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Predicting brain age during typical and atypical development based on structural and functional neuroimaging

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Abstract

Exploring typical and atypical brain developmental trajectories is very important for understanding the normal pace of brain development and the mechanisms by which mental disorders deviate from normal development. A precise and sex-specific brain age prediction model is desirable for investigating the systematic deviation and individual heterogeneity of disorders associated with atypical brain development, such as autism spectrum disorders. In this study, we used partial least squares regression and the stacking algorithm to establish a sex-specific brain age prediction model based on T1-weighted structural magnetic resonance imaging and resting-state functional magnetic resonance imaging. The model showed good generalization and high robustness on four independent datasets with different ethnic information and age ranges. A predictor weights analysis showed the differences and similarities in changes in structure and function during brain development. At the group level, the brain age gap estimation for autistic patients was significantly smaller than that for healthy controls in both the ABIDE dataset and the healthy brain network dataset, which suggested that autistic patients as a whole exhibited the characteristics of delayed development. However, within the ABIDE dataset, the premature development group had significantly higher Autism Diagnostic Observation Schedule (ADOS) scores than those of the delayed development group, implying that individuals with premature development had greater severity. Using these findings, we built an accurate typical brain development trajectory and developed a method of atypical trajectory analysis that considers sex differences and individual heterogeneity. This strategy may provide valuable clues for understanding the relationship between brain development and mental disorders.

KEYWORDS
autism spectrum disorder, brain age prediction, developmental heterogeneity, multimodal magnetic resonance imaging, predictor weights analysis

1 | INTRODUCTION

Brain development is a dynamic and complex process lasting throughout childhood, adolescence, and early young adulthood (Zhang et al., 2020). The results of this process are determined by both genetics and postnatal experiences (Niu, Zhang, Kounios, & Liang, 2020) and cause profound changes in brain structure and function to occur (Truelove-Hill et al., 2020). During this period, the brain is prone to atypical development (Truelove-Hill et al., 2020), and the resulting disrupted brain structures or connectivity can directly lead to neurodevelopmental or neuropsychiatric disorders (Dennis & Thompson, 2013). In addition, epidemiological studies have shown that about 75% of diagnosable mental disorders begin before the age of 24 (Kessler et al., 2005), suggesting that studying typical and atypical brain developmental trajectories is important for evaluating and intervening in mental disorders (Di Martino, Fair, et al., 2014).

In this context, neuroimaging techniques, such as magnetic resonance imaging, provide a powerful tool for investigating brain development (Cherubini et al., 2016). Many studies have also used these techniques to develop biomarkers to reliably establish the typical brain development trajectory (Cole, Marioni, Harris, & Deary, 2019); of these "predicted brain age" is the most promising (Franke & Gaser, 2019). Also, the difference between the predicted brain age and chronological age, the brain age gap estimation (BrainAGE), reflects premature development (PRD; brain age >chronological age) or delayed development (brain age <chronological age) (Franke & Gaser, 2019). Dosenbach et al. (2010) successfully predicted brain age using resting functional magnetic resonance imaging (rs-fMRI), and Franke, Ziegler, Klöppel, Gaser, and Initiative (2010) analyzed the characteristics of brain aging and the influence of different parameters on the prediction model through T1-weighted structural magnetic resonance imaging (sMRI). These early representative works analyzed brain age using the single-modal prediction model. Furthermore, the fusion of multimodal neuroimaging data addresses the disadvantages of poor accuracy by combining different types of features (Liem et al., 2017), and many studies have conducted in-depth analyses based on this (Liang, Zhang, & Niu, 2019; Niu et al., 2020). However, evidence has shown that there are significant sex differences in brain structure, function, and transcriptome (Liu, Seidlitz, Blumenthal, Clasen, & Raznahan, 2020), and many major psychiatric and neurological disorders show sex-related differences (Jahanshad & Thompson, 2017). Therefore, establishing a sex-specific brain age prediction model based on multimodal neuroimaging is essential for understanding typical and atypical brain development.

At the same time, studies have revealed that BrainAGE shows different deviations from the normal developmental trajectory for a variety of mental disorders (Borgwardt et al., 2013). Therefore, brain age prediction models are widely used in the analysis of mental disorders, such as schizophrenia (Truelove-Hill et al., 2020), epilepsy (Zhang et al., 2021), and anxiety disorder (Niu et al., 2020). Moreover, autism spectrum disorder (ASD), one of the most devastating neurodevelopmental disorders (Di Cicco-Bloom et al., 2006), has also been analyzed using the same method. He et al. (2020) used diffusion tensor imaging and rs-fMRI to analyze the relationship between the predicted brain age and chronological age of ASD individuals at different stages. Tunc et al. (2019) used sMRI and diffusion weighted imaging to predict the brain age and the BrainAGE in autistic patients and analyzed the relationship between BrainAGE and the severity of ASD. However, sex differences are widespread in ASD disorder (Striegel-Moore et al., 2009; Werling & Geschwind, 2013), so it is very necessary to build an accurate brain age prediction model based on the different sexes for further analysis.

Here, we used the PNC dataset of children, adolescents, and young adults (age = 8–23 years) to establish a sex-specific prediction model to describe typical brain development. The fusion of rs-fMRI with sMRI allowed the model to have a good generalization performance on four different independent test datasets. Furthermore, the predictor weights analysis of the brain structure and function revealed the similarities and differences between the male and female brain developmental process. We then calculated the BrainAGE of the healthy controls (NCs) and autistic patients (ASDs) in the ABIDE and the healthy brain network (HBN) datasets to find the atypical brain development characteristics of ASDs at the group level. Finally, we further refined and grouped individuals within the ASDs according to their developmental characteristics and researched the relationship between different developmental characteristics of the brain and clinical manifestations. The results revealed a high degree of individual heterogeneity of ASD.

2 | MATERIALS AND METHODS

2.1 | Subjects and datasets

2.1.1 | Training dataset

Philadelphia Neurodevelopmental Cohort (PNC) is a large-scale project funded by NIMH to understand how the brain development process affects cognitive development and why it is prone to mental disorders (Satterthwaite et al., 2014). This cohort supplied rich neuroimaging data during brain development. In this article, we selected 649 healthy male subjects and 740 healthy female subjects with both rs-fMRI and sMRI data from 1,629 original subjects to train the sex-specific prediction model, and excluded two individuals with unqualified preprocessing quality. These data had passed the quality check and those with missing phenotypic information had been eliminated. All MRI data were collected on a 3T Siemen's instrument in the University of Pennsylvania Hospital. See Table 1 for specific information.

2.1.2 | Independent test datasets

To evaluate the performance of the prediction model appreciably and accurately, we used multiple independent test datasets from different countries and experimental centers that had studied different races to verify the prediction accuracy. The Beijing dataset and the London

TABLE 1 Dataset description

Study		Sex	*N*	Age range	Mean age (*SD*)
PNC		Male	649	8.17–23.00	15.10 (3.51)
		Female	740	8.17–23.08	15.52 (3.58)
Beijing		Male	75	18–26	21.17 (1.81)
		Female	122	18–26	21.17 (1.83)
Cambridge		Male	75	18–30	20.99 (2.13)
		Female	121	18–30	21.07 (2.42)
HBN	NC	Male	83	5.02–21.19	10.44 (3.60)
		Female	81	5.42–19.49	10.49 (3.26)
	ASD	Male	196	5.23–20.37	10.89 (3.64)
		Female	44	5.58–21.48	11.25 (3.53)
ABIDE	NC	Male	560	8.01–23.00	13.68 (4.15)
		Female	181	8.04–23.00	12.41 (4.07)
	ASD	Male	541	8.00–23.00	14.07 (4.03)
		Female	87	8.06–23.00	12.75 (3.90)

dataset are both from the FCP project (http://fcon_1000.projects.nitrc.org/). MRI Imaging data were collected on a 3T instrument in Beijing, China and London, England, respectively, and all subjects were healthy. The age range of these two datasets was slightly larger than the training dataset, and these datasets were composed of individuals from Asia and Europe (Table 1), which can be a good test of the model generalization. All subjects in the two datasets meet the requirements, so no data is excluded.

The HBN is committed to creating a shared biological database (Alexander et al., 2017) that contains a large amount of multimodal imaging data from children and adolescents in New York City. These data were collected from three medical laboratory centers: (a) Staten Island (SI) center (1.5T scanning instrument), (b) Rutgers University (RU) laboratory (3T scanning instrument), and (c) Citigroup Biomedical Imaging Center (CBIC) (3T scanning instrument). From 264 individuals without any diagnostic labels, 165 healthy subjects with sMRI, rs-fMRI, complete phenotypic information and qualified preprocessing quality were selected for the model performance test. Similarly, 241 subjects that meet the requirements from 449 subjects with the ASD label were used for a subsequent atypical brain development analysis. And the age range of the HBN dataset is included in the training dataset. The details about these datasets are given in Table 1.

2.1.3 | ABIDE dataset

The Autism Brain Imaging Data Exchange (ABIDE) project has established a database containing a large number of resting functional and structural images of ASDs and NCs. This program has carried out two rounds of data collection, and thousands of pieces of data from many different experimental centers were collected together (Di Martino et al., 2017; Di Martino, Yan, et al., 2014). In this article, we used 741 healthy participants and 628 ASD patients that match the age range of the training dataset to analyze ASD (Table 1). Compared with the original data, we excluded 21 healthy subjects and 48 ASD patients, who lacked the corresponding neuroimaging data or failed the quality test in the preprocessing process. In addition, the Autism Diagnostic Observation Schedule (ADOS) scores in the ABIDE dataset was used in our research to discover the potential relationship between ASD and MRI images. The scores can be downloaded from the official website (http://fcon_1000.projects.nitrc.org/indi/abide/).

2.2 | MRI preprocessing and feature extraction

The preprocessing and feature extraction steps for all the neuroimaging data were completed in the MATLAB environment. The BN246 atlas was used to extract the structural and functional features of each brain region. BN246 atlas is a human brain network map containing 210 cerebral cortical regions and 36 subcortical regions, including detailed anatomical structure and accurate functional connection information (Fan et al., 2016). For detailed anatomical position division, refer to Table S2.

An automated pipeline was applied to preprocess the sMRI scans using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) in SPM12. This pipeline includes bias correction, spatial normalization, global intensity correction, affine registration, and segmentation. Then the preprocessed data were registered to MNI152 standard space using DARTEL registration, and 246 anatomical cortical regions were identified using the BN246 atlas. Finally, the gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes of each brain region were averaged, so that each subject had a total of 738 structural features.

Rs-fMRI data were preprocessed using the BRANT toolkit (Xu, Liu, Zhan, Ren, & Jiang, 2018). The main steps included slice timing, realignment, co-registration with the T1-weighted MRI, normalization, motion correction, global signal regression, 0.01–0.08 Hz filtering, and smoothing with a 6 mm Gaussian kernel. Then, functional connectivities were obtained between 246 brain regions by calculating correlation coefficients and using Fisher's *z*-transformation. Finally, a total of 30,135 functional connectivities were extracted as functional features for the brain age prediction model.

2.3 | Brain age prediction

2.3.1 | Sex-specific brain age prediction model

To reflect the different developmental characteristics of males and females, we established sex-specific brain age prediction models. The prediction model was constructed by integrating the partial least square regression (PLSR) with the stacking algorithm (Figure 1).

The PLSR method was used to establish a single-modal brain age prediction model based separately on structural or functional brain features. PLSR projects the independent and dependent variables into a new space, minimizes the sum of squares of errors, and finally

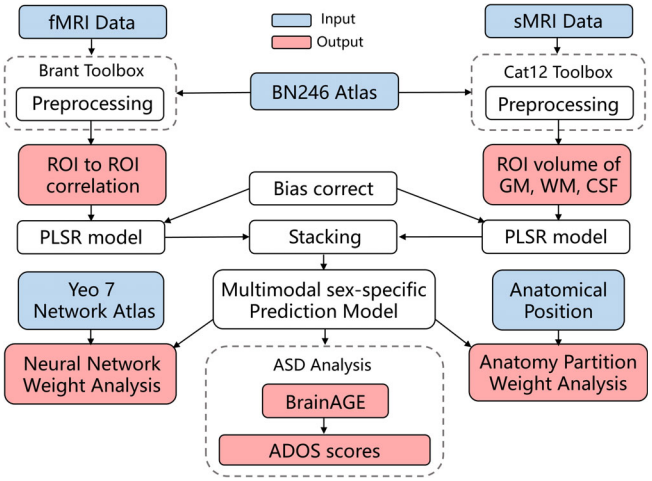

FIGURE 1 Overall flow chart. Blue means input; red means output. First, the Brant and Cat12 toolboxes were used for fMRI and sMRI preprocessing, respectively, and the BN246 atlas was used to extract the structural and functional features. Then, PLSR and a stacking algorithm were used to establish a multimodal sex-specific brain age prediction model. Next, the predictor weights within the functional network and anatomical location in BN246 atlas were analyzed. Finally, we explored the relationship between patients with different developmental characteristics and ADOS scores based on the BrainAGE of the ASDs

provides a linear regression model that meets the requirements (Geladi & Kowalski, 1986). In our model, 738 structural features or 30,135 functional features were projected into a new space as the independent variables. We defined the dimension of this new space as a priori, that is, the number of components after dimensionality reduction. The dimension of the space was also used as a hyperparameter and was determined through 10 times 10-fold cross-validation during the model training process. Specially, the male and female prediction models had different numbers of components in terms of functional and structural features, so the final multimodal brain age prediction model contained four different projection parameters. In addition, because predicted brain age as the dependent variable of the model had only one dimension, it did not need to be projected. In the new space, the problems resulting from a strong correlation between variables and from having far fewer samples than the number of characteristic variables were solved. Also, through inverse transformation, the importance of the features to the model could be quantified, which made the prediction model very interpretable.

Stacking algorithm is a kind of ensemble learning that can be used to integrate heterogeneous learners to obtain higher performance (Graczyk, Lasota, Trawiński, & Trawiński, 2010). After establishing the first-level learners (single-modal prediction model based on sMRI or rs-fMRI), the outputs can be viewed as the input of the second-level learner (stacking algorithm). To avoid over-fitting, we used 10-fold cross-validation to improve the model. First, two first-level learners trained with nine subsets of the training dataset and obtained the test results on the tenth subset. Second, the above step was implemented on 10 different subsets, and the average result was used as the input of the second-level learner. Then, the stacking algorithm utilized the output of the two first-level learners to construct a second-level learner and finally obtained a multimodal brain age prediction model. The whole process was trained on the PNC dataset, and the parameters of the second-level learner were directly used for testing on a different independent dataset.

2.3.2 | Bias correction

In brain age prediction studies, the correlation between BrainAGE and chronological age causes the brain age of young individuals to be overestimated while causing the brain age of older individuals to be underestimated. This problem has been mentioned in many studies (Beheshti, Nugent, Potvin, & Duchesne, 2019; Tunc et al., 2019), but the specific reason is not yet clear (Liang et al., 2019). To establish an accurate typical brain development trajectory, bias correction was carried out simultaneously with the stacking algorithm by regressing out the chronological age from the BrainAGE for each level of the two-level learner.

2.3.3 | Model test

Male and female sex-specific prediction models trained on the PNC dataset were tested on Beijing, Cambridge, HBN (NCs), and ABIDE (NCs) datasets. These four datasets came from different countries and medical centers and contained data from people with different ethnic origins (Table 1). The mean absolute error (MAE) and Pearson's correlation coefficient (R) between predicted brain age and chronological age were used to evaluate the performance of the prediction model on different test datasets.

2.4 | Predictor weights analysis

To evaluate the importance of brain structural or functional features on the brain age prediction model, we performed a predictor weights analysis by taking advantage of the good interpretability of the PLSR prediction model. Analyzing the high-weight predictors in the models established based on sMRI and fMRI could help to quantify the contribution of specific brain regions on brain age prediction and to understand the developmental trajectory of brain structure and function. The weight analysis of brain structural features, including the GM, WM, and CSF volume of each brain region, helped us to explore the characteristics of and differences between male and female brain structural development. Specifically, we calculated the structural feature weights of each brain subregion according to the anatomical position in the BN246 atlas (Table S2), and analyzed the brain subregions that play an important role in the development process. The Yeo 7 network atlas (Yeo et al., 2011) was used in the weight analysis of the brain functional features. Two hundred ten cortical subregions

in the BN246 atlas corresponded to seven different neural networks in the Yeo atlas, and thirty-six subcortical subregions were classified as the subcortical nucleus networks (SNs; Figure 1 and Table S2). Using this, we could study the functional changes during brain development from the perspective of these neural networks.

2.5 | BrainAGE analysis for the ASD subjects

After the sex-specific brain age prediction models were established and validated using the data from typical developmental subjects, we applied these models to investigate atypical development in two independent ASD datasets, the ABIDE and HBN datasets. Brain age was predicted for each ASD and NC individual based on the well-trained models. The BrainAGE, which denotes the difference between predicted brain age and chronological age, was obtained for each individual. For the group-level analysis, two-sample *t* tests were used to explore the significant differences in BrainAGE between ASDs and NCs.

To investigate the heterogeneity within the ASD group, we further divided the ASDs into a delayed developmental (DED) group and a PRD group according to the sign of BrainAGE difference between the ASDs and NCs. Because the ABIDE dataset and the training dataset are completely independent, image acquisition error, model generalization error, random error, and other reasons may cause the BrainAGE of healthy people to be non-zero. Therefore, the deviation results were obtained by subtracting the average BrainAGE of the NCs from the ASDs by sex. These two groups represented the different atypical brain development characteristics of the ASDs compared to healthy children or adolescents. Using two-sample *t* tests, we compared the group differences between the DED and PRD groups within the ASD group in terms of their ADOS scores, including the total score and three subscores, in the ABIDE dataset.

3 | RESULTS

3.1 | Brain age prediction model

In our model, the 738 structural features and 30,135 functional features of the male prediction model were projected to 7 components and 9 components, respectively, through PLSR. The structural and functional features of the female prediction model were reduced to 7 and 10, respectively. After bias correction, two sex-specific multimodal brain age prediction models were established based on the above configurations and tested on four independent test datasets (Table 2 and Figure 2).

The testing results implied that the sex-specific multimodal brain age prediction model had a good predictive performance for MRI data from the United States (HBN dataset ABIDE dataset), China (Beijing dataset), and the United Kingdom (Cambridge dataset). The significant correlation and the low MAE between predicted brain age and chronological age indicated that the model could overcome the influence of sample size and age distribution to a certain extent; it also had a good generalization performance on unknown data completely independent of the training data, which laid a solid foundation for the further analysis of ASD.

TABLE 2 Prediction performance on four independent datasets

	Male		Female	
Dataset	MAE	*R*	MAE	*R*
HBN_NC	1.34	.90	1.47	.88
Beijing	1.04	.84	1.32	.74
Cambridge	1.20	.83	1.10	.83
ABIDE_NC	1.24	.94	1.43	.92

Note: All Pearson correlation coefficients *R* in the table are statistically significant (p <.0001).

In addition, to validate the superiority of establishing a sex-specific prediction model, we retested the results on the same datasets using the prediction model without considering sex differences (Table S1). Although the model was tested on the same four independent test datasets mentioned above, the prediction model that did not consider sex differences showed a larger MAE than the sex-specific model, that is, a higher prediction error. This further showed that there were differences in brain development between men and women and that they should be investigated separately.

3.2 | Similarities and differences between males and females during typical brain development

For both models, the weight coefficients for the GM volume in most brain subregions were negative, which meant that the GM volume gradually decreased during the process of brain development. Subregions such as the thalamus, basal ganglia, precuneus, postcentral gyrus, and middle frontal gyrus showed very larger predictor weights in the model. In addition, the male prediction model also had high predictor weights for the precentral lobule, parahippocampal gyrus, lateral occipital cortex, amygdala, and hippocampus brain subregions, but the female prediction model did not have high weights in these regions. The females had higher predictor weights for the cingulate gyrus, inferior parietal lobule, posterior superior temporal sulcus, inferior frontal gyrus, and precentral gyrus (Figure 3a).

The predictor weights for the WM volume had the opposite pattern to that of the GM. That is, the weight coefficients for most of the brain subregions were positive, indicating that the WM volume increased with age during brain development from 8 to 23 years old. Many brain subregions, such as the middle frontal gyrus, precentral lobule, superior parietal lobule, postcentral gyrus, insular gyrus, basal ganglia, and thalamus, especially the precentral gyrus, showed very high predictor weights. The male prediction model also showed high predictor weights in the amygdala, inferior parietal lobule, superior temporal gyrus, and inferior temporal gyrus, whereas the female prediction model showed high weights in the superior frontal gyrus,

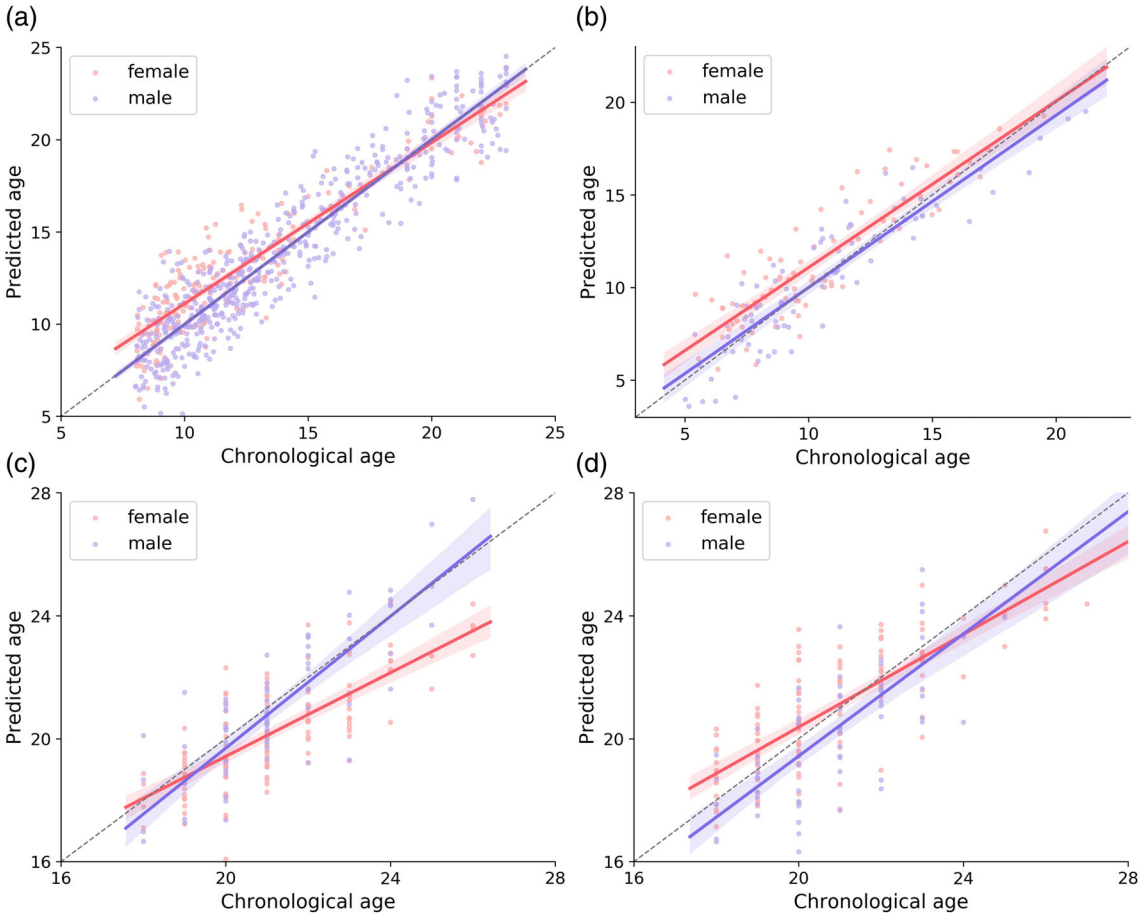

FIGURE 2 The prediction results of the sex-specific models on the four independent datasets with different countries, centers, and races. Red dots represent female individuals and blue dots represent male individuals. The shading indicates the 95% confidence interval. (a) NCs of the ABIDE dataset. (b) NCs of the HBN dataset. (c) Beijing dataset. (d) Cambridge dataset

orbital gyrus, parahippocampal gyrus, precuneus, and cingulate gyrus (Figure 3b).

Besides, the CSF volume was characterized by both positive and negative weight subregions, and the number of each was relatively balanced (Figure 3c).

Overall, brain subregions such as the basal ganglia, thalamus, and middle frontal gyrus played a very important role in the sMRI-based brain age prediction model. Different structural features corresponded to different weight coefficient values, but these parts had a similar pattern in male and female brain development. However, some subregions such as the inferior parietal lobule, parahippocampal gyrus, and amygdala often showed different weights in the male and female models. This might be due to the sex differences during brain development.

As for the functional network, it was obvious that the functional connections between the DM and the SN networks as well as the connections within the two networks had high predictor weights. Networks such as the VS, LM, DA, and FP networks, that were connected to the DM and SN networks also had high weights, which implies that the development of the DM and the SN networks are important parts of typical brain development. In addition, notice that the weight coefficients on the main diagonal of the heat map matrix were not very high and that most of the high weight coefficients appeared in other positions. This indicated that connections between networks were much more important than connections within networks during brain development (Figure 4). Note that, what was drawn in the figure is the importance of the functional network, that is, the functional weights, rather than the original functional connectivities. From Figure 4, we observed that there was a generally similar pattern of functional network weights for males and females according to their brain age prediction models. Only specific differences in details existed in the two models, such as that the connection within the SN network for females had the highest weight coefficient whereas the connection between the SN network and the DM network was the highest for males.

3.3 | BrainAGE for HCs and ASDs

BrainAGE showed significant differences between the NCs and ASDs (Figure 5). At the group level, the BrainAGE for the ASDs was −0.01, whereas that for the NCs was 0.19, and the ASDs had a deviation of

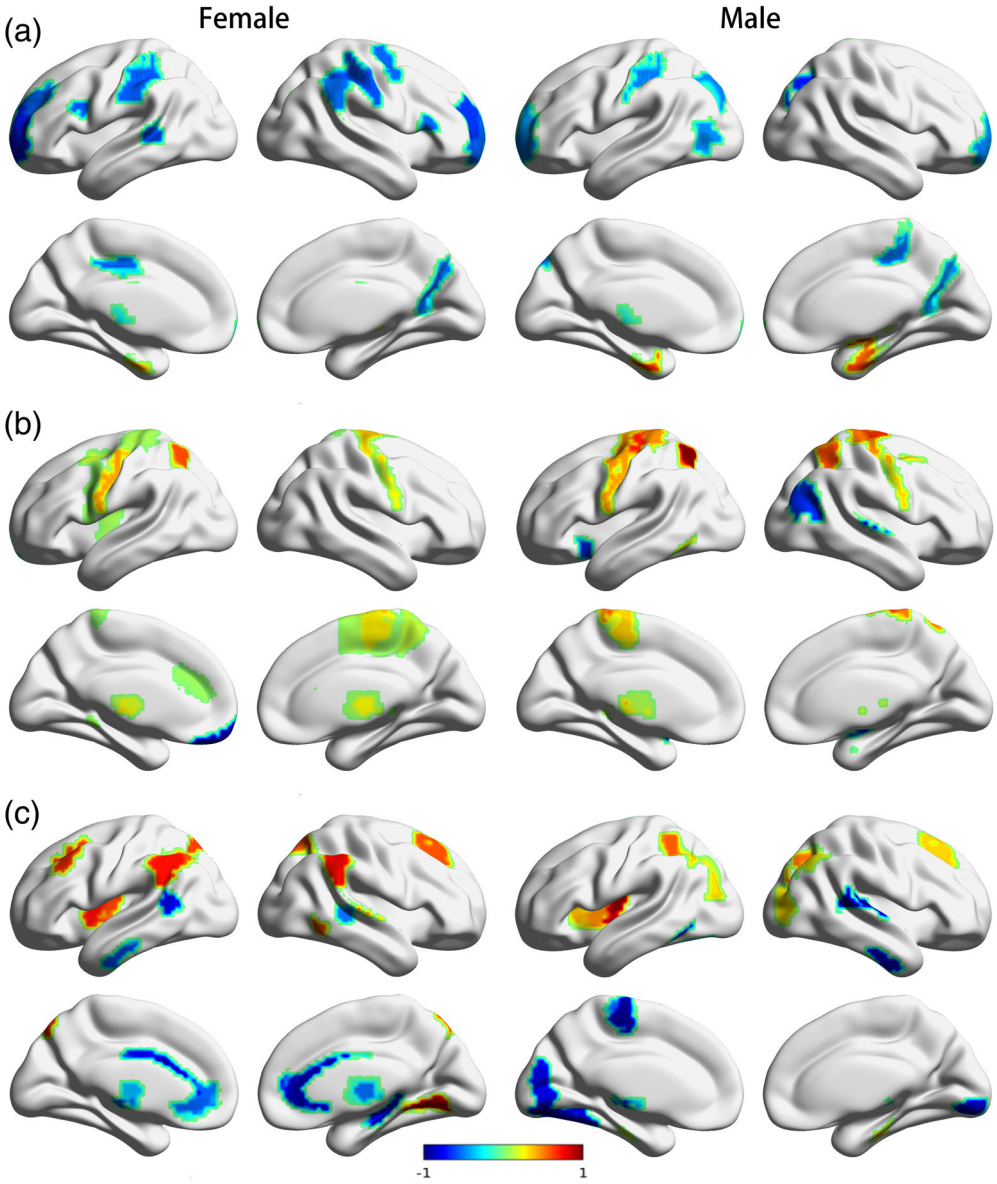

FIGURE 3 Distribution map of the top 10% (25 regions) structural predictor weights of the male and female brain age prediction models. The weights are sorted based on their absolute values, but the original weight values are drawn in the graph. The predictor weights of each sex and each type of feature had been normalized within the class. For example, for the GM volume weights of the 738 subregions in the male prediction model, we regard them as one class and normalize them. The color bar at the bottom represents the normalized weight result of each type of structural feature of each gender. Cool colors represent negative weights, and warm colors represent positive weights. (a) GM predictor weight distribution. Most of the weights were negative. (b) WM predictor weight distribution. Most of the weights were positive. (c) CSF predictor weights distribution. Positive and negative weights were relatively balanced

−0.20 ($p = .0157$, Cohen's $d = 0.13$) compared to the latter for BrainAGE. Similar results were found for the HBN dataset (Figure 5b). The BrainAGE of the ASDs was −0.16 and that of the NCs was 0.50; the former had a deviation of −0.34 ($p = .0287$, $d = 0.19$) relative to the latter. In general, the BrainAGE of the ASDs was lower than that of the NCs, which implies that ASD subjects have delayed brain development at the group level.

We found that the BrainAGE of the ASDs had a negative deviation compared with NCs at the group level. However, not all deviations for the ASDs were negative; in fact, a large portion of them were positive (Figure 5). Therefore, we divided all the ASDs in the ABIDE dataset into a PRD group (deviation >0, $n = 308$) and a delayed (DED) group (deviation <0, $n = 320$) based on the sign of the deviation values. Classical ADOS scores (communication subscore + social interaction subscore) were used to analyze the differences in clinical manifestations between the two groups with different patterns, and the p values were all corrected by the FDR method to P_{FDR} values (Table S3). The PRD group and the DED group had significant differences in the ADOS total score ($P_{FDR} = .0003$, $d = 0.38$), communication score ($P_{FDR} = .0299$, $d = 0.21$), social score ($P_{FDR} = .0006$, $d = 0.35$), and stereotyped behavior score ($P_{FDR} = .0089$, $d = 0.28$; Figure 5c). In addition, the total score and the three subscores of the PRD group were significantly higher than those of the DED group. Based on the P_{FDR} value and Cohen's d value, the principal difference between the two groups was in social and stereotyped behaviors, which are also the behaviors in which ASDs usually differ from healthy people. The PRD group had higher ADOS scores, indicating that the PRD subjects had more severe ASD clinical symptoms than the DED group. This finding suggests that there is heterogeneity in the brain development of ASD subjects.

To sum up, there was a definite connection between the brain development pattern and the clinical manifestations of ASDs: ASD individuals with premature brain development had a higher severity than individuals with delayed brain development. From another

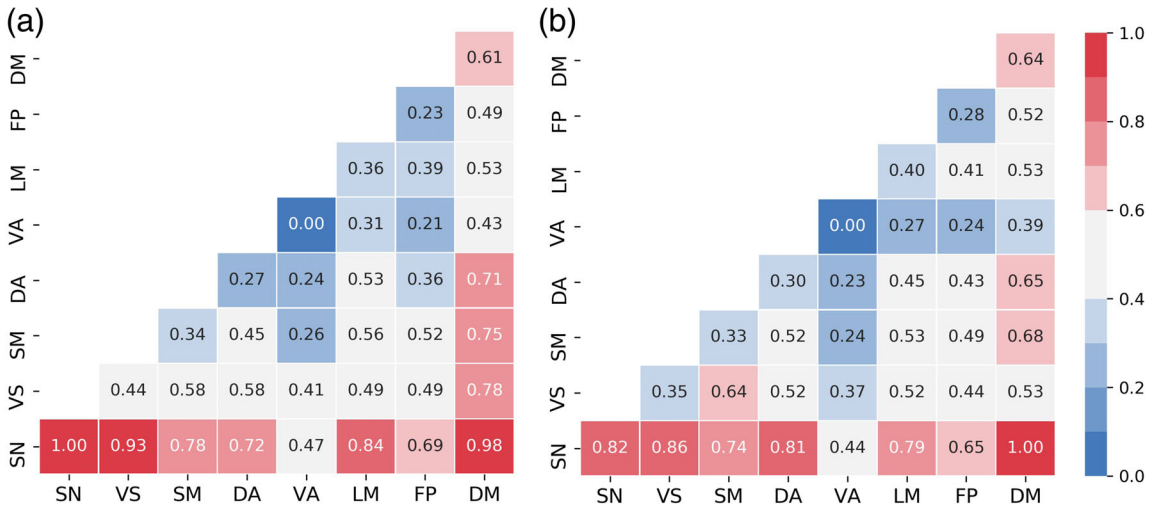

FIGURE 4 Functional network predictor weight heat map. The values in the heat map represent the normalized values of the predictor weights of different gender prediction models, respectively. Red means higher weights and blue means lower weights. (a) Weight distribution of the female functional network predictor. (b) Weight distribution of the male functional network predictor. SN, subcortical nuclei; VS, visual; SM, somatomotor; DA, dorsal attention; VA, ventral attention; LM, limbic; FP, frontoparietal; DM, default

perspective, the BrainAGE of ASDs at the group level was lower than that of NCs, but there obviously were two distinct developmental patterns within the ASD group. A high degree of heterogeneity within the ASDs was not easily observed in the analysis at the group level.

4 | DISCUSSION

In this article, we have established a high precision, sex-specific brain age prediction model, which showed good performance on different independent test datasets with different countries, races, and age ranges. A further predictor weights analysis showed that there was consistency in the changes in function and structure and sex differences during typical brain development. Based on this model, we found that the BrainAGE of the ASDs had a significant negative deviation compared with that of the NCs at the group level. More interestingly, the findings of the subgroup analysis indicated there are different clinical manifestations in ASD individuals with different developmental paces, which suggests that it may be pivotal to emphasize individual differences in atypical brain development and brain disorders.

According to epidemiological studies, most mental disorders begin at the developmental stage of the brain (Kessler et al., 2005), so focusing research on this stage can provide support for the early diagnosis and intervention of most mental disorders (Di Martino, Fair, et al., 2014). The brain changes in the whole age range include multiple stages such as development and aging, which are very complex. The changes in structure and function during the development of the brain have very unique characteristics, and it is critical for a more accurate understanding of atypical development (Truelove-Hill et al., 2020). Therefore, compared with researches in the whole age range (Bashyam et al., 2020; Cheng et al., 2021), we have established a more accurate typical brain development trajectory. And paying attention to the changes in the developmental period of the brain is more conducive to understand the typical brain development and analyze neurodevelopmental disorders.

Based on the above analysis, we established a model for predicting brain age during development. A sex-specific prediction model based on multimodal neuroimaging can synthesize brain function and structural features and better explain brain development, and this model also achieved good prediction accuracy and stability to new data. Liem et al. (2017) demonstrated that using multimodal neuroimaging can better predict brain age. The goal of this type of research is to make the prediction model have a low MAE, so that the calculation of BrainAGE will have lower error or uncertainty (Bashyam et al., 2020; Niu et al., 2020). Here, we took sex differences into consideration, and Table 2, Figure 2, and Table S1 show that the male and female sex-specific models had lower errors than the model that did not consider sex differences. This finding further shows that sex difference is a key factor affecting the performance of prediction models. Besides, existing brain age prediction work or the method of fusing multimodal images has a wide variety of methods. Conventional machine learning methods have no significant difference in prediction accuracy (Niu et al., 2020). Therefore, under the premise of ensuring accuracy, the interpretability and generalization of the model has become another focus. PLSR has a very good explanatory nature and the principle is simple and easy to understand. With the stacking algorithm, our prediction model has a very general performance. This method is also very suitable for multimodal brain age prediction model that consider gender differences.

It is worth noting that in the Beijing and London datasets, there is a certain deviation between the fitting line of the female samples and the reference line. The correlation of female samples in the Beijing dataset was only .74, which was the lowest among eight independent

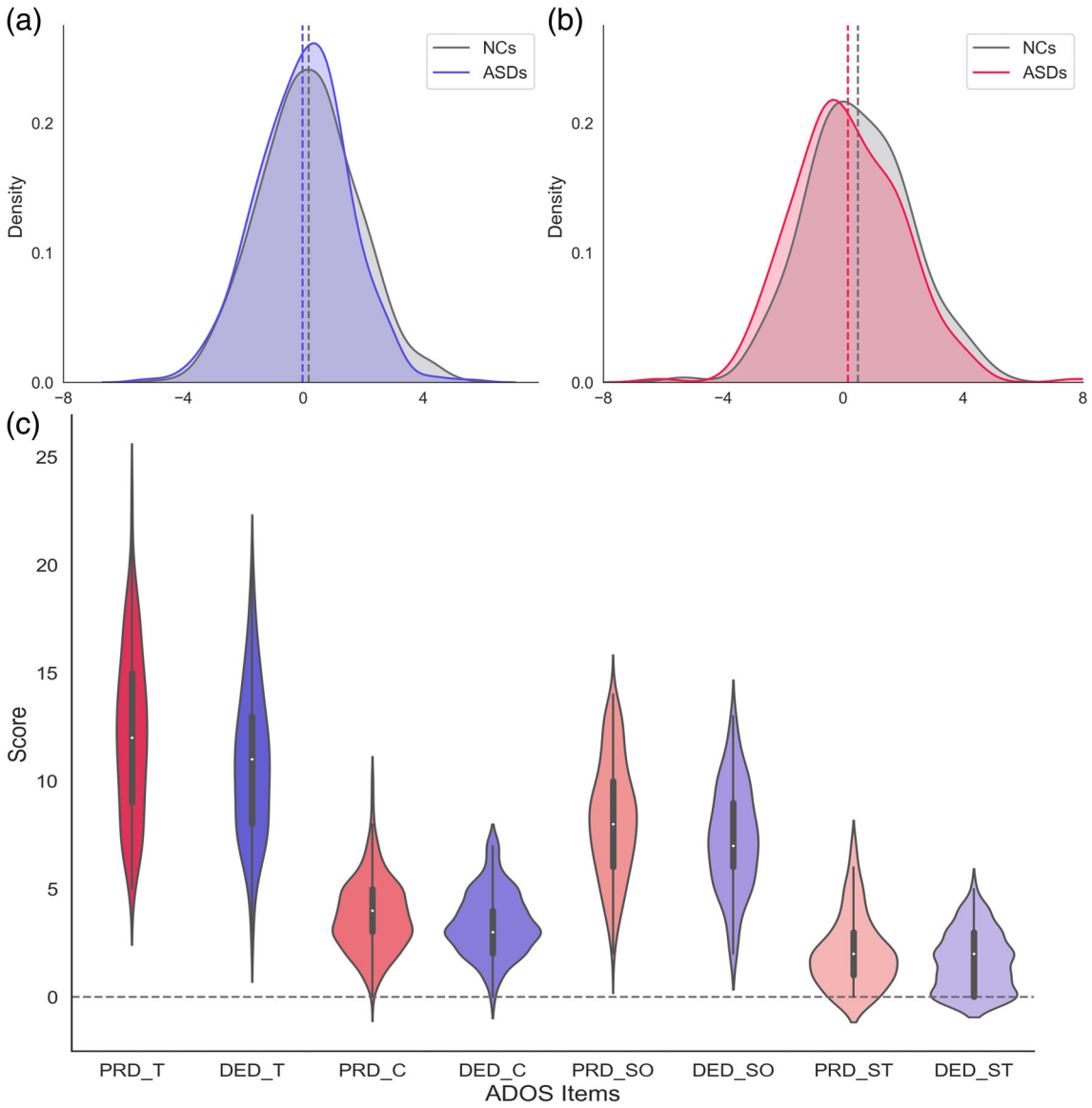

FIGURE 5 BrainAGE between NCs and ASDs and its relationship with the ADOS scores in the ABIDE dataset. (a) Density map for the ABIDE dataset. The dotted line is the average value of the BrainAGE for the NCs and ASDs, respectively. (b) Density map for the HBN dataset. The dotted line is the average value of the BrainAGE for the NCs and ASDs, respectively. On both datasets, the BrainAGE for the NCs was higher than that for the ASDs. (c) Comparison between the PRD group and DED group on ADOS scores. The PRD group is the warm color, and the DED group is the cool color. In four items, the scores of the PRD group were all significantly higher than the DED group. PRD, premature development; DED, delayed development; T, Total; C, Comm; SO, Social; ST, stereo_behav

tests. This might be caused by many reasons. For example, in the London and Beijing datasets, the chronological age was in the form of integers, and our predicted brain age was accurate to a decimal, which would inevitably cause certain errors. In addition, the age range of the two was slightly larger than the training dataset, and generalization errors would inevitably occur in the process of independent testing. Even so, the existing results still have a good correlation in statistical significance and there is a better prediction result for predicting brain age.

On the other hand, the prediction model established by PLSR had excellent interpretability, and the results of the predictor weights analysis showed that there are differences and similarities in the structural and functional changes of males and females during typical brain development. The predictor weights of GM volume were generally negative, whereas those of WM volume were the opposite, mostly positive (Figure 3). Anatomy and neuroscience generally show that the volume of GM gradually increases from birth to 4 years old, and then starts to decrease and that the volume of WM increases steadily until it reaches a plateau around the age of 20 (Pfefferbaum et al., 1994). This is highly similar to the results of our study. The internal mechanism for these changes is the genetic manifestation of progressive (myelination [Benes, Turtle, Khan, & Farol, 1994]) and degenerative (synaptic pruning [Purves & Lichtman, 1980]) processes during brain development (Silk & Wood, 2011). In addition, brain

subregions like the basal ganglia, thalamus, and middle frontal gyrus play very important roles during development. Apart from these regions, some previous studies have shown obvious sex differences in the GM of the cingulate gyrus (Xin, Zhang, Tang, & Yang, 2019), amygdala (Zaidi, 2010), inferior frontal gyrus, and posterior temporal regions (Wilke, Krageloh-Mann, & Holland, 2007), and areas with obvious gender differences in the WM are mainly concentrated in the cingulate and temporal regions (Hsu et al., 2008; Wilke et al., 2007). These evidences have also been replicated in our work (Figure 3).

Functional characteristics also undergo changes during brain development (Davis et al., 2009; Dosenbach et al., 2010). In our study, functional connections related to the SN and DM networks played a very important role, and a portion of the connections between the SM and the FP networks also had high weights. The predictor weights for the functional network of males and females were very similar overall (Figure 4). Previously, Cui et al. (2020) found that the differences between males and females in the local functional topography of the association cortex are the greatest during adolescence and that these differences can encode the maturity of the brain. Additionally, the functional network connections that we found with high predictor weights had a lot of overlap with the association cortex, which shows that these high-weight functional connections play a major part in the brain maturation process. Complementarily, the DM network is usually activated when the brain is not involved in a task and has been shown to change significantly during brain development (Supekar et al., 2010), and the SN network involves many important functions, such as regulation, emotion, and memory, and plays a vital role in adolescence (Goddings et al., 2014). Also, changes in cortico-cortical connectivity and subcortical regions are increasingly recognized as providing a unique insight into understanding typical brain development (Hwang, Bertolero, Liu, & D'esposito, 2017; Müller et al., 2020). These evidences are consistent with the findings in our work.

In addition, it can be seen from Figure 3 that the top 10% of the weights of the GM, WM, and CSF volumes were mostly located in the SN, LM, and DM networks and that they were mostly connected to the SN and the DM networks, which means the structural and functional changes during brain development have a certain consistency. In addition, the main sex differences in brain structural predictor weights are concentrated in subregions such as the amygdala, parahippocampal gyrus, and inferior parietal lobule. Zaidi (2010) and Sun et al. (2015) showed that there was sexual dimorphism in these structures. The amygdala plays a very important role in modulating the storage of memory for emotional events (McGaugh, 2004), memory (Aggleton, 2000), and processing emotion (Kilpatrick & Cahill, 2003). The inferior parietal lobule allows the brain to process information and helps in selective attention and perception, such as math ability, the ability to rotate 3-D figures, and sense relationships between body parts (Sabbatini, 1997; Zaidi, 2010). The parahippocampal gyrus is related to the integrative and maintenance functions of the episodic buffer (Luck et al., 2010) and is the main point of cortical input for the hippocampus and an important part of the hippocampus function (Van Hoesen, 1982). Extensive evidence shows that there are significant differences in male and female hippocampal function and anatomy (Madeira & Lieberman, 1995). Therefore, when building a prediction model based on brain structure and function, sex differences need to be taken into account.

BrainAGE shows different deviations for different mental disorders (Borgwardt et al., 2013); thus, an accurate typical brain development prediction model is helpful for clearly distinguishing the differences in the developmental characteristics of different mental disorders. We built a brain age prediction model with excellent generalization performance and stability based on the brain development characteristics of the different sexes (Table 2). In our study, the BrainAGE of the ASDs was significantly smaller than that of NCs at the group level, and this was reproducible on two independent datasets (Figure 5a,b), which shows that the results have a certain degree of stability. Tunc et al. (2019) has also showed that ASD caused a delay in the brain development of patients and that their BrainAGE had a negative correlation with ADOS scores. Further, ASD is a heterogeneous syndrome and has obvious sex differences (Lin, Ni, Lai, Tseng, & Gau, 2015), so we trained the sex-specific model in order to analyze ASD disorders objectively and accurately.

In most studies, the BrainAGE analysis of mental disorders is based on conclusions drawn at the group level. However, we found that although the BrainAGE of ASDs is overall lower than that of NCs, there were still both delayed and PRD characteristics within the ASD group (Figure 5a,b). Based on this, we divided ASDs into a delayed development group and a PRD group and analyzed the ADOS scores between two groups. Figure 5c shows that the PRD group and the DED group had significant differences in the four AODS items and that the scores of the PRD group were significantly higher than those of the DED group. This finding may not be completely consistent with the results of Tunc et al. (2019). This might have been because we directly divided the ASDs into two groups based on brain developmental characteristics rather than subjectively choosing to divide boundaries. Also, we used a larger sample size for training and testing, which allowed the prediction model to contain the attributes of the cross-datasets and ensured the stability of the results. The classical ADOS has four items: total score, communication score, social score, and stereotyped behavior score, which correspond to the prevalence characteristics of ASD (Sajdel-Sulkowska, Xu, McGinnis, & Koibuchi, 2011). Figure 5c and Table S3 indicate that the differences between the delayed and PRD groups were mainly manifested in social and stereotyped behaviors, which shows that these two types of cognitive indicators may be the main factors that cause the difference between ASD patients and healthy people. In addition, the higher scores in the PRD group suggest that ASDs with premature brain development may have a higher severity of disorder. Faster maturation could potentially restrict the plasticity of the brain, and repetitive experiences and negative encouragement could aggravate this process (Tooley, Bassett, & Mackey, 2021). Furthermore, most of the existing behavioral and neuroimaging-based studies are carried out at the group level, which makes it difficult for the research results to be promoted in clinical. Because of the large heterogeneity of individual patients in clinic, group-level research is not applicable. Our research

distinguishes subgroups according to different developmental characteristics of patients, which can alleviate the problem of heterogeneity to a certain extent. Future research may use this as a basis to explore more individualized methods to describe ASD patients, so as to provide new support for related diagnosis and intervention. In short, ASD is a highly heterogeneous mental disorder, and the discovery of its potential characteristics requires to be investigated at the individual level. Therefore, we not only need to observe the overall performance of the whole dataset, but also to dig into the potential individual differences within it.

The present work still has several potential limitations. First, the label used in the training process for the brain age prediction model was chronological age, and the true brain age is actually unknown, so the predicted brain age calculated by the prediction model may have some problems. Perhaps, what we did could be considered to be an explanatory method to introduce the cognitive scores used in the work of Niu et al. (2020) and Kramer et al. (2020) into brain age prediction work. Second, brain development is a complex and dynamic process, but our weight analysis was limited to cross-sectional data from the subjects during MRI scans; the use of longitudinal data could improve the study of the changes in brain function and structure. Third, in our work, we often used linear models to simplify problems and obtain good interpretability, but most of the actual issues are very complicated, and nonlinear models may achieve better results (Niu et al., 2020). In the future, we will use more types of neuroimaging to build a better-performing brain age prediction model. Some other techniques such as genetic analysis can be used in combination with neuroimaging data to explore the differences between ASDs and NCs on different scales. Besides, the new individualized research method will further analyze the difference and relationship between ASDs and NCs, so that related research can be better transformed into clinical applications.

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CONFLICT OF INTEREST

The authors declared no potential conflict of interests.

DATA AVAILABILITY STATEMENT

All datasets used in this study can be obtained through the references or the official website in the manuscript. The relevant codes in the paper are available upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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