluster A5 (Precentral/Postcentral Gyrus).

Differences in GM volume asymmetry between ASD + ADHD and ASD-only

GM asymmetry differences between ASD + ADHD and ASD-only were shown in Fig. 2b and Table 2: relative to the ASD-only, the ASD + ADHD showed significantly increased rightward asymmetry in Cluster B2 (Medial Frontal Gyrus) and decreased rightward asymmetry in Cluster B1 (Inferior Frontal/ Superior Frontal/Middle Frontal/Medial Orbitofrontal Gyrus).

Differences in GM volume asymmetry between ASD-only and TDs

Compared to TDs, ASD-only exhibited significantly decreased rightward asymmetry in Cluster C1(Parahippocampa/Fusiform Gyrus), Cluster C2(Medial Frontal/Superior Frontal/Anterior Cingulum Gyrus), and Cluster C3 (Middle Frontal/Precentral Gyrus) (Fig. 2c, Table 2).

Differences in GM volume asymmetry between ADHD-only and TDc

GM asymmetry differences between ADHD-only and TDc were shown in Fig. 2d and Table 2: relative to the TDc, the ADHD-only showed significantly increased rightward

Table 2 Coordinates and AI values of clusters with significant differences in between-group comparisons

	Cluster	Location	MNI coordinates			voxels	t-value
			x	y	z		
ASD + ADHD vs TDc	A1	Fusiform/Inferior Temporal Gyrus	40.5	−18	−36	136/89	−3.295
	A2	Inferior Frontal/Superior Temporal Gyrus	48	22.5	−9	286/110	−3.491
	A3	Medial Frontal Gyrus	3	−4.5	57	142	−3.097
	A4	Medial Orbitofrontal Gyrus	12	45	−6	30	−2.841
	A5	Precentral/Postcentral Gyrus	57	−10.5	24	206/199	−3.213
ASD + ADHD vs ASD-only	B1	Inferior Frontal/Superior Frontal/Middle Frontal/Medial Orbitofrontal Gyrus	24	33	−22.5	96/72/47/43	−3.908
	B2	Medial Frontal Gyrus	43.5	30	13.5	130	3.432
ASD-only vs TDc	C1	Parahippocampa/Fusiform Gyrus	30	−60	−4.5	72/20	−4.254
	C2	Medial Frontal/Superior Frontal/Anterior Cingulum Gyrus	13.5	45	25.5	266/ 127/30	−4.429
	C3	Middle Frontal/Precentral Gyrus	55.5	9	45	109/91	−4.210
ADHD-only vs TDc	D1	Parahippocampa/Hippocampus/Fusiform Gyrus	24	−10.5	−19.5	562/238/144	7.132
	D2	Caudate nucleus	16.5	−4.5	24	121	5.818

ASD autism spectrum disorder, *ADHD* attention deficit hyperactivity disorder, *ASD + ADHD* the comorbidity of ASD and ADHD, *ASD-only* ASD without ADHD, *TDc* typically developing controls, *ADHD-only* ADHD without ASD. Some clusters are located in multiple brain regions with larger voxel values; therefore, the voxel column gives the voxel values for all brain regions. For example, A1 is mainly located in the fusiform and inferior temporal gyrus, and their voxel values are 136 and 89, respectively

asymmetry in Cluster D1 (Parahippocampa/Hippocampus/Fusiform Gyrus) and decreased leftward asymmetry in Cluster D2 (Caudate nucleus).

The 6 mm and 10 mm Gaussian smooth kernels

As shown in Supplementary Table 1, different Gaussian smooth kernels did not influence much on the main resulting brain regions.

Subset of 3 T-acquired data

As shown in Supplementary Table 2, one of the ASD + ADHD vs TDc results from the primary analysis (i.e., medial orbitofrontal gyrus volume AI) was no longer significant in the 3 T-only subset analysis, but two other effects now became significant (i.e., supramarginal gyrus volume AI in ASD + ADHD vs TDc and inferior frontal gyrus volume AI in ASD-only vs TDc) in this analysis.

Brain-behavior relationships

ASD + ADHD (n = 42) exhibited a negative correlation between the SRS-total score and the AIs in Cluster A3 (Medial Frontal Gyrus) ($r_{partial} = -0.384$, $p = 0.017$). However, this correlation ceased to be significant after adjustment for multiple comparisons. No significant associations were found between any clusters and the ADI-R-social score and between other clusters and the SRS-total score.

The effect of age

From 6 to 18 years of age, Cluster A1 showed decreased rightward asymmetry over time in ASD + ADHD ($r_{partial} = -0.404$, $p = 0.009$); Cluster A5 exhibited increased rightward asymmetry with age in TDs ($r_{partial} = 0.193$, $p = 0.005$). The scatters and line plots in Fig. 3 visualize the above correlations.

Discussion

Although the diagnostic criteria for ASD + ADHD have been established, the underlying neurobiological basis of this disorder remains unclear. Here, we systematically investigated the GM volume asymmetry alterations in ASD + ADHD versus ASD-only, ADHD-only, and TDc. Core findings in our study are shown below: (1) Significantly altered GM volume asymmetries mainly located in the frontal, temporal, postcentral, and fusiform regions in ASD + ADHD compared with TDs. (2) ASD + ADHD displayed altered GM volume asymmetries in the prefrontal regions responsible for executive function and Theory of Mind (ToM) compared with ASD-only; (3) The fusiform gyrus was the shared region in altered GM volume asymmetry in ASD + ADHD and ADHD-only compared with TDc; the fusiform, medial frontal, and precentral gyrus were the shared regions in ASD + ADHD and ASD-only; the inferior and superior temporal, inferior frontal, medial orbitofrontal, and postcentral gyrus were specific to ASD + ADHD relative to ASD-only; and the inferior and superior temporal, inferior

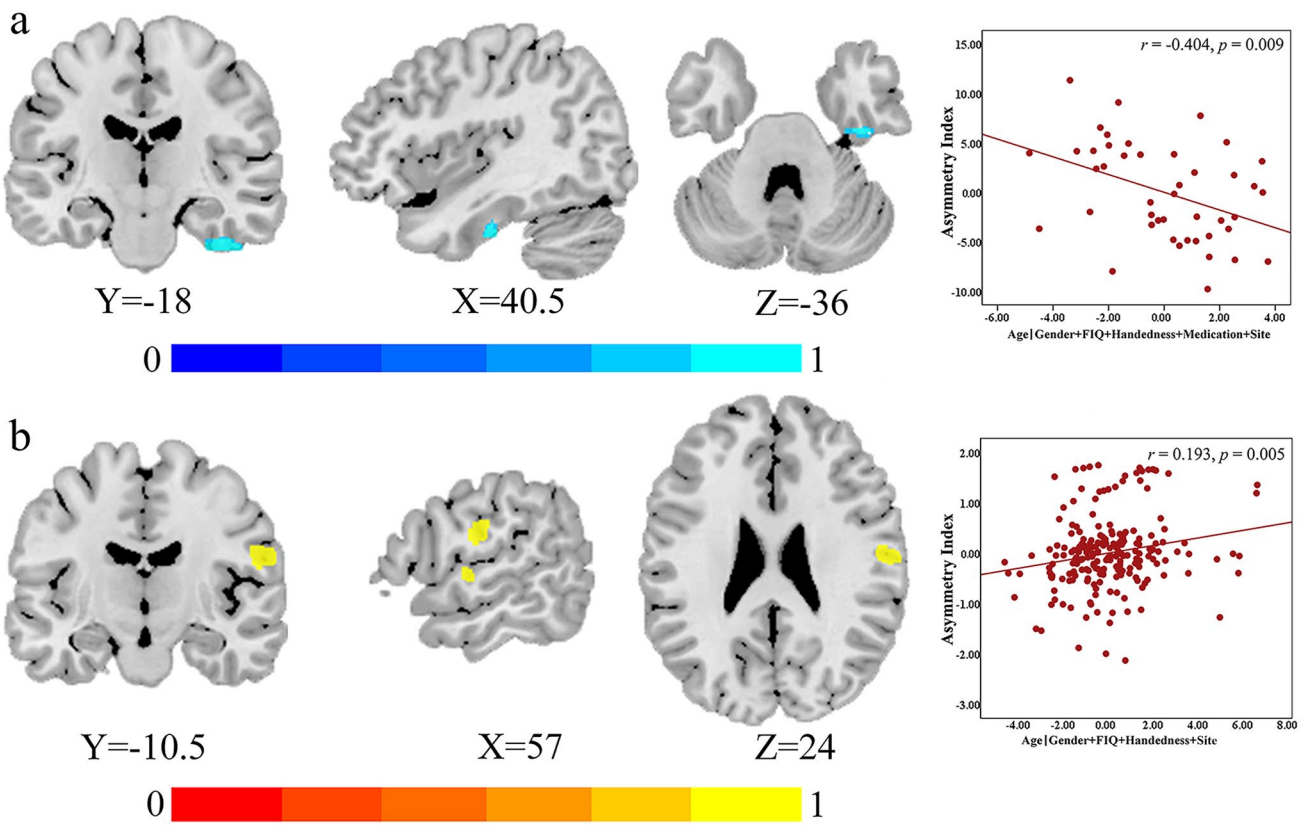

Fig. 3 Relationships between AIs and age. **a** Cluster A1 showed decreased rightward asymmetry over time in ASD + ADHD ($r_{partial} = -0.404$, $p = 0.009$). **b** Cluster A5 exhibited increased rightward asymmetry with age in TDs ($r_{partial} = 0.193$, $p = 0.005$). $P < 0.05$ (FDR correction) was considered significant. *AI* asymmetry index, *ASD* autism spectrum disorder, *ADHD* attention deficit hyperactivity disorder, *ASD + ADHD* the comorbidity of ASD and ADHD, *TDc* typically developing controls, *FIQ* full intelligence quotient

frontal, medial frontal, medial orbitofrontal, precentral, and postcentral gyrus were specific to ASD + ADHD relative to ADHD-only.

ASD and ADHD often co-occur, which may be due to shared pathogenic mechanisms [21]. Specifically, the study on the psychological processes associated with ASD + ADHD has been structured around executive dysfunction and ToM deficits [22]. The ToM and executive function are both implicated in the cognitive functions of inhibitory control. The ToM ability is the overall development of individual executive functions [23]. Such functions are generally known to be mediated by the prefrontal cortex [24].

The prefrontal cortex is a key brain area that integrates information from multiple cortical and subcortical regions and converges updated information into output brain structures [25]. It plays an important role in cognitive processes, emotion regulation, and sociability [25]. Asymmetry dysfunction of the prefrontal cortex has been identified in various neuropsychiatric disorders, particularly in ASD and ADHD. For example, in ASD, one study with a large sample size showed that ASD exhibited significantly decreased thickness asymmetries in the orbitofrontal and medial frontal regions and altered surface area asymmetries in the medial and lateral orbitofrontal regions compared to controls [17]. Meanwhile, Postema et al. performed the largest sample size study to date on brain structural asymmetry of ADHD and reported that ADHD had significantly decreased surface area rightward asymmetry in the medial orbitofrontal region compared to controls [18]. In our study, significantly altered GM volume asymmetries were widely distributed in the prefrontal regions (medial frontal/medial orbitofrontal/inferior frontal gyrus) in ASD + ADHD compared with TDs. The prefrontal cortex has important functions not only in executive functions but also in TOM [24, 26], suggesting that disrupted laterality of prefrontal regions might be particularly important in ASD + ADHD.

ADHD and ASD often show different deficit patterns of executive function. ADHD usually displays more deficits in inhibitory control and sustained attention, whereas problems in planning and cognitive flexibility are often more serious in ASD [27]. Studies have shown that ASD + ADHD is associated with more severe executive dysfunctions than a single diagnosis, and with deficit patterns in both disorders

[27]. For ToM impairments, ASD is more pronounced, and ADHD is intermediate between TDc and ASD [28]. In addition, the ToM deficits in ADHD occur later than in ASD. Although this research field is still in its infancy, the findings have demonstrated that comorbid ADHD contributes to increased ToM deficits in ASD [29]. In our study, GM volume asymmetry in the medial frontal gyrus was altered in both ASD + ADHD and ASD-only patients compared with TDc, suggesting that this brain region is the common neuroimaging basis for the ToM deficits and executive dysfunctions in both disorders. In addition, when comparing ASD + ADHD with ASD-only, significantly different brain regions were all located in the prefrontal cortex. This may be related to the fact that combined ADHD would increase the ToM deficits and executive dysfunctions in ASD.

It has been demonstrated that the superior temporal gyrus is a crucial language and social cognition region not only in normally developed subjects but also in language-impaired individuals [30]. Social cognition is about the processing of information such as facial expressions, eye gaze, and physical movement by individuals during social interactions. Its main purpose is to perceive and understand an individual's mental state [30]. For language function, during embryonic and early postnatal development, the right superior temporal gyrus shares language processing capabilities with the left superior temporal gyrus [31]. Nevertheless, the case begins to change in later development, with the left superior temporal gyrus displaying a distinct advantage in language processing [31]. Structural abnormalities in the superior temporal gyrus have been reported frequently in ASD but rarely in ADHD. For example, Boddaert et al. revealed decreased GM concentration in the bilateral superior temporal sulcus in children with ASD compared with TDc [32]. Using VBM, Wang et al. reported that the GM volume in the right superior temporal gyrus was smaller in ASD than in TDc [30]. Bigler et al. demonstrated that the lateralization of the superior temporal gyrus was failed in ASD [30]. In our study, only in the ASD + ADHD group, the GM volume asymmetry alteration in the superior temporal gyrus was significant. Previous studies have demonstrated that the presence of ADHD was associated with greater impairments in language processing and social communication in ASD [7, 8]. In our study, ASD + ADHD had higher SRS-total scores than ASD-only. We speculated that the unique GM volume asymmetry alteration in the superior temporal gyrus was due to the more severe social communication impairments in ASD + ADHD.

Few studies have reported abnormal postcentral gyrus volume in patients with ASD or ADHD and results have been inconsistent. For example, one study that included 29 children and adolescents with ADHD and 29 TDc showed decreased volume in the postcentral gyrus in ADHD relative to TDc [33]. Another study reported increased postcentral gyrus volume in both ASD and ADHD children and adolescents compared to age-matched TDc [34]. Yet, the results did not survive multiple comparison corrections. Mizuno et al. used a relatively large sample size (92 ASD + ADHD and 141 TDc) and reported that ASD + ADHD showed decreased left postcentral gyrus volume than TDc. The postcentral gyrus, as the primary somatosensory cortex, is responsible for somatosensory activity. Sensory problems are prominent symptoms in individuals with ASD and are applied in the DSM-5 diagnostic criteria for ASD [1]. Interestingly, previous research has demonstrated that children with ASD + ADHD were associated with greater impairments in sensory processing than those with either ASD-only or ADHD-only [35]. The unique GM volume asymmetry abnormality in the postcentral gyrus in ASD + ADHD may further reflect the greater impairments of sensory processing in this disorder. In addition, sensory problems can lead to social communication deficits and repetitive behaviors, which are the core symptoms [36] in ASD and are also related to attentional deficits [37]. Therefore, in children and adolescents with ASD + ADHD, impaired sensory processing may stem from the abnormality of the postcentral gyrus, which in turn could result in core symptoms in ASD + ADHD (impaired social communication, repetitive behavior, and attentional deficits).

For the fusiform gyrus, the right side is responsible for facial recognition processing, and the left side for visual word form [38]. Previous research reported increased leftward volume asymmetry in the posterior temporal fusiform gyrus in ASD [39]. Patients with ASD have abnormalities in face memory skills and face emotion recognition. The altered fusiform gyrus has been demonstrated to be an important cause of these impairments in ASD [39]. Previous study has shown lower cortical thickness of the fusiform gyrus in children with ADHD [40]. ADHD has impairments in emotion modulation for facial stimuli, which is related to the function of the fusiform gyrus [41]. The abnormality of the GM volume asymmetry in the fusiform gyrus in ASD + ADHD may be associated with the above deficits in both ASD and ADHD.

Interestingly, we did not find any GM volume asymmetry alterations in the corpus callosum or basal ganglia in ASD + ADHD, despite these regions are frequently reported as abnormal in both ASD and ADHD. Meanwhile, we found that there were both shared and disorder-specific GM volume asymmetry alterations in the three groups compared with TDc. This demonstrates that the neurobiology basis of ADHD + ASD may be different from that of ASD-only or ADHD-only [42, 43]. In a temporal discounting task, ADHD + ASD showed both unique and more severe brain-behavior correlations compared to ASD-only and ADHD-only [44]. These findings suggest

that ASD + ADHD is neither an endophenocopy nor an additive pathology, but an entirely different neuroanatomical pathology [44].

In ASD + ADHD, the GM volume rightward asymmetry in Cluster A1 exhibited an age-related decrease. In TDc, this cluster showed rightward asymmetry. This finding suggests that the severity of the abnormality in Cluster A1 may increase with age. It remains unclear whether these GM volume asymmetry changes result from genetics, the environment, or both. Prior studies indicated that motor behavior lateralization begins even before birth and may have a potential causative effect on the development of subsequent behavior and brain lateralization [45]. The research on the post-mortem human cerebral cortex anchored the cerebral biology of language lateralization to the molecular genetic level [46]. These results further demonstrate the importance of early identification and intervention for ASD + ADHD. This would be a critical area for future longitudinal research.

Our study has certain limitations. First, some patients with ASD + ADHD and ASD-only in this study were receiving medication, which may influence their brain structure [47]. Second, our data were collected from 6 sites in ABIDE II and 1 site in the ADHD-200 Sample database, each using different scanning devices and parameters, which would lead to differences between sites in the average asymmetry measured for some regions. The medication and site biases were minimized by using these effects as covariates when conducting statistical analyses. Each site was treated as a separate binary variable in the GLM to covary by site, which can include demographic, clinical and technical heterogeneity. Meanwhile, sensitivity analysis was conducted on the subset of 3 T acquired data and showed similar main results to the primary analysis. However, relative to the single-centre study, variabilities between different sites could still contribute to reduced statistical power. In reality, researchers often publish separate papers based on a single centre that collects participants in a particular way. Therefore, the field overall has the same problem. In this setting, multi-site studies could better reflect the real-world heterogeneity, therefore with more generalizable results than single-centre studies [17]. Finally, we investigated the relationship between abnormal GM volume asymmetry and age, but we did not conduct a longitudinal study of the age effect on GM asymmetry due to sample limitations. Higher-powered studies with longitudinal designs and larger numbers of participants are needed in the future.

In this study, we explored the GM volume asymmetry alterations in ASD + ADHD versus ASD-only, ADHD-only, and TDc. We found that there were both shared and disorder-specific GM volume asymmetry alterations in the three groups compared with TDc. This finding demonstrated that ASD + ADHD is neither an endophenocopy nor an additive pathology of ASD and ADHD, but an entirely different neuroanatomical pathology. The present study may provide structural insights into the neural basis of ASD + ADHD.

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Data availability The data used in our study were obtained from the ABIDE database and the ADHD-200 Sample database and are publicly available at http://fcon_1000.projects.nitrc.org/indi/abide/ and http://fcon_1000.projects.nitrc.org/indi/adhd200/.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval All subjects and/or carers provided informed consent. Experiments were approved by the Institutional Review Board at each site.

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