Research on Pattern Classification of Autism Spectrum Disorder Related to the Diagnosis of Attention Deficit Hyperactivity Disorder

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Abstract: Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are common neurodevelopmental disorders. Clinically, there is extensive overlap between the symptoms of both disorders, which poses a major diagnostic challenge. This study examined the heterogeneity of ASD and ADHD by selecting indicators derived from neuropsychological and/or neuroimaging tests, and using the Support Vector Machine (SVM) algorithm to conduct research on high-functioning ASD and ADHD, so as to further elucidate the significance of different indicators in the differentiation of these two disorders. From January 2018 to June 2019, 33 children with high-functioning ASD, 35 with high-functioning ADHD and 30 typically developing (TD) children were recruited in the community during the same period and enrolled in the study. All participants were required to avoid taking neuropsychiatric drugs for 1 week before functional magnetic resonance imaging was conducted, and to stay awake and to minimize head motion during scans. Then, the collected brain image data were preprocessed to ReHo index on the dparsfa (http://www.restfmri.net/forum/DPARSF) platform, and differences in the regional homogeneity (ReHo) value of the three groups of subjects were compared and analyzed using Statistical Parametric Matching software, which took into account ReHo classification characteristics. Spearman's correlation analysis was carried out to analyze the voxel values of the extracted difference masses correlated with the category labels, and the support vector machine method was employed to respectively test the classification accuracy of the single ReHo index for the three groups of participants and the accuracy of constructing model discrimination type in joint behavioral indexes. A comparative analysis of differences in ReHo characteristics among the three groups showed differences in SupraMarginal_R, Parietal_Sup_L, Parietal_Inf_R and Cerebelum_Crus2_L ($P < 0.05$). The distribution of relative ReHo values in this mass region was TD>ASD>ADHD, and the difference was statistically significant ($P < 0.05$). Further extracting voxel values of the three groups, using the participants' differential masses as characteristics, it was found that the maximum classification Accuracy (ACC) and Area Under Curve (AUC) of the brain resting-state local consistency index (ReHo) were 60.74% and 0.6671, respectively. Compared with the classification using resting-state local consistency (ReHo) features alone, the maximum ACC and AUC in combination with ReHo index and specific scale features were 73.53% and 0.7943, respectively. Classification accuracy was improved when combining a specific scale with the ReHo index, and this may prove more helpful for clinical auxiliary diagnosis.

Keywords: Autism Spectrum Disorder; Attention Deficit Hyperactivity Disorder; Local Consistency; Support Vector Machine

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1 Introduction

Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are both common neurodevelopmental disorders with onset in early childhood. ASD is characterized by impairments in social interaction, restricted interests and repetitive behaviors, inattention, and hyperactivity/impulsiveness which is disproportionate to the development level [1]. Although these two disorders are, by definition, associated with their own unique core symptoms, extensive overlap in clinical symptomatology is observed. Approximately 30–50% of individuals with ASD have symptoms of ADHD. At the same time, a large number of individuals with ADHD share the characteristics of ASD, the most common being social and communication difficulties (66%) [2-3].

According to the 2011–2012 National Children's Health Survey data, among 1,496 children aged 2–17 years old who were diagnosed with ASD, about 20% were diagnosed with ADHD before ASD, and the time interval was about 3 years (95% confidence interval 2.3-3.5) [4]. The high overlap and co-occurrence of symptoms of ASD and ADHD pose significant diagnostic challenges. Considering the cost and consequences of delayed treatment, it is crucial to diagnose and predict the consequences of sick children with the highest level of accuracy as early as possible. At present, the clinical diagnosis of ASD and ADHD mainly depends on the individual's medical history, neuropsychological evaluation and clinical observations, though the diagnoses are subjective. Considering the variability of descriptive diagnoses, more and more studies began to focus on identifying specific biomarkers of different mental disorders by employing various neuroimaging, behavioral and cognitive measurement indicators [5]. However, few studies use early-onset features to predict the future trajectory of ASD or ADHD in children. Most studies only separate patients from the control group, but do not distinguish different patient groups, and group labels (e.g., patients and controls) are determined by clinical diagnosis, which cannot reflect the inherent heterogeneity and dimensions of complex neurodevelopmental disorders.

The high level of overlap between the two disorders causes major difficulties in identifying biomarkers, and at the same time, it also prompts people to question the existing classification methods of mental diseases. The National Institute of Mental Health of the United States proposed that mental illness is a brain disease, and set forth the Research Domain Criteria (RDoC) of mental illness. This diagnostic framework regards mental disorders as advanced neurological diseases, and seeks a new classification method of mental disorders based on the correlation between behavior and brain mechanisms by defining the dimension of brain dysfunction that crosses the traditional disease classification [6]. However, at present, the understanding of brain behavior is limited, and the principle of RDoC may be compromised by too many artificial rules. The biggest concern about RDoC is that it attempts to address the limitations of current diagnostic methods while ignoring an understanding of the etiology and clinical characteristics of clinical syndromes. However, the idea that the behavior dimension can cross the traditional diagnostic category is increasingly recognized.

It is suggested that data indicators from multiple sources (neuroimaging, behavioral and cognitive measurement indicators, etc.) should be integrated, and different combinations of genetic and environmental factors with gradient patterns may produce different degrees of neurodevelopmental disorders, which echo the severity of clinical symptoms [7-8]. This idea does not deviate from the current diagnosis and classification system, but also takes into account the available etiological, clinical and neuroscientific data. Coupled with the development of machine learning, we can use algorithms to infer the difference patterns between groups. Therefore, the pattern classification analysis of neuroimaging data is important in testing the diagnostic utility of neuroimaging-based mental disease markers, and it can provide inspiration for the future research of cross-diagnostic approaches based on neuroscience.

In recent years, the development of neuroimaging technology has brought about great opportunities to explore the brain mechanisms underlying neurodevelopmental disorders. In particular, rs-fMRI technology is popular because it can non-invasively detect spontaneous neuronal activity in the basic state of human brain and identify global brain functional circuits without adhering to a specific experimental paradigm; it also requires fewer subjects and produces highly consistent results. Although neuroimaging-based markers offer great potential, the inconsistency in the current classification

literature highlights the need to carry out further experimental work.

Traditional research methods usually analyze the images of two or more groups of subjects. In general, Rs-fMRI studies have found that, compared with typically developing (TD) individuals, individuals with ADHD show higher amplitude of low-frequency fluctuation (ALFF) and ReHo values in left and right superior frontal gyrus, and lower ALFF and Reho values in sensory motor cortex and bilateral anterior cingulate, middle cingulate and posterior cingulate [9-10]; In groups with ASD, a dynamic increase of ALFF is found in bilateral lateral prefrontal cortex, bilateral orbitofrontal cortex and medial prefrontal cortex, while a dynamic decrease of ALFF is found in bilateral talus sulcus, fusiform gyrus, lingual gyrus and posterior cingulate gyrus. Moreover, a dynamic decrease of ReHo is found in bilateral talus sulcus, fusiform gyrus, lingual gyrus and parahippocampal region [11-12]. A comparative study between ASD and ADHD shows that both disorders are characterized by different network abnormalities and coupling abnormalities. In 2011, Cauda et al. [13] found abnormal connectivity of ASD temporal lobe marginal area, and abnormal connectivity between striatum and globus pallidus in ADHD. In 2013, Di Martino et al. [14] found that ASD and ADHD was associated with similar reductions in default network area connectivity. It is also found that the deficiencies implicated in ASD and ADHD are not solely confined to specific brain region abnormalities, but manifest in the form of system or regional abnormalities; that is, regions interact with each other, and a problem in one region may cause a deficiency in one or more other regions. In 2018, Kernbach et al. [15] used the rs-fMRO data of a large data set involving males aged 7 to 21 years old who were classified as TD or with ASD or ADHD. The results showed that males with ADHD and ASD shared abnormal coupling of temporal parietal cortex; ASD was mainly characterized by alterations of resting-state connectivity of the default network, while ADHD was largely associated with the default mode network and dorsal attention network. In 2018, Jung et al. [16] comparatively analyzed 86 subjects with ASD, 83 with ADHD and 125 classified as TD. The results showed that, compared with ASD, functional connections in limbus, vision, the default network, body movement, dorsal attention network, frontopontine and ventral attention network were increased in individuals with ADHD. Compared with the ADHD group, functional connectivity of the left occipital sulcus and right anterior central sulcus related to the dorsal attentional network was enhanced in the ASD group.

Some new studies have broken the traditional analytic methods, using machine learning pattern recognition technology (see Figure 1) to make use of all available empirical information (including differences in brain images and behavioral data) to classify or predict the data, and to explore the biological indicators of rs-fMRI by machine learning. In 2018, Zhao et al. [17] added disease clinical characteristic indicators to rs-fMRI analysis to distinguish different neuropsychiatric diseases such as ASD and ADHD, which significantly improved the classification accuracy compared with previous pure data-driven analysis, offering further insight into the identification of both disorders. In 2018, Jung M et al. [18] analyzed and compared the rs-fMRI data of 86 boys with ASD, 83 boys with ADHD and 125 TD boys by using a machine learning technique, and found that the classification accuracy of ADHD and ASD was 79.3% by using resting-state functional connection index.

In a word, rs-fMRI distinguishes ASD from ADHD to some extent, and the classification accuracy is improved when combined with related clinical indicators. We have reason to believe that, at present, rs-fMRI may be a relatively good biological indicator for the differentiation of these two disorders, and it may be more effective when combined with other social cognitive tasks and clinical features of diseases. However, there is still a lack of research in this area, and further research and empirical evidence are needed.

Considering the inherent heterogeneity and dimensions of complex neurodevelopmental disorders such as ASD and ADHD, it is necessary to construct a multi-index joint differential model for both disorders in order to improve the clinical diagnostic rate. Previous studies have found that rs-fMRI distinguishes ASD from ADHD to some extent, and the classification accuracy is significantly improved when combined with related clinical indicators. However, few studies have been conducted, and further research is needed.

2 Research Object

Admission criteria of the ASD group: (1) Two attending child psychiatrists should form a clinical diagnosis based on the DSM-5 diagnostic criteria of

ASD at the same time, and individuals who receive an inconsistent diagnosis will not be admitted into the group; (2) participants aged 6–17 years old, with a Wechsler intelligence score > 80; (3) The participant's legal guardian should provide consent for their child's participation in the research. Exclusion criteria of the ASD group: (1) Confirmed history of craniocerebral trauma and serious physical disease; (2) Nervous system diseases and other mental diseases (e.g., Rett syndrome, mental retardation and ADHD, etc.); (3) those who take neurological and psychiatric drugs. Admission criteria of the ADHD group: (1) Two attending and child psychiatrists should form a clinical diagnosis based on the DSM-5 diagnostic criteria of ADHD at the same time, and individuals who receive an inconsistent diagnosis will not be admitted into the group; (2) aged 6–17 years old, with a Wechsler intelligence score > 80; (3) The participant's legal guardian should provide consent for their child's participation in the research. Exclusion criteria of the ADHD group: (1) Confirmed history of craniocerebral trauma and serious physical disease; (2) Nervous system diseases and other mental diseases (e.g., oppositional defiant disorder, specific learning disorder, ASD and mental retardation, etc.); (3) those who take neurological and psychoactive drugs. The entry criteria for the TD group: (1) Aged 6~17 years, with a Wechsler intelligence score > 80; (3) The participant's legal guardian should provide consent for their child's participation in the research. Exclusion criteria of the TD group: (1) Confirmed history of craniocerebral trauma and serious physical disease; (2) Nervous system diseases and mental diseases; (3) those who take neurological and psychoactive drugs. High-functioning children with ASD and ADHD were enrolled in the outpatient clinic of Children's Mental Health Research Center of Brain Hospital affiliated to Nanjing Medical University from January 2018 to June 2019, and participants assigned to the normal control group was recruited during the same period. A total of 98 participants were enrolled, including 33 children with ASD, 35 with ADHD and 30 TD children and adolescents. This study was approved by the Medical Ethics Committee of Brain Hospital of Nanjing Medical University, China (2019-KY112-01). All of the legal guardians of the participants provided written consent for their child's participation in the research.

3 Methods

3.1 Assessment Instrument

The professionally trained evaluators ensured that all participants recruited from the Children's Psychological Research Center of our hospital underwent a detailed evaluation, and that the following datasets were filed:

(1) Self-report general information questionnaire: general demographic data were collected, and these data included demographic data, clinical data related to diseases, general information related to the mother and child during pregnancy, general information at birth, past history and family history, etc.

(2) The Griffith Empathy Measure Parent Ratings (GEM-PR) [19]: This rating scale is used to measure empathy in children and adolescents. It is divided into two dimensions: cognition and emotion, and contains 23 items. Each item is rated according to nine grades ranging from "strongly disagree" to "strongly agree". It has high reliability and validity among Chinese adults (CFI = 0.822, RM Sea This scale is filled out by parents.

(3) The Behavior Rating Inventory of Executive Function (BRIEF) [20-21]: this scale evaluates executive function in children aged 6–18 years. Defined as appropriate inhibition control by changing and adjusting his/her emotions and behaviors, which is mainly used to evaluate the cognitive ability of children; The metacognition index is a measure of task initiation, working memory, planning, organization and self-monitoring, and reflects the ability of self-managing cognitive tasks and supervising their performance; that is, the ability to actively solve problems in different situations. This scale was completed by the participants' parents or legal guardians. It has good reliability and validity, and is suitable for the Chinese cultural context.

(4) The Autism Diagnostic Observation Schedule (ADOS) [22]: The ADOS is an evaluation tool for which each item is graded according to 0 ~ 2 levels. It mainly evaluates communication, reciprocal social interaction, imagination/creativity, rigid behaviors and restricted interests, and is used to determine the severity of core symptoms in ASD children. This tool has good reliability and validity.

(5) The Chinese version of the Swanson, Nolan and Pelham version IV scale (SNAP-IV) [23]: This scale consists of 26 items, including three dimensions: attention, hyperactivity and oppositional defiance. Each item is

scored according to a scale ranging from 0 ~ 3 (0, never; 1, sometimes; 2, often; 3 very often), and evaluates the severity of core symptoms in ADHD children. The scale has good reliability and validity.

(6) The Wechsler Intelligence Scale for Children 4th Edition Chinese Version (WISC-IV) [24]: This scale consists of 10 core sub-tests and four supplementary sub-tests. Besides the total IQ, the test results of the 10 sub-tests are combined into four indexes. The final results include: total IQ, speech comprehension index, perceptual reasoning index, working memory index and processing speed index. It is mainly used for intelligence testing in children aged 6–16 years.

3.2 Image Data Acquisition

All participants in the group were required to refrain from using psychopharmacological drugs for at least 24h prior to MRI scanning. Before entering the scanning room, participants were requested to remove all metal articles from their person, such as keys, coins, and mobile phones. Participants were instructed to remain still during scanning, and to stay awake with eyes closed. The scanning parameters are as follows: structural phase scanning parameters: pulse repetition interval time = 2530 ms, echo time = 3.34 ms, fault thickness = 1.33 mm, inversion angle = 7, return time = 1100 ms, scanning field = 256×256 mm, matrix = 256×192, and cumulative scanning time = 8 min and 7 s. Static scanning parameters: Gradient Echo Pulse Sequence (GRE)- Echo Planner Imaging (EPI) sequence is used for imaging. Repetition time = 2000 ms, echo time = 30 ms, scanning field of view = 240 mm×240 mm, acquisition matrix = 64×64, flip = 90, thickness = 4 mm, layer spacing = 0 mm, and scanning layer number of 30 layers. Scan time: 4 min and 44 s [25].

3.3 Image Index Processing

All the data were processed using Data Processing and Analysis for the Brain Imaging (DPABI) V4.3 toolkit (http://www.restfmri.net/forum/DPABI) and the Data Processing Assistant for Resting-State fMRI (DPARSF) software package. The data processing methods were as follows: (1) The images of the first 10 time points of each participant were removed to ensure the stability of image signals; (2) time correction and head movement correction were performed, and the data of participants whose head movement translation and rotational movements measures were greater than 3 mm and 3, respectively, were excluded; (3) the image was registered after head motion correction to a standardized space; (4) linear drifts on the image were calculated; (5) filtering at 0.01-0.08Hz was performed; (6) using the covariate regression method, white matter, cerebrospinal fluid and whole brain signals of whole brain images were regressed to eliminate the influence of physiological noises such as respiration and heartbeat; (7) When smoothing, the half-height full-width Gaussian kernel was 6mm, and the ReHo index was obtained. smReHo was selected for further analysis.

3.4 Machine Learning Part Data Processing

In this study, the SVM method was used for three classifications and left-out cross-validation, the latter of which was carried out for the training set every time, and the optimal parameter C was selected. Then, the model was trained according to the optimal parameter C. The average of the final prediction accuracy of 98 times was taken as the final measure of model accuracy. First, regression covariates (age, sex, IQ) were applied to the ReHo data of three groups of participants, and analyzed using SPM12. The statistical results showed that the card threshold $P<0.001$ and the cluster size>20 voxels, and the cluster set of 126 voxels was obtained, which was used as the classification feature of ReHo. The extracted voxel values of the difference lumps were respectively correlated with the category labels by Spearman, and the correlation coefficients were ranked according to size (from small to large), from the first 5% to 100%; every 5% was taken as the step length in order to finally obtain the optimal ACC of the first 85% edge features.

4 Results

4.1 General Information

There were no significant differences in age, sex and IQ among the three groups ($P > 0.05$), as shown in Table 1 below.

Table 1 General clinical data of the three groups

Project	**ASD (n=33)**	**ADHD (n=35)**	**TD (n=30)**	***P value***
Age (years)	9.18±2.66	9.30±1.52	9.33±2.16	0.582
Gender (male: female)	28/5	30/5	27/3	0.557
intelligence quotient	104.9±17.87	105.1±14.52	106.5±10.21	0.593
ADOS-(A+B) score	19.65±4.43	-	-	-
Total SNAP-IV score	0.95±0.23	1.83±0.19	0.52±0.05	0.028
Hyperactive impulse	1.20±0.13	2.04±0.15	0.45±0.12	0.047
lack of concentration	0.95±0.17	1.94±0.17	0.65±0.10	0.032

Note: ASD: autism spectrum disorder; ADHD: attention deficit hyperactivity disorder; TD: typically-developing children; ADOS-(A+B): total score of communication and social interaction on the Autism Diagnostic Observation Scale; total score of SNAP-IV: total score of inattention+hyperactivity on the SNAP-IV scale.

4.2 ReHo Results of the Three Groups

In this study, the correlation between features and tags was ranked, and the part with a larger correlation value was selected to represent the training features. The maximum ACC of single ReHo was 60.74%, and the AUC was 0.6671. The maximum ACC of the ReHo joint scale was 73.53% and the AUC was 0.7943. Among the three groups, differences ($P < 0.05$) were observed in the right superior marginal gyrus (SupraMarginal_R), left superior parietal gyrus (Parietal_Sup_L), right inferior parietal gyrus (Parietal_Inf_R) and left cerebellar angle area 2 (Cerebelum_Crus2_L left cerebellar angle area 2) (see Figure 1, Table 2) The position of voxel masses and the distribution of the relative values of ReHo in this lump area was TD>ASD>ADHD, and the difference was statistically significant ($P<0.05$) (see Figure 2 for the relative ReHo values of the three groups). Figure 3 illustrates the ROC curve for the SVM classifier.

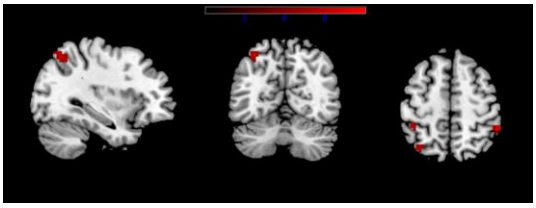


Figure 1 Location of voxel clumps selected by features

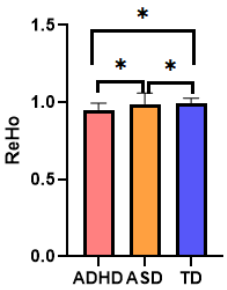
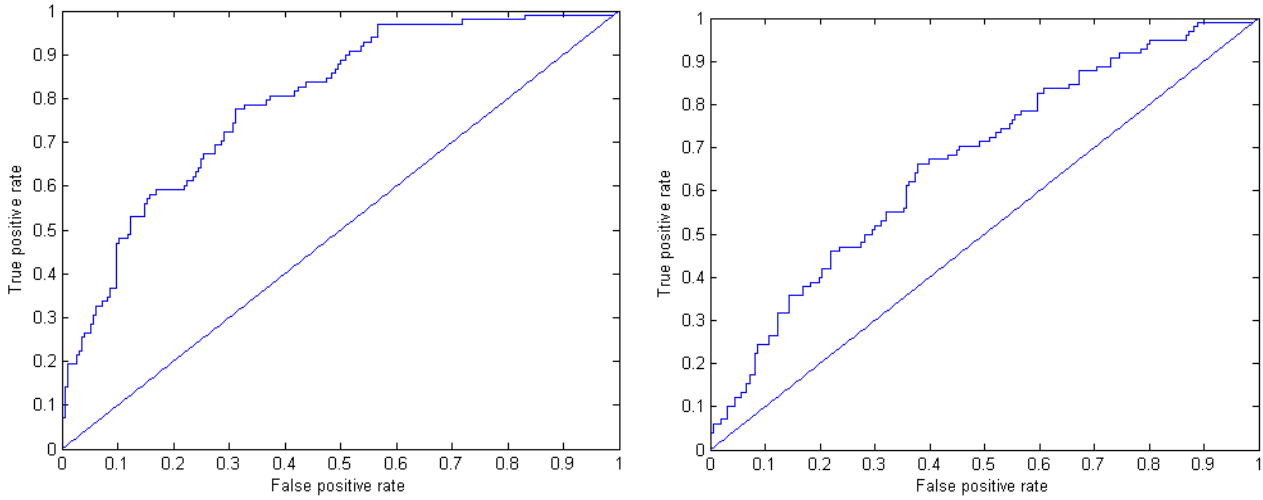


Figure 2 ReHo mean diagram of the three participant groups

Note: *P < 0.05



3.1 ROC curve of single ReHo value (AUC = 0.6671) 3.2 ROC curve of REHO value combined scale (AUC = 0.7943)

Figure 3 Schematic diagram of the ROC curves for each SVM classifier

Table 2 Differences in ReHo distribution among the three participant groups

Brain region	MINI coordinates			Body cluster	Peak intensity
	X	y	z		
SupraMarginal_R (superior gyrus of right margin)	63	-27	45	43	11.9439
Parietal_Sup_L (left top last time)	-33	fifty-six	64	24	8.7753
Parietal_Inf_R (Lower corner of right edge)	54	-45	57	12	9.7179
Cerebelum_Crus2_L (left cerebellar angle area 2)	0	-87	-24	36	9.6721

5 Discussion

At present, the clinical diagnosis of ASD and ADHD mainly depends on medical history, neuropsychological evaluation and clinical behavioral observations. Considering the variability associated with this descriptive diagnosis, a growing body of research is placing greater emphasis on identifying specific biomarkers of different mental diseases, through the use of various neuroimaging, behavioral and cognitive measurement tools and indicators. It would be helpful to diagnose and treat these children by objectively examining their cognitive and neuropsychological defects and biological markers. This study made a good attempt to apply machine learning to neuropsychology, neuroimaging and the clinical diagnosis of two disorders. The current research was based on relatively pure sample data related to children with ASD and ADHD. The date were analyzed and calculated using the ReHo index, and the researchers classified the resting state ReHo characteristics of the whole brain of high-functioning children and adolescents with ASD and ADHD, as well as those of TD children, which provided a basis for the clinical auxiliary diagnosis of ASD and ADHD. In this study, among the three groups, differences were observed ($P < 0.05$) in the right superior marginal gyrus (Sup_R), left superior parietal gyrus (Sup_L), right inferior parietal gyrus (INF_R) and left cerebellar angle area 2 (Cerebellum_Crus2_L), and in this mass. Based on the correlation between features and tags, the part with a larger correlation value is selected as training features. When the ratio was 85%, the maximum ACC was 73.225%.

The portion of the lower area of the parietal lobe surrounding the posterior ascending branch of the lateral sulcus is called the superior marginal gyrus, and the area surrounding the superior temporal sulcus is termed the angular gyrus. The angular gyrus is related to the multifunctional combined cortex; it is implicated in spatial perception, attention and social cognition, and is akin to an information workstation [26-27]. Angular dysfunction will block the connection between the visual cortex and main language areas, leading to dyslexia [28]. Previous studies have found increased angular gray matter volume in children with ASD, which may be related to social defects and repetitive stereotyped behaviors [29-30]. FMRI study has found weaker local functional connectivity in children with ASD, and some studies have observed decreased ReHo in the angular gyrus and weaker local functional connectivity in children with ADHD [31]. In this study, it was found that children with ASD and ADHD had damage to the superior marginal gyrus (SupraMarginal_R). Furthermore, compared with TD children, the ReHo value in this area was lower, which was similar to the findings of some previous studies. The parietal lobe is located between the frontal lobe, temporal lobe and parietal lobe, including the posterior central gyrus, superior parietal gyrus and inferior parietal gyrus. The parietal lobe of the brain is mainly composed of the cortex, which senses and monitors the response of various parts of the body to external stimuli. This area plays an important role in the process of concentration [31]. Previous studies have found that the ReHo value in the parietal lobe of children with ASD is decreased [32-33], while frontal-parietal cortex function in children with ADHD is weaker overall and correlated with the core symptoms of ADHD [34], which is consistent with the abnormal results obtained in this study regarding ReHo of brain regions in children with ASD and ADHD. Cerebellum plays a prominent role in motor function, but its role in language, cognition and emotion regulation has long been neglected [35]. It is found that children with ASD show obvious delays in the initial stage of language and language development, and cerebellar abnormalities may play a key role in ASD [36], as manifested by abnormal volume of cerebellar region [37], asymmetric changes [38] and weakening of cerebellar connection [35]. At the same time, this study found abnormal functional connectivity between cerebellum and the left middle frontal gyrus, right middle frontal gyrus, right superior temporal gyrus and left marginal lobe in ADHD children, which may be one of the brain mechanisms implicated in

core symptoms such as attention deficit, hyperactivity and cognitive dysfunction [39]. Although it was found that children with ASD and ADHD had ReHo abnormalities in the left cerebellar angle, as evidenced by previous studies, their corresponding meanings are often different. The relative separation of brain and cerebellar motor areas in children with ASD is often involved in non-motor cognitive processes, and is the result of dysfunction in regulation and control in this area [40], while abnormalities of cerebellar area in ADHD are more associated with motor language cognitive process during motor process [41-42].

This study employed the SVM method to screen the characteristics of the three groups of participants. The single ReHo index showed that ACC was 60.74%, AUC was 0.6671, and discrimination was not high, which may be related to the small number of samples involved. A large sample study used published ADHD-200 data sets to evaluate the predictive ability of a group of three different feature extraction methods and 10 different pattern recognition methods. ReHo, low frequency fluctuation amplitude (ALFF) and independent component analysis graphs (RSN) were tested. Combined with a ALFF+ReHo combination graph containing relevant information, individuals with ADHD can be distinguished from normal controls; ALFF+ReHo+RSN. This is similar to the accuracy of the ReHo classification in this study [43], wherein the ReHo index was combined with the executive function scale index, and was classified and predicted, which was higher than ReHo alone. It is found that ASD and ADHD are often related to executive function impairment, and this feature is far beyond the severity and long-term relationship with psychopathology. Both of them are associated with deficits in visuospatial working memory, sustained attention, feedback response and cognitive flexibility, while impairments in processing speed and working memory maintenance are more serious in children with ADHD [44]. A recent study of ASD showed that classification using behavioral metrics (social responsiveness scale scores) is superior to classification based on rs-fMRI data analysis [45]. Brain-based biomarkers are obviously at a disadvantage compared with behavioral measurements, since the latter are designed according to diagnostic criteria. Once the diagnosis has a more biological basis, instead of just relying on observations and interviews, it is possible to achieve an early and more objective diagnosis.

Although neuroimaging-based markers have potential, the inconsistency in the current classification literature indicates that further experimental work must be carried out. Several factors, including the age of the participants, the type of classifier used and the sample size, caused these inconsistencies. Moreover, it is necessary that future studies use samples of younger children to test the predictive ability of early recognized brain features. In addition, the features identified in the existing literature are likely to reflect causal or compensatory differences in brain function and structure, and these features may be different to the most predictive features in the early stage. In a cross-sectional survey, key information needed for accurate classification may be ignored. Therefore, research should screen young children prospectively and track the occurrence of symptoms longitudinally.

This study had some limitations that should be noted. For example, although participants with relatively "pure" ASD and ADHD were screened using a series of scales at the beginning of the study, this form of screening cannot completely guarantee that those exhibiting a small number of mixed features are not mixed. This may explain why the classification accuracy was not high in this study. Neurodevelopmental disorders tend not to appear in isolation, and there are often different forms of mixing. In the case of ASD and ADHD, there may be subgroups of individuals with both of these disorders and exhibit mixed behavioral symptoms [46-47]. Therefore, for the purposes of diagnosis and treatment, it is critical to identify, insofar as possible, the mixed characteristics of ASD and ADHD. Due to the limitation of objective conditions, this study was not included in the ASD+ADHD group. It is also worth noting that the studied sample consisted of high-functioning children; thus, the findings may not be applicable to low-functioning children with ASD and ADHD. Children with mental retardation experience great difficulties in social cognition, and these social difficulties are exacerbated in the case of ASD and/or ADHD [48]. Future research should also examine the influence of intelligence factors on children with both of these disorders.

In addition, to achieve classification specificity, the classifier must be tested on large samples that are representative of a variety of disorders, and this may be achieved through the use of neuroimaging databases, such as ABIDE and the UCLA Multimodal Connection Database, which can facilitate large samples and testing of the classifier. A classification model should be accurately defined and verified in the research site and population [5].

Moreover, given that it is possible measure its sensitivity and specificity, this biomarker may have high diagnostic performance in terms of its classification potential. However, until now, although a series of potential markers have been found in neuroimaging research, there is a lack of consensus regarding the proposed mechanism, and the relationship between this biomarker and neuropathology remains unclear; thus further research is needed.

6 Conclusion

Clinically, there is extensive overlap between the symptoms of ASD and ADHD, which poses a major diagnostic challenge. This study examined the heterogeneity of ASD and ADHD by selecting indicators derived from neuropsychological and/or neuroimaging tests, and using the Support Vector Machine (SVM) algorithm to conduct research on high-functioning ASD and ADHD. In this comprehensive study, we confirmed that children with ASD and ADHD showed different impairments as evidenced by social cognitive and brain function tests, and classification accuracy was improved after integrating multiple internal phenotypic indicators, which may be helpful for the clinical diagnosis of both disorders. In the future, further research should be conducted involving participants with broader cognitive abilities. This could be achieved by using larger samples of different age groups to better define the characteristics of the two disorders, and combining other aspects of brain structure and function to determine effective pharmacological and behavioral interventions.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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