Profiling brain morphology for autism spectrum disorder with two cross-culture large-scale consortia

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ABSTRACT

We explore neurodevelopmental heterogeneity in Autism Spectrum Disorder (ASD) through normative modeling of cross-cultural cohorts. Leveraging large-scale datasets from Autism Brain Imaging Data Exchange (ABIDE) and China Autism Brain Imaging Consortium (CABIC), the model identifies two ASD subgroups with distinct brain morphological abnormalities: subgroup "L" is characterized by generally smaller brain region volumes and higher rates of abnormality, while subgroup "H" exhibits larger volumes with less pronounced deviations in specific areas. Key areas, such as the isthmus cingulate and transverse temporal gyrus, were identified as critical for subgroup differentiation and ASD trait correlations. In subgroup H, the regional volume of the isthmus cingulate cortex showed a direct correlation with individuals' autistic mannerisms, potentially corresponding to its slower post-peak volumetric declines during development. These findings offer insights into the biological mechanisms underlying ASD and support the advancement of subgroup-driven precision clinical practices.

INTRODUCTION

Autism Spectrum Disorder (ASD), or autism, is a lifelong neurodevelopmental condition characterized by impairments in social communication and the presence of repetitive, unusual sensorymotor behaviors [1,2]. The global prevalence of ASD is estimated to be approximately 1% in children [3], with different rates reported in specific regions, such as 2.8% in children aged 8 years in the United States [4] and 0.7% in children aged 6 to 12 years in China [5]. Several factors, including improved survey methodologies and diagnostic practices, increased public awareness and access to services, have contributed to this increase in prevalence [3,6]. Over time, understanding of ASD has developed from a categorical diagnosis to a dimensional perspective of neurodiversity [7]. This change redefined autism as a spectrum that includes a wide range of characteristics within a unified framework [8]. However, expanded diagnostic criteria, actually too low [9], have introduced significant heterogeneity within ASD. And this heterogeneity suggests that the term "spectrum" encompasses multiple subgroups with distinct etiological phenotypes [10,11].

Current treatments for ASD, such as behavioral and speech therapies, provide benefits to some individuals but show limited overall effectiveness [12]. In fact, there is limited evidence that any type of early intervention has produced significant and broad effects on the main autistic outcomes [13]. Traditional case-control neuroimaging studies, which assume ASD and typical developing groups as homogeneous entities, often fail to account for subgroup differences [14]. This has led to inconsistent findings across brain regions and participants, further complicating efforts to identify reliable brain-behavior biomarkers. The decreasing effect sizes in group comparison studies over time [15] highlight the difficulty of constructing mechanistic models of ASD. Data-driven clustering techniques have emerged as a promising approach to address this complexity by leveraging cognitive and behavioral profiles alongside patterns of brain morphology and function. Various clustering methods [16–20] have been used to identify meaningful subgroups, in order to uncover the neurobiological mechanisms of ASD and provide insights into subgroup-specific traits [8,21]. Despite decades of effort, inconsistencies in sample selection, classification methods, and feature selection between studies remain significant challenges [21]. These issues have limited the ability of clustering techniques to consistently identify robust and replicable subgroups.

Inconsistencies in ASD studies may be due to altered neurodevelopmental adaptations [22] and selection biases [23]. These limitations highlight the need to group variables with strong biological relevance for the ASD subgroups [24]. Individual differences in sex, intelligence, medication use, and comorbidities [25,26], along with methodological variability [27] in data acquisition and analysis, still

complicate the interpretation of the results of neuroimaging studies. In response to these challenges, normative modeling[28] techniques offer a promising framework by capturing the full range of neurobiological variation[14]. This approach enables standardized assessments by comparing an individuals brain morphology to population-based references[29]. In ASD research, references are often built on internal or public datasets[18,20,30,31], but the relatively small sample size limits the generalizability and reliability of the results. Recently, the Lifespan Brain Chart Consortium (LBCC, https://github.com/brainchart/lifespan) provided neurodevelopmental variations throughout life through the most inclusive data available[32], providing a robust framework for us to achieve percentile-based comparisons of ASD with considerable statistical power.

This study adjusted the LBCC normative models in two large-scale cross-cultural ASD consortia: the China Autism Brain Imaging Consortium (CABIC)[33] and the Autism Brain Imaging Data Exchange (ABIDE)[34,35]. Focusing on childhood development, we used the largest-scale brain charts[32] to explore neurodevelopmental heterogeneity in ASD before adolescence. We classified ASD into subgroups using spectral clustering based on Out-of-Sample (OoS) centile scores, a biological measure which quantified brain morphological deviations of ASD from normative growth. A Support Vector Machine (SVM) with Recursive Feature Elimination and Cross-Validation (RFECV) identified key brain regions driving subgroup classification. The ABIDE-based classifier was then applied to CABIC to identify similar subgroups. Brain-behavior analyses were performed separately for each dataset to identify reproducible subgroup-specific correlations. From a perspective of brain morphology, this work disentangles the mechanisms of mixed neurosubtypes and provides new insight into the biological complexity of ASD.

RESULTS

Brain Morphological Profiles Reveal Two Distinct Autism Subgroups

We first analyzed the ABIDE dataset. The distributions of the OoS centile scores across 34 bilateral Desikan-Killiany[36] cortical volumes ranged from 0 to 1 (Fig. S1a in the Supplementary Information). OoS scores estimate the morphological variations of each participant in 34 brain regions compared to the median regional volumes of the population (50th centile, equivalent to a 0.5 OoS score). Relative to 0.5, individuals with more atypical phenotypes have more extreme scores. A ShapiroWilk test on the 34 OoS scores indicated that none followed a normal distribution (Table 1, column 2). Using spectral clustering on the OoS scores, we identified two distinct clusters with the highest silhouette coefficient among cluster solutions ranging from two to ten (Figure 1a). All p-values for between-subgroup comparisons (two-sample t-tests for the paracentral and pars orbitalis regions, and rank-sum tests for all other regions) were < 0.001). One subgroup, referred to as "L", exhibited generally smaller OoS scores, while the other, referred to as "H", displayed larger scores (Table 1, columns 5 and 7).

Certain regions of the brain showed significant differences in their OoS score distributions between the two subgroups (Figure 1g, Fig. S1b in the Supplementary Information. For CABIC results, please see Fig. S2a and S2b in the Supplementary Information.). Subgroup H exhibited greater variability in the occipital lobe, particularly in the lingual gyrus, pericalcarine cortex, and cuneus. In contrast, subgroup L showed more pronounced reductions in these regions compared to the normative benchmark (0.5). Other regions, such as the pars opercularis and superior temporal gyrus, also exhibited subgroup-specific changes. The results of the Shapiro-Wilk test for OoS scores (Table 1, columns 4 and 6) indicated that more regions of the brain in subgroup H followed a normal distribution compared to subgroup L. Broader variability was observed in regions such as the entorhinal cortex in subgroup L and the pericalcarine in subgroup H, highlighting further subgroup-specific clustering.

Distinct Structural and Age Differences Between Subgroups

The median OoS scores before clustering (Figure 1b; Table 1, column 3) reveal a mixed pattern of deviations across brain regions. Most regions exhibit reduced volumes, particularly in the occipital lobe. However, some regions, such as the precuneus, paracentral lobule, transverse temporal gyrus, and insula, show slightly higher OoS scores. This combined pattern reflects overlapping structural deviations from both subgroup H (Figure 1c, top) and L (Figure 1c, bottom), obscuring the distinct morphological differences that become evident after clustering. For instance, although subgroup L shows smaller volumes in the insula and precuneus, the larger volumes in subgroup H predominantly drive the combined result in the whole population. In contrast, smaller volumes of the lingual gyrus and the middle temporal gyrus in subgroup L have a stronger influence on the overall result. Some regions, such as the

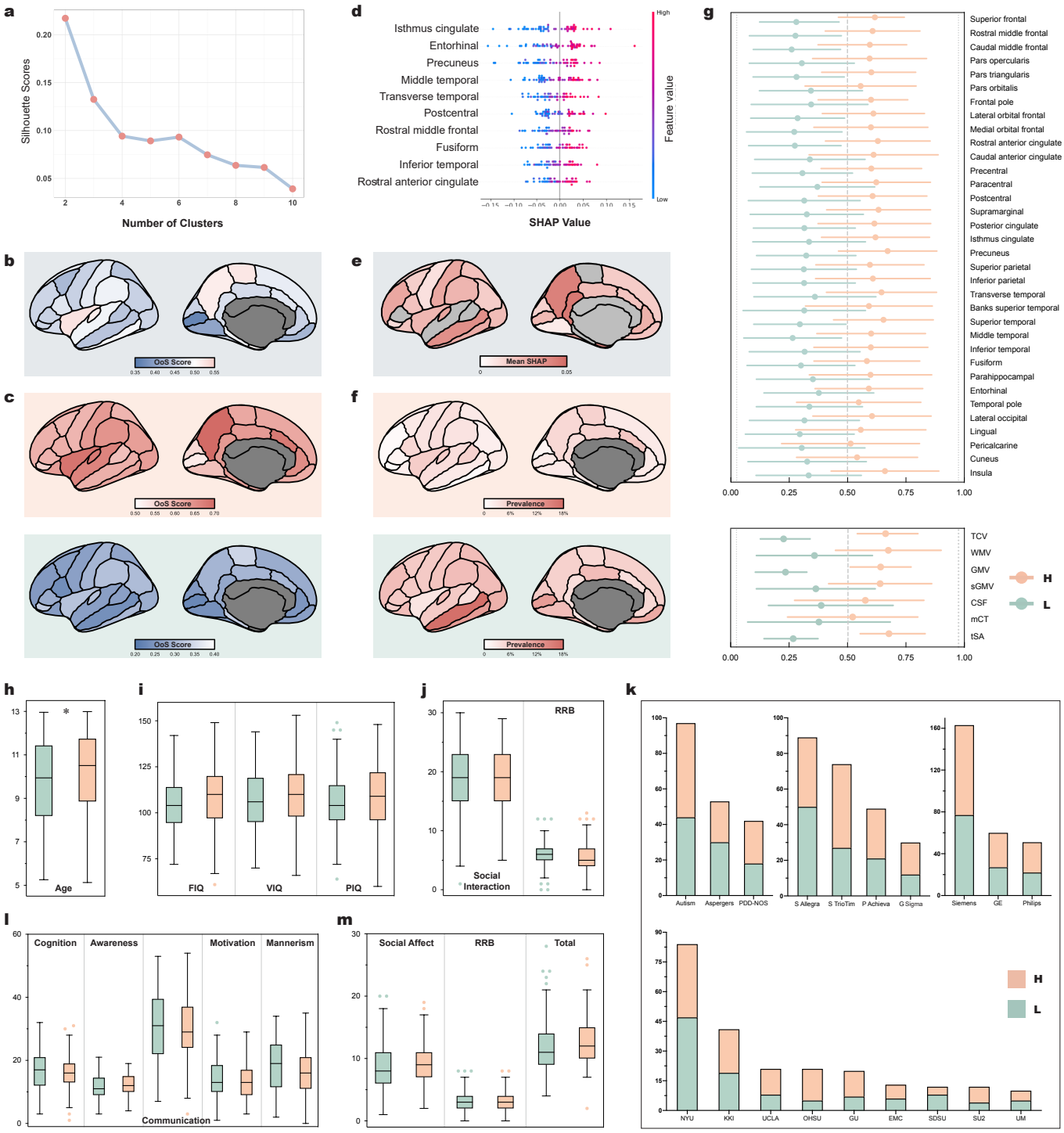

Figure 1: Clustering-derived subgroups reveal distinct brain morphological patterns in ASD from ABIDE dataset.
a, Silhouette scores across different clustering solutions (2 to 10 clusters). The highest silhouette score indicates two distinct subgroups. **b,** Median OoS scores of 34 cortical regions before clustering. **c,** Median OoS scores of ASD subgroup H (top) and L (bottom). **d,** SHAP summary plot displaying the top 10 brain regions with the highest contributions to the SVM model's predictions. **e,** The mean SHAP values across the 29 selected cortical regions contributed to the classification. **f,** Prevalence maps depicting the proportion of participants with extreme (2.5% for subgroup L, 97.5% for subgroup H) structural anomalies. **g,** OoS scores across 34 cortical regions (top) and global measures (bottom) for subgroup H (orange) and L (green). TCV, total cortical volume; WMV, total white matter volume; GMV, total cortical gray matter volume; sGMV, total subcortical gray matter volume; CSF, total ventricular cerebrospinal fluid volume; mCT, mean cortical thickness; tSA, total surface area; Dots indicate the mean value of OoS scores, bars indicate the standard deviation. See Supplementary Information Fig. S1b and Fig. S1d for detailed density plots. Distribution of participant ages (**h**); IQ scales (**i**); ADI-R (**j**); PDD category (**k**, top left), MRI scanner model (**k**, top middle), manufacturer (**k**, top right), and data collection site (**k**, bottom); SRS (**l**); and ADOS (**m**) across the two subgroups, with subgroup L participants being significantly younger than those in subgroup H ($p = 0.02$). Note, the left hemispheres are plotted in **b, c, e, and f** just for visualization purposes. For plots **h, i, j, l and m**, the center line shows the median; the box limits represent the 25th and 75th percentiles; the whiskers show the minimum and maximum values; and the dots represent potential outliers.

pericalcarine cortex, are almost entirely influenced by subgroup L. Meanwhile, regions like the inferior and superior temporal gyrus exhibit volumes close to the normative average because of the contrasting characteristics of both subgroups effectively canceling each other out.

To identify the regions of the brain most associated with morphological abnormalities, we calculated the prevalence of abnormalities for each region in the two subgroups. For subgroup L, the prevalence represents the percentage of participants with OoS scores below 0.025 (2. 5% centile), while above 0.975 (97. 5% centile) for subgroup H. Subgroup L (Figure 1f, bottom; Table 1, column 8) exhibited the highest prevalence of abnormalities in regions such as the middle and inferior temporal gyrus, pericalcarine cortex, frontal pole, and medial orbital frontal gyrus. In contrast, subgroup H (Figure 1f, top; Table 1, column 9) generally exhibited less severe abnormalities, with a concentration in the insula, transverse temporal gyrus, and caudal anterior cingulate. Participants in subgroup L were significantly younger than those in subgroup H (Figure 1h, $p = 0.02$, Table S1 in Supplementary Information). However, no significant differences were observed in the category PDD $p = 0.32$, the MRI scanner model $p = 0.07$ and the manufacturer $p = 0.86$, the data collection site $p = 0.16$ (Figure 1k), IQ (Figure 1i, see Table S1 in Supplementary Information for details), or scores from ADI-R (Figure 1j), SRS (Figure 1l), and ADOS-2 (Figure 1m). The corresponding results for CABIC are shown in Supplementary Information Fig. S3.

Machine Learning Reveals Subgroup Morphological Features

The optimized SVM model for the identification of subgroups demonstrated robust predictive performance. It used a polynomial kernel with a regularization parameter $C = 0.1$ and a kernel coefficient $\gamma = 1$. The model achieved a high classification accuracy ($0.95, p < 0.001$) and a F1 score ($0.94, p < 0.001$) in five cross-validation folds. 1d shows the SHAP summary plot for the top 10 selected features. 1e and Table S2 in Supplementary Information summarize the mean SHAP values for all 29 selected regions. SHAP values quantify the contribution of individual brain regions to the predictions of the model, with higher values indicating stronger influence. Among the regions, the isthmus cingulate, entorhinal cortex, precuneus, and middle temporal gyrus emerged as the most predictive features. Higher SHAP values for these regions were strongly associated with subgroup H, while lower values corresponded to subgroup L. These findings indicate different volumetric patterns in the cingulate, temporal, and parietal areas, effectively distinguishing the two subgroups.

Distinct Structural Covariance Patterns Across Subgroups

Structural covariance analysis on OoS scores revealed significant correlations between brain regions, with distinct patterns observed across ASD subgroups and control group (2c). These patterns were reproduced in both the ABIDE and CABIC datasets. In subgroup H, enhanced covariation was identified between the isthmus cingulate and the caudal middle frontal region (ABIDE: $z = 2.88, p = 0.00$; CABIC: $z = 2.25, p = 0.02$). In subgroup L, the parahippocampal gyrus showed reduced covariation with the entorhinal cortex (ABIDE: $z = -2.07, p = 0.04$; CABIC: $z = -3.25, p = 0.00$). Similarly, reduced covariation was observed between the posterior cingulate and the entorhinal cortex (ABIDE: $z = -2.12, p = 0.03$; CB: $z = -2.64, p = 0.01$) and between the insula and the entorhinal cortex (ABIDE: $z = -3.30, p = 0.00$; CABIC: $z = -2.18, p = 0.03$). An increased covariation was observed in subgroup L between the parahippocampal gyrus and the lateral occipital cortex (ABIDE: $z = 1.97, p = 0.05$; CABIC: $z = 2.04, p = 0.04$).

Brain-Behavior Correlations in Subgroup H

We examined correlations between cortical region volumes (OoS scores) and clinical measures in the ABIDE and CABIC datasets, identifying significant associations that were consistent between both datasets. All significant correlations were found within subgroup H. The transverse temporal gyrus showed positive correlations with ADOS Total and Social Affect scores (2a). In the CABIC dataset, moderate correlations were observed for ADOS Total ($r(198) = 0.17, p = 0.02$) and Social Affect ($r(191) = 0.21, p = 0.00$). Stronger correlations were identified in the ABIDE dataset for ADOS Total ($r(93) = 0.24, p = 0.01$) and Social Affect ($r(93) = 0.20$, $p = 0.04$). The inferior temporal gyrus was positively correlated with ADOS RRB, with a slightly stronger correlation in ABIDE ($r(94) = 0.19, p = 0.05$) compared to CABIC ($r(189) = 0.17, p = 0.02$). The volumetric centile of the isthmus cingulate is correlated with SRS Autistic Mannerisms, showing a higher correlation in ABIDE ($r(58) = 0.33, p = 0.01$) than in CABIC ($r(192) = 0.14, p = 0.04$). No significant correlations were identified between structural covariance patterns and cognitive behavior outcomes.

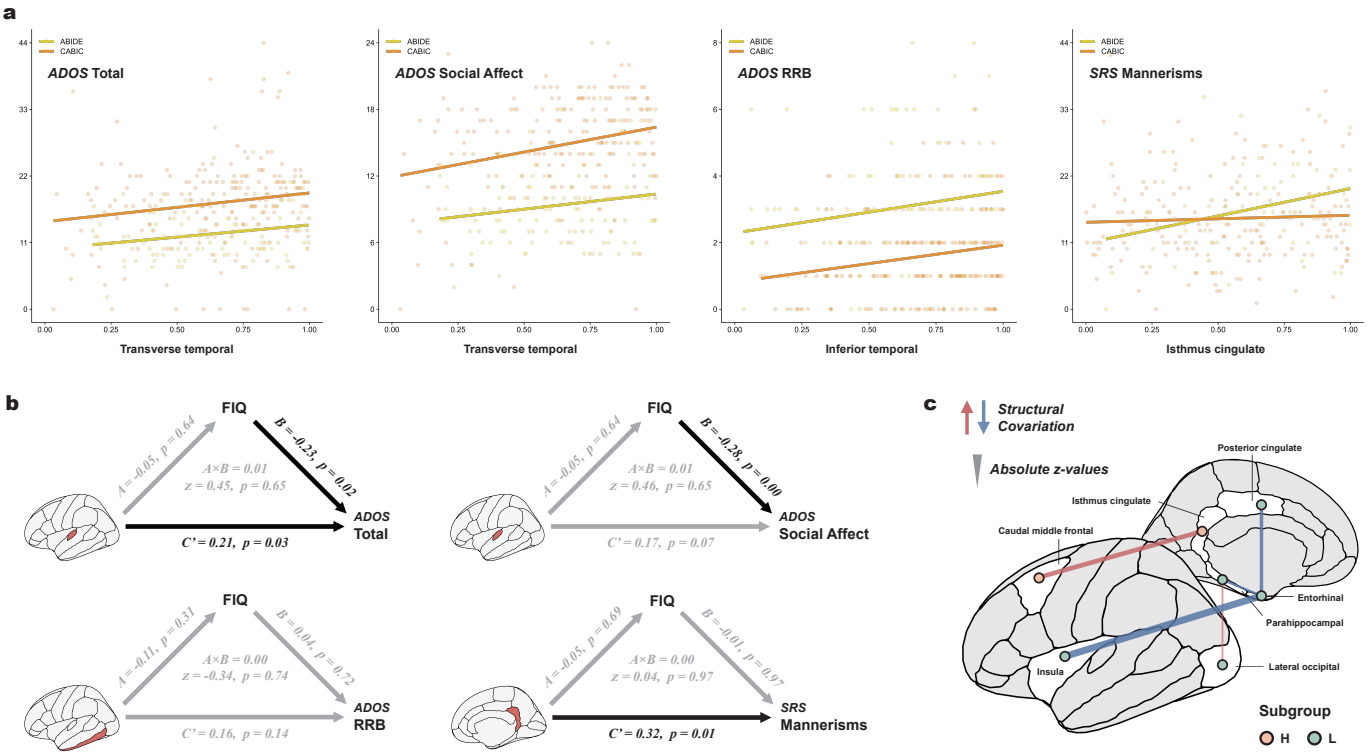

Figure 2: Brain-behavior correlations and structural covariations of Out-of-Sample scores.
a, Reproducible correlations between brain region volumes, measured as Out-of-Sample (OoS) scores, and clinical measures across ABIDE and CABIC datasets (subgroup H only). **b,** Mediation models for significant brain-behavior associations identified in subgroup H (ABIDE cohort only). Black solid arrows represent significant effects, while gray arrows indicate non-significant ones. Top: transverse temporal; bottom left: inferior temporal; bottom right: isthmus cingulate. **c,** Significant structural covariations across ABIDE and CABIC datasets. Positive z-values (red lines) indicate stronger covariance in ASD participants compared to controls, while negative z-values (blue lines) reflect weaker covariance.

As a common comorbidity of ASD, intellectual disability is closely associated with atypical brain morphological developmental patterns that accompany individual differences in intellectual functioning. To examine whether Full-Scale Intelligence Quotient (FIQ) mediates the relationships between brain morphology and cognitive behaviors within clusters, mediation analyses were conducted on the significant correlations we found in subgroup H. Results revealed direct effects for specific cortical regions (2b). The transverse temporal gyrus showed a direct effect on ADOS Total ($C' = 0.21, p = 0.03$), while the isthmus cingulate exhibited a direct effect on SRS Autistic Mannerisms ($C' = 0.32, p = 0.01$). No mediation effects through FIQ were observed. Neither direct nor indirect effects were significant for correlations to ADOS RRB or Social Affect.

DISCUSSION

This study used the ABIDE and CABIC datasets to discover distinct brain morphological subgroups of ASD within a young male cohort. We identified two subgroups characterized by significant differences in OoS scores in 34 cortical regions. Machine learning models showed a high predictive accuracy in distinguishing these subgroups based on their brain morphology. Furthermore, structural covariance and brain behavior correlation analysis illustrated different patterns of morphological relationships and their associations with clinical measures, especially in subgroup H. The consistent correlations across both the ABIDE and CABIC datasets highlight the robustness and reproducibility of our results across diverse cohorts. We will now discuss these findings from several neurobiological and neurodevelopmental perspectives to enhance our understanding of the distinct morphological patterns identified.

Two Subgroups Suggest Different Neurobiological Basis

Studies have reported extremely large or small head circumferences in individuals with ASD, possibly related to different subgroups. Early brain overgrowth is one of the most consistent findings in ASD research [37]. Abnormal increases in brain size during early development suggest that atypical cell proliferation significantly contributes to ASD symptoms [38]. Ultrasound studies have detected head enlargement during the second trimester in individuals later diagnosed with ASD [39]. iPSC-based studies reveal enlarged em-

bryonic stage brain cortical organoids (BCOs) in babies with ASD, with larger BCOs associated with more severe social symptoms[40]. MRI scans of these individuals show overgrowth in primary auditory and somatosensory cortices, while undergrowth in the visual cortex[40]. This neuronal overproduction, caused by the acceleration of the cell cycle, results in impaired differentiation and ultimately disrupts neural functions[41].

Smaller brain volumes are also frequently reported in ASD. A meta-analysis[42] identified volumetric reductions in a large cluster of regions, including the parahippocampal gyrus and entorhinal cortex. Higher levels of autistic traits have been associated with a smaller total cortical volume (TCV), a lower cortical thickness, a smaller surface area and a lower gyrification[43,44]. One potential explanation for this global brain underdevelopment is impairment caused by insufficient blood circulation and oxygen saturation[45]. For example, children with complex congenital heart disease (CHD) also demonstrate cognitive difficulties similar to those observed in ASD and have an increased likelihood of developing ASD[46]. Similarly, head enlargement also coincide with greater increases in height often[44]. Therefore, brain overgrowth could be part of the broader physical growth dysregulation[47] too. These evidences provide the distinct neurobiological basis for the subgroups identified in our study. The different underlying physiological mechanisms may explain the inconsistent effectiveness of commonly used pharmacological treatments.

Hypothesis of Abnormal Brain Morphology Specific Functional Impairment Pathways

Abnormal neural migration and cortical laminar organization in ASD[48] suggest that structural abnormalities are unlikely to be localized. Postmortem studies have identified focal laminar disorganization and mis-migrated neurons in the prefrontal and temporal cortex, particularly in layers 2, 3, and 4[48]. Layers 2 and 3 support information exchange between cortical regions, while layer 4 receives sensory inputs[49]. Disruptions in these layers can cause profound miscommunication between the sensory and higher-order cognitive regions. Key regions in our clustering analysis (such as the precuneus, isthmus cingulate, and entorhinal cortex; 3a, *a*~*c*) are primarily involved in higher-order association networks (3a). This aligns with the concepts of functional information flow in the brain[50], suggesting different pathways of impairment as the basis for the heterogeneity of ASD. Inconsistencies in information flow reported by previous ASD studies[21,51] may arise from two distinct structural impairment patterns identified in our study.

The regional volume abnormalities identified in our study involve distinct functional brain regions in the two subgroups. Subgroup L showed a notable prevalence in the middle temporal gyrus, inferior temporal gyrus, pericalcarine cortex and frontal pole (3a, *d*~*g*), while subgroup H in the caudal anterior cingulate, transverse temporal cortex, and insula (3a, *h*~*j*). Drawing on the spatial distributions[52] of 7 large-scale functional networks[53], we constructed a schematic (3b) of the latest 15 large-scale functional networks of the brain estimated from individuals[54] (3a). This perspective revealed different pathways of functional impairment in the regions with a high prevalence of abnormalities for each subgroup. Subgroup L exhibited an atypical morphology mainly affecting Visual – Dorsal Attention – Frontoparietal – Language and Default networks (DN) (3b, green path), while subgroup H affected the Auditory and Somatomotor – Cingulo-Opercular and Salience/Parietal Memory (SAL/PMN) – Frontoparietal networks (3b, orange path), indicating disturbances in peculiar unimodal sensory integration and multimodal cortical functions. This phenomenon may hint at the presence of distinct abnormal brain functional circuits from first- to third-order networks in the subgroups.

For example, in adults without ASD[55], increased gray matter volume in regions of the somatomotor network was associated with greater attention to detail, while changes in regions of the visual network were associated with poor imagination. These findings suggest potential cognitive patterns in two subgroups of ASD that have yet to be discovered. In typically developing children, the principal functional gradient[52] of the cortical organization reflects differentiation within unimodal sensory areas, progressing from the somatomotor and auditory cortex to the visual cortex. The transition from childhood to adolescence extends this organization to higher-order association cortices[56]. Brain maturation appears to involve a shift from local to distributed network architecture. The distinct morphological abnormalities in these two ASD subgroups, observed before this transition begins, raise a critical question: How do these "morphological foundations" disrupt their development from childhood to adolescence? These structural impairment pathways in childhood are likely to contribute further to heterogeneity in ASD during and after adolescence.

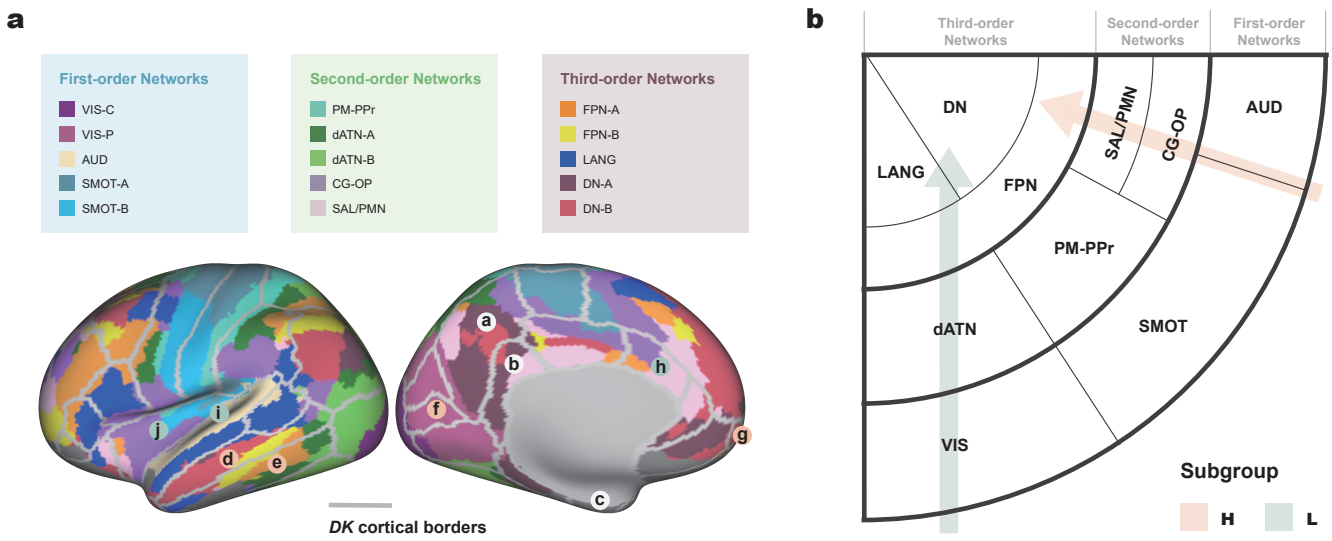

Figure 3: The theoretical brain functional network impairment model of two ASD subgroups.
a, A brain map combining the 34 Desikan regions[36] with the latest 15 large-scale brain functional networks estimated from individuals[54]. *a*, precuneus; *b*, isthmus cingulate; *c*, entorhinal; *d*, middle temporal; *e*, inferior temporal gyrus; *f*, pericalcarine; *g*, frontal pole; *h*, caudal anterior cingulate; *i*, transverse temporal; and *j*, insula. **b,** A schematic of the potential spatial distributions of distinct functional impairment networks inferred from 34 cortical regions with high abnormal prevalence for two subgroups. VIS, Visual (C, Central; P, Peripheral); SMOT, Somatomotor; AUD, Auditory; dATN, Dorsal Attention; PM-PPr, Premotor-Posterior Parietal Rostral; CG-OP, Cingulo-Opercular; SAL/PMN, Salience/Parietal Memory; FPN, Frontoparietal; LANG, Language; DN, Default networks.

Understanding the Heterogeneity from a Developmental Perspective

Different network-based vulnerabilities suggest that interventions targeting specific impairments within each subgroup could be more effective. Interestingly, we found no significant differences in cognitive or behavioral measures between the subgroups. Although there distinct patterns of structural covariation between subgroups, but no significant correlations with autism-related behaviors. Structural covariance reflects long-term developmental changes. Reduced structural covariance may indicate disruptions in shared developmental pathways, while enhanced covariance could result from compensatory adaptations in response to atypical neurodevelopmental trajectories in ASD. This implies that morphological deficiencies may activate compensatory mechanisms during development, leading to similar cognitive and behavioral outcomes. The observed age difference between subgroups, though minor, could have significant implications during sensitive developmental periods. Lifespan trajectories[32] of 34 brain regions show an early steep increase in volume, followed by a near-linear decline. The middle temporal gyrus peaks at 7.8 years, while the caudal anterior cingulate peaks at 9.2 years[32], possibly related to the result that subgroup L is generally younger than subgroup H. These distinct structural abnormalities likely reflect differences in the timing of atypical developmental processes.

The isthmus cingulate, a key region in subgroup clustering, typically peaks in volume at 3.8 years. The lack of age-related decline in cortical volume was consistently found in subgroup H in both the ABIDE and CABIC datasets (See Supplementary Analysis and Fig. S1f). However, subgroup H aligns with normative references before age 5, while subgroup L shows smaller initial volumes (Fig. S1e). In subgroup H, an increase in structural covariance between the caudal middle frontal cortex (peaking at 7.75 years) and the isthmus cingulate (2c) suggests synchronized developmental trajectories. This may reflect precocious caudal middle frontal development, delayed isthmus cingulate development, or both regions following similarly abnormal patterns[22]. Correlation analyses link larger isthmus cingulate volumes in subgroup H directly with more pronounced autistic mannerisms (2a). These evidence hint at delayed development of the isthmus cingulate in subgroup H. With a normal OoS distribution ($p = 0.06$; Table 1, column 6) in this subgroup, this morphological change appears to represent a homogeneous and quantifiable pattern. In subgroup L, the parahippocampal gyrus (peaking at 10.63 years) shows reduced covariance with the entorhinal cortex (peaking at 22.67 years) but increased covariance with the lateral occipital cortex (peaking at 5.21 years). This pattern suggests a precocious development of the parahippocampal gyrus and/or the delayed lateral occipital cortex in this subgroup. Enhanced structural covariances may also reflect compensatory adaptations to mitigate structural disadvantages inherent in abnormal developmental patterns. This highlights

the need for longitudinal studies to explore how brain maturation influences behavior at different stages of development in ASD.

Reproducibility across Datasets and Implications for Biomarker Development

One key contribution of this study is the reproducibility of brain-behavior associations across the ABIDE and CABIC datasets. Cross-dataset validation confirms that the findings reflect stable neurobiological characteristics. In subgroup H, an enlarged transverse temporal gyrus may impair precise auditory processing. This disruption can affect auditory responsiveness and the ability to integrate and understand information during social interactions. It may also damage early language perception and acquisition, particularly before a diagnosis of ASD is made. Research has found that when ASD is accompanied by cognitive learning needs, head enlargement becomes even more pronounced[44]. This suggests a shared mechanism linking brain overgrowth with impaired intellectual functioning. Alternatively, cognitive impairments might mediate the relationship between this overgrowth and ASD. Although intelligence moderates the relationship between ASD traits (ADOS total score), transverse temporal gyrus abnormality remains a direct indicator (2b). This suggests impaired primary sensory perceptual function that is directly disrupted by abnormal sensory input. The inferior temporal gyrus (ITG) is also uniquely associated with restricted interests and repetitive behaviors (ADOS RRB), despite the low prevalence of structural abnormalities in subgroup H. This region plays a crucial role in object recognition[57]. Disruptions in these functions can lead to a tendency to focus repetitively on objects or details. The involvement of IFG in perceptual and cognitive processes can also influence how individuals respond to environmental stimuli, further impacting RRB. In particular, the correlation between ITG and RRB was no longer significant after controlling for FIQ. This suggests that variations in intelligence may obscure the relationship. ITG might be specifically associated with certain dimensions of RRB while individuals with higher FIQ could develop other cognitive strategies to regulate RRB, reducing the apparent role of ITG in these behaviors.

We classified ASD subtypes solely based on brain morphology, assuming a causal relationship between brain structure and cognition. However, this relationship is inherently complex, thus interpreting the brain in regions goes against its interconnected nature. Although subgroup L exhibited a higher prevalence of structural abnormalities, suggesting more extensive morphological variations, we did not find reproducible brain-behavior associations between cohorts. Several factors may explain these findings. First, cognitive impairments related to structural abnormalities in subgroup L might be more sensitive to cultural differences. Second, the validity of ASD diagnoses in subgroup L might be questionable. The best predictor of a DSM-IV diagnosis has been found to be often the specific clinic attended, rather than any defining characteristic of the individual[58]. This indicates that current diagnostic tools may not capture the nuanced behaviors directly related to brain abnormalities in subgroup L. Considering global reduction in brain volume, which may result from cardiogenic etiological damage, our findings highlight the urgent need for new methods and paradigms to enable deep phenotyping and reduce the reliance on behavioral scales for differentiation. Third, heterogeneity within subgroups may also contribute to the limited reproducibility findings. Behavioral paradigms targeting brain regions with a normal distribution of OoS scores could better reveal subgroup-specific relationships between brain morphology and cognitive behavior.

Limitations & Future Direction

Some limitations in this study should be noted. First, previous research highlights atypical structural connectome asymmetry in ASD[59], while we could not fully evaluate hemispheric differences within subgroups using LBCC trajectories. Second, the cross-sectional nature of the data limits causal inferences about how these abnormalities of the brain morphology arise and their relationships with ASD symptoms. Future research should thoroughly investigate brain function and cognitive differences between these subgroups while exploring how demographic, environmental, and developmental factors shape brain-based subtypes. Combining longitudinal data $invivo$ and $invitro$[41] could expand cohort diversity and provide deeper insights into the neurobiological and molecular mechanisms underlying different subtypes. When designing research cohorts to study further, focus on more representative ASD prototypes[60] could help reduce heterogeneity within subgroups. More attention should be paid to people with more severe ASDs, such as minimally verbal autism, who remain underrepresented in brain imaging studies[61], partly due to the challenges of collecting neuroimaging data, especially in young children. Our research strategy uses structural magnetic resonance imaging, feasible in natural sleep or sedation, with significant clinical potential. However, multimodal approaches with higher ecological validity are essential to identify neurosubtypes that include these samples. At the same time, replication with different clustering algo-

rithms is required to confirm the stability of these findings. More nuanced clustering strategies should be explored, as disease variations may exist within the range of normal variation [62], and multiple subpopulations may also exist in typically developing populations. Finally, translational studies using animal models are essential for understanding the mechanisms underlying these different subtypes. Such studies can provide critical information on how abnormalities in brain morphology develop [63].

Conclusion

Linking specific brain morphology abnormalities to cognitive or behavioral impairments in ASD is challenging. Different biological mechanisms can lead to similar behavioral outcomes, complicating the identification of neural correlates. This overlap may explain the difficulty in replicating neuroimaging findings between studies or cohorts. Using the largest brain normative datasets and two large-scale cross-cultural consortiums, we applied normative modeling to disentangle the heterogeneity of brain morphology in ASD. By breaking the ASD population into smaller and more morphologically homogeneous subgroups, we identified two subtypes of morphological abnormalities. We identified significant correlations between cortical regions and autistic traits across both consortia, with particular emphasis on the isthmus cingulate cortex, as well as the transverse and inferior temporal gyri. Based on the abnormal prevalence of regional volumes, we found two structural impairment pathways that could disrupt sensory to higher cognitive functions. These findings highlight the importance of untangling mixed biological mechanisms and offer insight to develop effective subgroup-driven individualized interventions. In conclusion, our study provides a reference for elucidating the etiological mechanisms of neurodevelopmental disorders and advancing future subgroup-driven precision clinical practice.

MATERIALS AND METHODS

Participants and Data Preprocessing

Participants were selected from the Autism Brain Imaging Data Exchange (ABIDE) cohort [34,35]. The original dataset includes 1,833 autistic and 1,838 non-autistic individuals aged 264 years from 56 sites. All diagnoses were based on the DSM-IV or DSM-V criteria. To align with the objectives of our study, we focus on male participants under 13 years of age. This age range reflects our interest in brain development during childhood and early adolescence.

We used T1-weighted MRI data from the ABIDE cohort. The acquisition parameters are publicly available at ABIDE website. Data quality was assessed through a combination of automated checks using (MRIQC) [64] (version 22.0.6) and manual visual inspections. Images with severe motion artifacts, segmentation errors, or structural abnormalities were excluded from further analysis. Pre-processing performed through the Connectome Computation System (CCS) pipeline [65,66]. FreeSurfer (toolbox: version 6.0.0) was used for skull removal, cortical reconstruction, segmentation, and registration in the Montreal Neurological Institute (MNI) template. Each T1-weighted image was segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF).

The total cortical volume (TCV) was calculated as the sum of the GM and WM volumes, following the LBCC method [32]. The mean cortical thickness (CT) was calculated as a weighted average of the thicknesses of the left and right hemispheres. The total surface area (SA) was determined by summing the surface areas of white matter of both hemispheres. Regional brain volumes for 34 bilaterally averaged cortical regions were evaluated using Desikan-Killiany parcellation [36]. To reduce site-related variability, we applied ComBat harmonization [67]. This process was implemented using (*neuroCombat*) R package.

Normative Scoring and Clustering Analysis

To assess how the brain morphology of each participant aligned with age-standardized normative trajectories, we used the out-of-sample (OoS) centile score [32]. First, all non-ASD individuals from the site-harmonized ABIDE data set were employed to estimate cohort-specific statistical offsets. The centile scores of each brain measurement were then estimated for all individuals with ASD compared to the offset trajectory (see *Methods: Centile scoring of new MRI data* in the original LBCC work [32]). This approach takes advantage of the generalized additive models for location, scale, and shape (GAMLSS) [68] framework to estimate statistical offsets such as mean, variance, and skewness. These offsets capture individual deviations from typical brain development. OoS scores are comparable between age and cohort. The scoring process was conducted with the publicly available code from Lifespan Charts website.

Using OoS scores from 34 brain regions as classification features, we applied spectral clustering [69] among individuals with ASD in the ABIDE cohort. Spectral clustering was selected for its ability to detect nonlinear data structures, which are common in brain imaging datasets. Unlike k-means clustering, which relies on centroid-based optimization, spectral clustering transforms the data into a lower-dimensional space using the eigenvalues of a similarity matrix. Before clustering, the Jarque-Bera test was performed to determine whether OoS scores follow a normal distribution.

Clustering analysis was implemented using the *kernlab* package R. We tested clusters of 2 to 10 to identify the optimal solution. The quality of clustering was evaluated using the Silhouette Coefficient (SC) [70], which assesses both within-cluster cohesion and between-cluster separation. SC values range from -1 to 1, with higher scores indicating better defined clusters. The optimal number of clusters was decided by the highest SC score.

Key Brain Regions for Subgroup Classification

We developed a predictive model using machine learning with individual OoS scores from 34 regions of the brain as input characteristics. We trained a Support Vector Machine (SVM) classifier [71] with Recursive Feature Elimination and Cross-Validation (RFECV). This was implemented using the *scikit-learn* library in Python. Combining recursive feature elimination (RFE) [72] with cross-validation allows the model to iteratively identify the most informative features while maintaining generalizability and robustness. The data set was divided into 80% training sets and 20% testing sets. Using a linear SVM as the base estimator, RFECV removed less important features in a stepwise manner, with performance monitored through 5-fold cross-validation. This process ensured that the final feature set balanced predictive power and reduced over-fitting.

Following feature selection, we fine-tuned the SVM model by performing a grid search to optimize key hyperparameters, including regularization strength (C) and kernel coefficients (γ). The model was evaluated across different kernel functions, such as linear, polynomial, and radial basis functions, to determine the best configuration. Once optimized, the model was trained on the selected features to achieve optimal classification performance. SHapley Additive exPlanations (SHAP) [73] were applied to quantify the contribution of each brain region to the model predictions.

Structural Covariance Network Analysis

To investigate morphological relationships of a specific cluster, we constructed structural covariance analysis [74] on OoS scores of each two regions. Pearson's correlation analysis was performed on residuals obtained from linear regression models that controlled for site effects and TCV OoS scores. To enable statistical comparison, correlation coefficients were normalized using Fishers r-to-z transformation, defined as:

$$Z = \frac{1}{2}\log_e\left(\frac{1+r}{1-r}\right), \tag{1}$$

where r represents the Pearson correlation coefficient between two regions. The difference (cluster i/ii vs. normal control) in transformed correlation coefficients was calculated using:

$$z = \frac{Z_1 - Z_2}{\sqrt{\frac{1}{n_1-3} + \frac{1}{n_2-3}}}, \tag{2}$$

where n_1 and n_2 are the two sample sizes being compared. The resulting z-values were converted to p-values using the cumulative distribution function of the standard normal distribution.

Cluster Differences and Brain-Behavior Analysis

We investigated differences between clusters and demographic, technical and clinical variables. For categorical variables, such as subtypes of perinatal developmental disorders (PDD), scanner models, and manufacturers, Chi-square tests were employed. For data collection sites, Fishers exact test was used with Monte Carlo simulations to approximate p values. To ensure robust analysis, sites with fewer than 10 participants were excluded. For other continuous variables, statistical methods were selected based on data distribution: the Wilcoxon rank sum test was used for nonnormally distributed data, and the two-sample t-test for data shows normal distribution. The effect sizes were calculated using Cramér's V for categorical variables and Cohens d for continuous variables. Statistical significance was set at $p < 0.05$.

To further explore brain-behavior relationships within clusters, we performed correlation analyses using Full-Scale Intelligence Quotient (FIQ), ADOS-2 (Social Affect and Restricted and Repetitive Behaviors, RRB), ADI-R (Social Interaction and RRB), and SRS subscales. Pearson's correlation was applied to most measures, while Spearman's correlation was used for ADOS-2 RRB scores due to their limited range. In these analyzes, the effects of the site and the OoS scores of TCV were controlled.

For each group, we also examined partial correlations to investigate structural covariance between 34 brain regions and their association with cognitive behaviors. For each participant, the partial covariance scores of two regions were calculated as

$$\text{partial_p} = \text{residual}_{region1} \times \text{residual}_{region2},$$

The resulting partial covariance scores were then correlated with the same measurements with the same correlated methods.

Finally, we performed mediation analyzes to examine whether FIQ mediates the relationships between brain morphology and cognitive behaviors within clusters. Linear models were used to estimate direct and indirect effects, with adjustments for site and OoS scores of TCV. All brain morphology and cognitive behavior variables were standardized to ensure comparability among participants. The significance of indirect effects was assessed using the Sobel test.

Detection of Reproducible Results Between Datasets

We applied the ABIDE-based classifier to an independent dataset from the China Autism Brain Imaging Consortium (CABIC) [33], which is a multicenter collaboration among clinical and research institutions in China. It is designed to collect neuroimaging, demographic, and behavioral data on children and adolescents with ASD. Diagnoses in the CABIC cohort were based on DSM-IV, DSM-V, or ICD-11 criteria and validated using ADOS and ADI-R. The dataset includes 1,400 participants, comprising 983 autistic individuals and 514 typically developing controls. Detailed MRI acquisition parameters are publicly accessible at CABIC Site.

CABIC participants, aged 1 to 13 years, tend to exhibit more severe ASD symptoms, resulting in lower variability within clusters. Although this homogeneity is clinically valuable, it poses challenges in detecting subtle brain-behavior relationships. In contrast, the ABIDE cohort provides greater behavioral differences, enhancing the ability to identify nuanced patterns in brain structure. By leveraging these complementary datasets, our goal was to identify results that are reproducible across both cohorts. We repeated the statistical, structural covariance, and correlation analyses on CABIC cohort. However, the limited FIQ data in CABIC restricted the replication of mediation analysis with sufficient statistical power. Therefore, mediation analysis was conducted on the ABIDE cohort only.

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Conception and Design: X-R.F., X-N.Z. Data Analysis: X-R.F. MRI Data Preprocessing: Y.H., CABIC. Initial Drafting of the Manuscript: X-R.F. Critical Review and Editing of the Manuscript: All authors contributed to the critical review and editing of the manuscript.

AUTHOR COMPETING INTERESTS

Competing interests

The authors declare no competing interests.

DATA AVAILABILITY

The datasets analyzed in this study are publicly available. The ABIDE dataset can be accessed from the Autism Brain Imaging Data Exchange repository at ABIDE website. The CABIC dataset is available upon request through the CABIC Data Sharing Initiative at CABIC website.

CODE AVAILABILITY

All code used in the analyses is available at https://github.com/XueruFan/ASD-Project. For detailed information on how to use these codes, please contact the first author by email.

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TABLES

Table 1: Group comparisons of regions morphology between overall and two ASD subgroups.

Region	OoS Scores						AbP[1] (%)	
	All		L		H		L	H
	p	Median	p	Median	p	Median		
Superior frontal	0.01	0.48	0.02	0.28	0.37	0.62	5.56	2.70
Rostral middle frontal	0.01	0.46	0.02	0.25	0.32	0.60	7.94	0.68
Caudal middle frontal	0.00	0.42	0.00	0.26	0.05	0.60	6.35	2.70
Pars opercularis	0.00	0.47	0.00	0.23	0.07	0.61	6.35	4.73
Pars triangularis	0.00	0.45	0.02	0.28	0.02	0.60	6.35	1.35
Pars orbitalis	0.01	0.46	0.06	0.33	0.11	0.56	5.56	0.68
Frontal pole	0.00	0.48	0.02	0.34	0.03	0.60	11.90	2.03
Lateral orbital frontal	0.00	0.46	0.01	0.26	0.06	0.63	7.94	2.03
Medial orbital frontal	0.00	0.42	0.00	0.26	0.04	0.61	10.32	2.70
Rostral anterior cingulate	0.00	0.45	0.00	0.25	0.04	0.65	4.76	2.70
Caudal anterior cingulate	0.00	0.47	0.01	0.30	0.00	0.68	3.97	6.76
Precentral	0.00	0.45	0.01	0.26	0.17	0.60	6.35	3.38
Paracentral	0.01	0.52	0.05	0.34	0.10	0.62	4.76	5.41
Postcentral	0.00	0.48	0.01	0.29	0.05	0.64	7.14	4.05
Supramarginal	0.00	0.49	0.01	0.31	0.04	0.65	7.94	3.38
Posterior cingulate	0.00	0.46	0.02	0.29	0.04	0.64	7.94	5.41
Isthmus cingulate	0.00	0.47	0.00	0.27	0.06	0.64	3.97	4.05
Precuneus	0.00	0.52	0.04	0.29	0.02	0.70	5.56	4.73
Superior parietal	0.00	0.44	0.00	0.27	0.08	0.60	7.94	2.70
Inferior parietal	0.00	0.45	0.07	0.30	0.02	0.63	7.94	2.03
Transverse temporal	0.00	0.52	0.02	0.32	0.03	0.68	7.94	6.08
Banks superior temporal	0.00	0.44	0.00	0.26	0.02	0.59	3.97	5.41
Superior temporal	0.00	0.49	0.00	0.26	0.04	0.67	6.35	4.05
Middle temporal	0.00	0.44	0.02	0.24	0.06	0.61	17.46	2.70
Inferior temporal	0.00	0.49	0.05	0.30	0.04	0.62	11.90	0.68
Fusiform	0.00	0.45	0.01	0.26	0.09	0.59	10.32	1.35
Parahippocampal	0.00	0.49	0.02	0.33	0.01	0.63	3.17	2.70
Entorhinal	0.01	0.51	0.05	0.40	0.04	0.62	6.35	0.68
Temporal pole	0.00	0.44	0.03	0.36	0.02	0.58	10.32	1.35
Lateral occipital	0.00	0.46	0.01	0.28	0.02	0.63	9.52	2.70
Lingual	0.00	0.40	0.00	0.24	0.01	0.58	7.94	2.70
Pericalcarine	0.00	0.36	0.00	0.23	0.01	0.53	11.90	2.70
Cuneus	0.00	0.46	0.01	0.25	0.03	0.55	6.35	1.35
Insula	0.00	0.53	0.02	0.31	0.02	0.69	3.17	6.08

[1] AbP: Prevalence of abnormalities.

SUPPLEMENTARY INFORMATION

Supplementary Analysis

Brain Growth Charts and Age-Related Changes in OoS Scores for ASD Subgroup

To investigate potential developmental trajectories in ASD subgroups, here we illustrated the normative growth trajectories for volumes of the bilaterally averaged cortical regions with ABIDE dataset. The analysis focused on three brain regionstransverse temporal, inferior temporal, and isthmus cingulatethat exhibited reproducible correlations across both datasets. The subgroup-specific brain charts (Fig. S1e) were upgraded from the LBCC charts and adjusted by leveraging all the samples from the ABIDE. Then, we applied Generalized Additive Mixed Models (GAMM) using the *gamm4* R package to explore the relationship between OoS scores and age within subgroup H across the CABIC and ABIDE datasets.

$$\text{OoS score} \sim s(\text{Age}, \text{bs} = \text{"tp"}, \text{k} = 4) + \text{TCV}$$

Although OoS scores are adjusted for age-related effects, examining residual variability allows us to gain additional insights into brain-cognition relationships within specific subgroups.

In the transverse temporal region (Fig. S1f, left), CABIC presented a non-significant positive trend with age ($R^2 = 0.07$, $p = 0.56$, $F = 0.57$), while ABIDE displayed a marginally significant trend ($R^2 = 0.06$, $p = 0.04$, $F = 4.10$). For the inferior temporal region (Fig. S1f, middle), CABIC showed a moderate but non-significant trend ($R^2 = 0.20$, $p = 0.22$, $F = 1.49$), while ABIDE exhibited a flat, non-significant pattern ($R^2 = 0.07$, $p = 0.46$, $F = 0.56$). The most robust findings were observed in the isthmus cingulate (Fig. S1f, right). CABIC demonstrated a significant positive association between OoS scores and age ($R^2 = 0.13$, $p < 0.001$, $F = 72.69$), suggesting meaningful developmental changes in this region. ABIDE also showed a positive trend, albeit with a smaller effect size ($R^2 = 0.12$, $p = 0.02$, $F = 5.51$).

Supplementary Figures

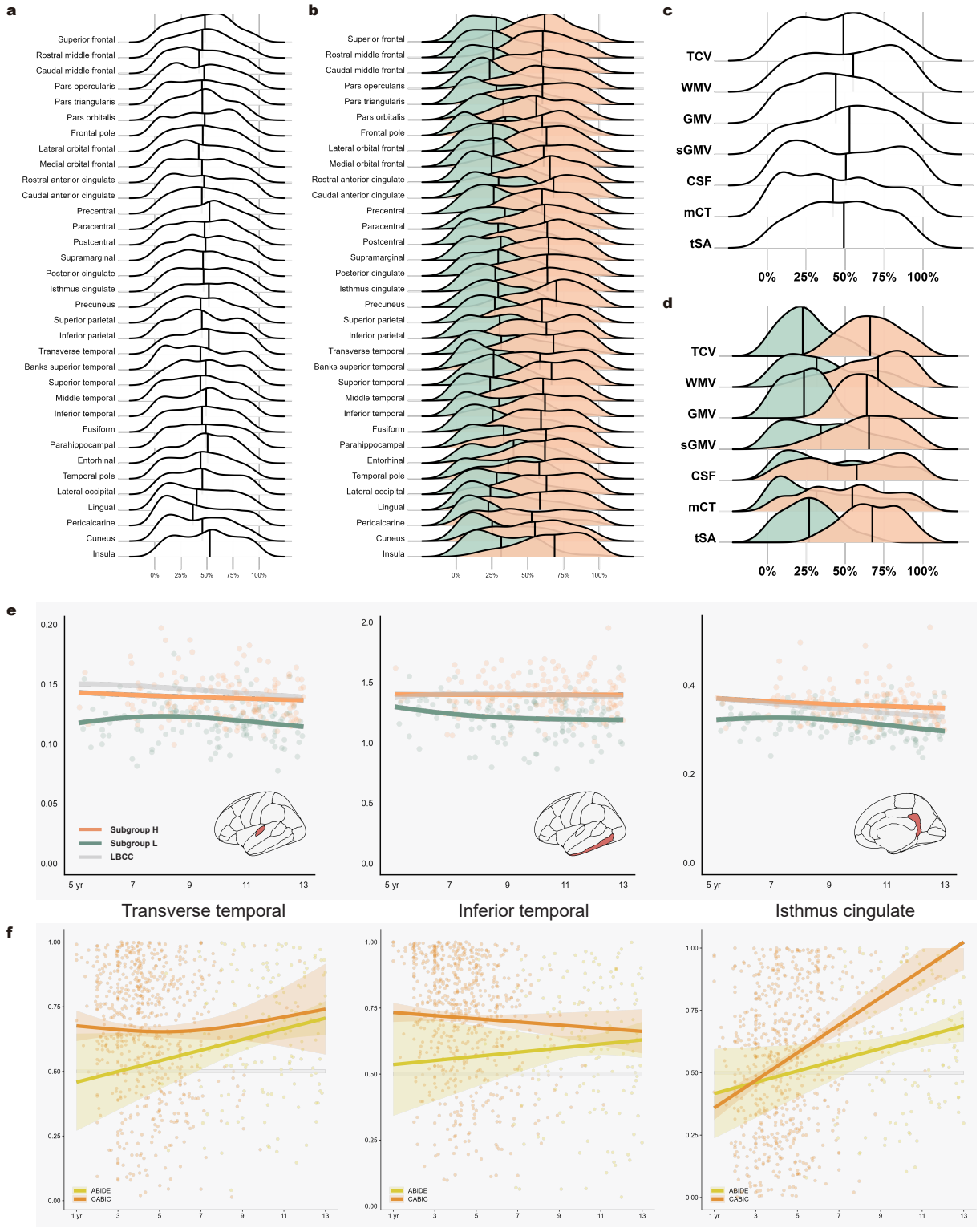

Figure S1

a, Distributions of ABIDE Out-of-Sample (OoS) scores across 34 cortical regions before clustering. **b,** Distributions of ABIDE OoS scores across 34 cortical regions after clustering. **c,** Distributions of ABIDE OoS scores across global measures before clustering. **d,** Distributions of OoS scores across global measures after clustering. **e,** ABIDE Subgroup-specific brain charts of cortical regional volumes of transverse temporal (left), inferior temporal (middle), and isthmus cingulate (right). **f,** The developmental effects of OoS scores in individuals from subgroup H were modeled using GAMM across the ABIDE and CABIC datasets. In plots **b**, **d**, and **e**, orange for subgroup H and green for subgroup L. TCV, total cortical volume; WMV, total white matter volume; GMV, total cortical gray matter volume; sGMV, total subcortical gray matter volume; CSF, total ventricular cerebrospinal fluid volume; mCT, mean cortical thickness; tSA, total surface area.

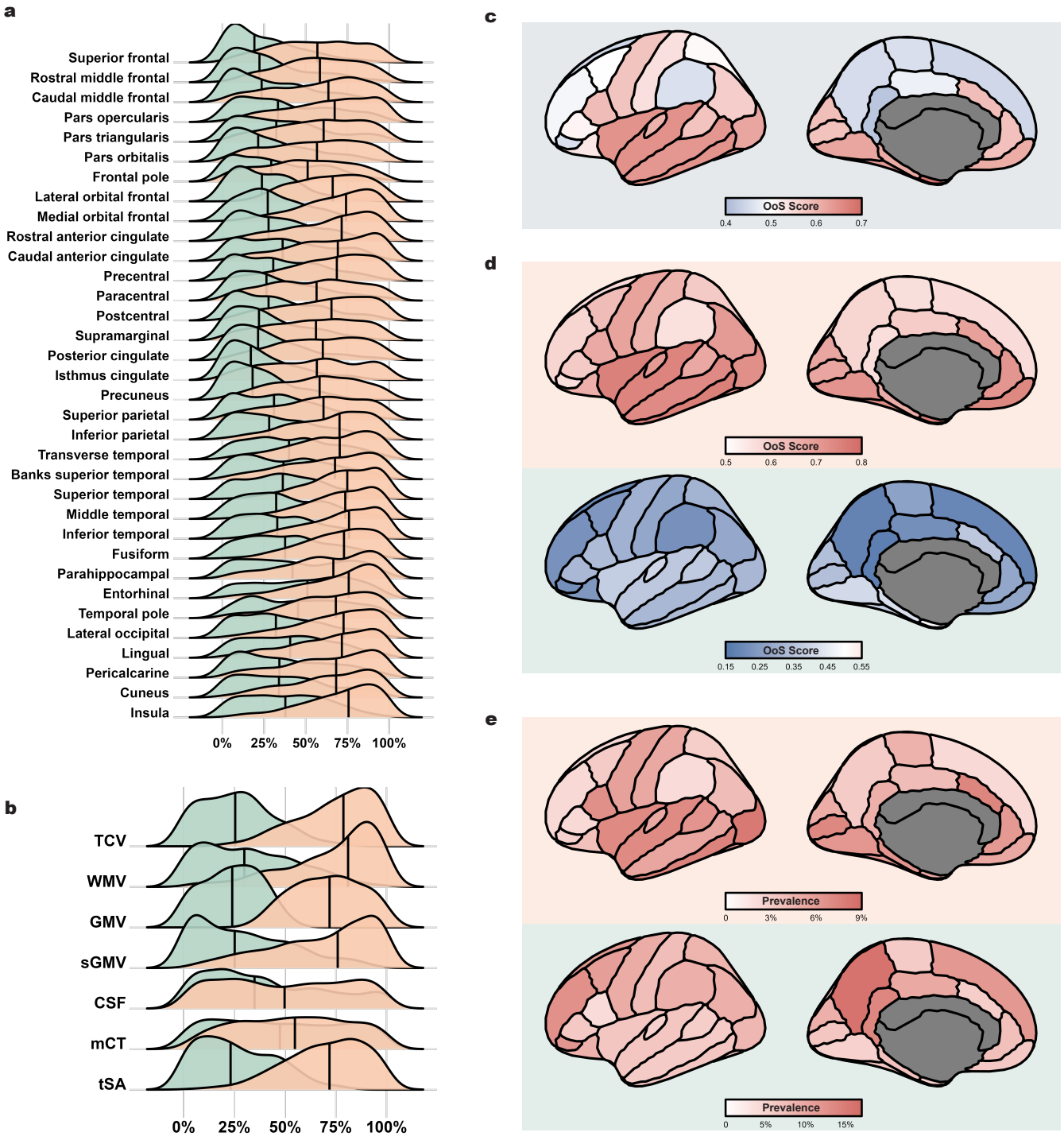

Figure S2. Brain morphology of two CABIC subgroups.
a, Distributions of Out-of-Sample (OoS) scores across 34 cortical regions after clustering. **b,** Distributions of OoS scores across global measures after clustering. TCV, total cortical volume; WMV, total white matter volume; GMV, total cortical gray matter volume; sGMV, total subcortical gray matter volume; CSF, total ventricular cerebrospinal fluid volume; mCT, mean cortical thickness; tSA, total surface area. **c,** Median OoS scores of 34 before cortical regions before clustering. **d,** Median OoS scores of ASD subgroup H (top) and L (bottom). **e,** Prevalence maps depicting the proportion of participants with extreme (top, 97.5% for subgroup H; bottom, 2.5% for subgroup L) structural anomalies. Note, the left hemispheres are plotted in **c, and d** just for visualization purposes.

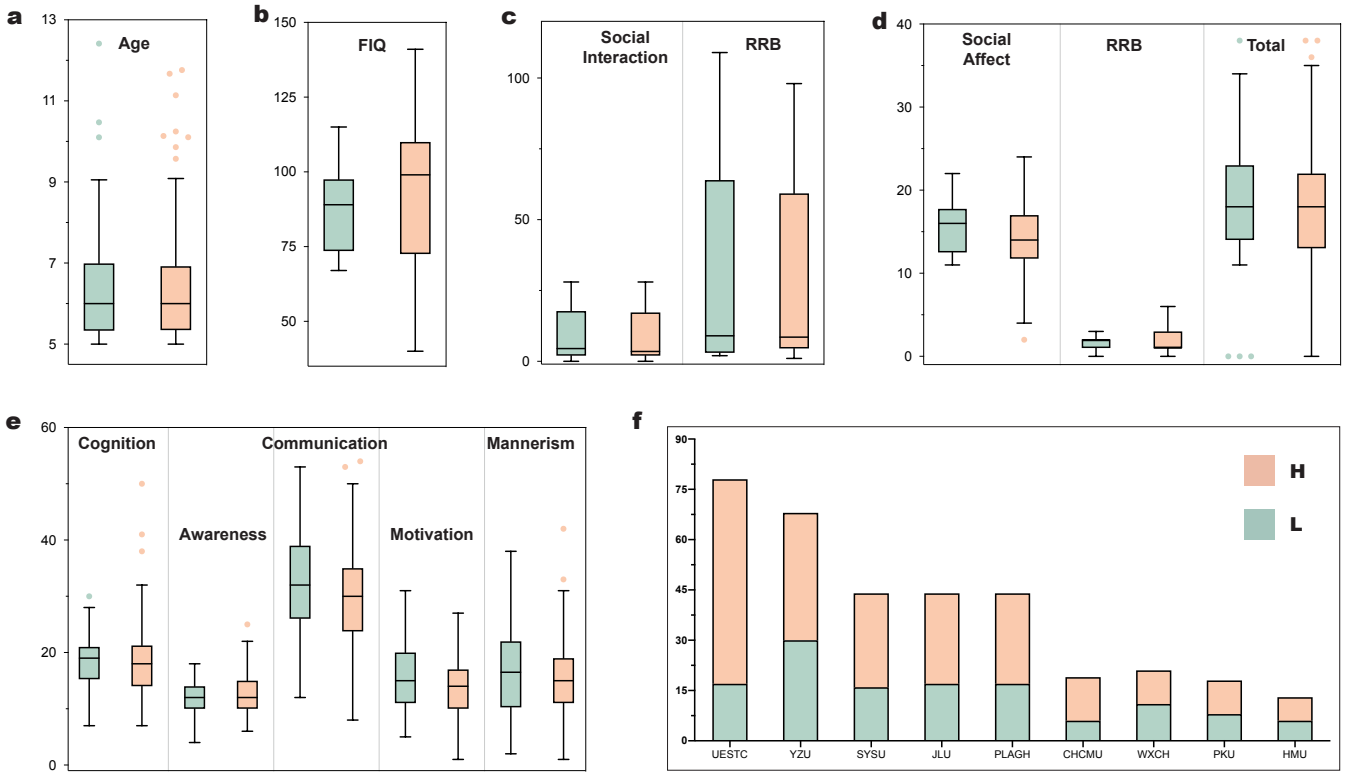

Figure S3. Differences between two CABIC subgroups.
Distribution of participant ages (**a**); FIQ scales (**b**); ADI-R (**c**); ADOS (**d**); SRS (**e**); and data collection site (**f**) across the two subgroups of CABIC, with no significant difference between them. For plots **a** to **e**, the center line shows the median; the box limits represent the 25th and 75th percentiles; the whiskers show the minimum and maximum values; and the dots represent potential outliers.

Supplementary Tables

Table S1. Statistical comparison between two clustering ASD groups for different measures.

Phenotype		Group(N)	Median	Mean	SD	Shapiro-Wilk Test	Rank-Sum Test	Two-sample t-Test	Cohen's d
Age		H (148)	10.51	10.25	1.87	0.00	0.02		-0.30
		L(126)	9.94	9.65	2.09	0.00			
IQ	PIQ	H (115)	109	109.43	18.05	0.77		0.11	-0.21
		L(111)	104	105.76	16.21	0.19			
	VIQ	H (116)	110	109.51	17.23	0.70		0.16	-0.19
		L(106)	106	106.29	16.94	0.45			
	FIQ	H (139)	110	108.66	18.39	0.26		0.09	-0.21
		L(117)	104	105.02	15.83	0.28			
ADOS-2	RRB	H (108)	3	3.06	1.84	0.00	0.94		0.02
		L(100)	3	3.09	1.85	0.00			
	Social Affect	H (107)	9	9.36	3.44	0.00	0.11		-0.18
		L(100)	8	8.73	3.76	0.00			
	Total	H (108)	12	11.62	4.75	0.00	0.15		-0.14
		L(100)	11	11.84	4.75	0.00			
	Severity	H (107)	7	7.16	1.78	0.00	0.18		-0.23
		L(100)	7	6.71	2.14	0.00			
ADI-R	RRB	H (120)	5	5.56	2.66	0.01	0.14		0.16
		L(103)	6	5.96	2.38	0.02			
	Nonverbal	H (120)	8	8.12	2.96	0.15	0.14		0.29
		L(28)	9.5	9.07	3.40	0.00			
	Verbal	H (120)	15	15.35	4.33	0.01	0.44		0.09
		L(103)	16	15.75	4.35	0.07			
	Social	H (119)	19	18.84	5.52	0.04	0.77		0.04
		L(103)	19	19.07	5.68	0.07			
SRS	Autistic Mannersims	H (67)	16	16.49	6.96	0.53	0.15		0.22
		L(69)	19	18.10	7.54	0.04			
	Motivation	H (67)	13	13.73	6.38	0.18		0.68	0.07
		L(69)	14	14.17	6.38	0.52			
	Communication	H (67)	29	30.43	10.48	0.89		0.93	-0.01
		L(69)	31	30.28	11.67	0.38			
	Cognition	H (67)	17	16.57	6.60	0.74		0.39	0.15
		L(69)	17	16.57	6.60	0.42			
	Awareness	H (67)	12	12.25	3.84	0.12		0.62	-0.09
		L(69)	11	11.93	3.73	0.39			

Table S2. Mean SHAP values for all 29 selected regions.

Region	Mean SHAP value
Isthmus cingulate	0.05
Entorhinal	0.04
Precuneus	0.04
Middle temporal	0.04
Fusiform	0.03
Transverse temporal	0.03
Rostral middle frontal	0.03
Postcentral	0.03
Inferior temporal	0.03
Rostral anterior cingulate	0.03
Supramarginal	0.02
Insula	0.02
Pericalcarine	0.02
Frontal pole	0.02
Lateral occipital	0.02
Posterior cingulate	0.02
Superior parietal	0.02
Pars opercularis	0.02
Caudal anterior cingulate	0.02
Medial orbital frontal	0.02
Lateral orbital frontal	0.02
Superior frontal	0.02
Inferior parietal	0.02
Caudal middle frontal	0.02
Cuneus	0.01
Pars orbitalis	0.01
Temporal pole	0.01
Precentral	0.01
Lingual	0.01

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