



Temporal and spatial variability of large-scale dynamic brain networks in ASD

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by significant impairments in social-cognitive functioning. Prior studies have identified abnormal brain functional connectivity (FC) patterns in individuals with ASD, which are associated with core symptoms and serve as potential biomarkers for diagnosis. However, the patterns of temporal and spatial variability in dynamic functional connectivity networks (dFCNs) in ASD and their relationship with ASD behaviors remain underexplored. This study uses fuzzy entropy to analyze the temporal variability and spatial variability of dFCNs, aiming to reveal distinctive FC patterns in ASD and identify new biomarkers. We conducted a comparative analysis between ASD and healthy controls (HCs), examining the association with clinical symptoms. Our findings indicate increased FC temporal variability in sensorimotor, subcortical, and cerebellar networks in ASD compared to HCs. Additionally, increased spatial variability was observed primarily in visual, limbic, subcortical, and cerebellar networks. Notably, these variability patterns correlated with symptom severity in ASD. Utilizing these spatiotemporal variability features, we developed multi-site classification models that achieved high accuracy (81.25%) in identifying ASD. These results provide novel insights into the neural mechanisms and clinical characteristics of ASD, suggesting that integrated spatiotemporal dFCN features may enhance diagnostic accuracy.

Keywords ASD · Dynamic functional connectivity · Temporal variability · Spatial variability

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction, communication, and repetitive behaviors [1]. The prevalence of ASD has been rising, reaching 3.79% among individuals aged 3–17 years in the United States in 2022 [2]. Previous studies have shown that brain functional connectivity (FC) at different scales is abnormal in ASD, and these abnormal FC patterns are not only related to core symptoms but can also serve as meaningful biomarkers to identify ASD [3]. However, the temporal and spatial variability patterns of dynamic FC network (dFCN) in ASD and their relationship with the behaviors of ASD remain unclear.

FC analysis using resting-state functional magnetic resonance imaging (rs-fMRI) is a pivotal method for investigating ASD's neural mechanisms [4]. Traditional static FC (sFC) approaches focus on consistent connectivity patterns throughout the scanning period. For example, reduced sFC between the medial prefrontal cortex and medial parietal

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regions has been observed in ASD [5]. Increased intrinsic FC between primary sensory and subcortical networks in ASD has also been reported [6]. However, sFC assumes stable connectivity, potentially overlooking temporal fluctuations. In contrast, dynamic FC (dFC) analysis accounts for these temporal changes, offering a more comprehensive view of brain network dynamics [7]. Recent studies have demonstrated that dFC analysis reveals abnormal connectivity patterns in ASD across both temporal and spatial dimensions. For example, Fu et al. reported increased whole-brain step-wise functional network reconfiguration in ASD across spatial scales, particularly in the cerebellar and sensorimotor domains [8]. Jia et al. found significant abnormalities in the temporal dynamics of DMN connectivity, which were closely associated with communication impairments and repetitive behaviors in ASD [9]. These findings underscore the potential of dFC to provide new insights into the disrupted neural mechanisms underlying ASD.

Variability, as a key feature of dFC, has become a widely used metric to capture the dynamic reorganization of brain networks in various neurodevelopmental disorders, including ASD. In particular, the temporal variability of functional architecture related to specific brain regions has become a tool for assessing the dynamic reconfiguration of these regions into distinct functional modules over time [10]. In this context, fuzzy entropy has been introduced as a tool for quantifying temporal variability in dFC, offering a robust approach to capture the complexity and dynamic fluctuations in brain networks [11, 12]. Fuzzy entropy-based temporal variability has been shown to be closely associated with social symptoms in ASD [13], underscoring its potential as a valuable marker for understanding the neural mechanisms underlying these symptoms. However, the spatial dimension of dFC variability remains underexplored in ASD research. Studies have shown that resting-state brain networks exhibit significant spatial variability in addition to temporal fluctuations [14]. Given that brain reconfiguration is inherently dynamic in both temporal and spatial dimensions [15], incorporating spatial variability could provide a more comprehensive view of the underlying neural processes [16]. Therefore, this study aims to extend the application of fuzzy entropy by not only quantifying temporal variability but also investigating spatial variability, with the goal of revealing the unique dynamic patterns of brain network reorganization in ASD and providing novel insights into its core clinical symptoms.

Indeed, FC not only elucidates the neural mechanisms of ASD but also contributes to identifying biomarkers. Prior studies have demonstrated the utility of FC features in ASD classification, achieving notable accuracies [17]. Furthermore, integrating temporal and spatial features of dFCNs has shown promise in improving classification accuracy, as

evidenced by studies on cognitive disorders like Alzheimer's and Parkinson's diseases [18, 19]. Therefore, it is essential to explore and incorporate the temporal and spatial properties of dFCN to enhance multi-site classification accuracy in ASD.

This study aims to explore the temporal variability and spatial variability of dFCNs in ASD using fuzzy entropy. First, we utilized rs-fMRI data from six sites of the Autism Brain Imaging Data Exchange (ABIDE) and applied ComBat harmonization for site effect correction. Second, we used sliding window analysis to construct dFCNs and employed fuzzy entropy to quantify their temporal variability and spatial variability. Third, we identified regions with extreme variability and analyzed group differences and correlations with clinical symptoms. Finally, we developed a multi-site classification model for distinguishing ASD from healthy control (HC) based on these variability features.

Materials and methods

Participants

All rs-fMRI data in this study were obtained from the publicly available datasets ABIDE (http://www.fcon_1000.projects.nitrc.org/indi/abide/). To ensure that consistent time points were maintained for all subjects from different sites as suggested by other studies [20], we selected six data sites from ABIDE I and ABIDE II, including the New York University Langone Medical Center (NYU) I and II Sample1, the San Diego State University (SDSU) I and II, and Stanford University (SU) I and II. Detailed information on data acquisition and inclusion criteria for subjects can be found in the Supplementary Materials. Finally, 284 subjects were retained, including 137 ASDs and 147 HCs. The ASD and HC groups were matched in age, sex, mean framewise displacement (FD), and FIQ scores.

To assess core ASD symptoms, we used the Autism Diagnostic Interview-Revised (ADI-R), focusing on three domains: social communication, verbal abilities, and restricted and repetitive behaviors (RRB). The ADI-R scores reflect the severity and specific characteristics of ASD [21]. Demographic information is provided in Table 1.

fMRI data preprocessing

Rs-fMRI images were preprocessed using the DPARSF (<http://rfmri.org/DPARSF>). The preprocessing steps for each subject are as follows: (a) remove the first five volumes; (b) time-slicing and head motion correction; (c) all functional images were normalized to Montreal Neurological Institute standard space with resampling to $3 \times 3 \times 3$

Table 1 Demographic details of the participants

	ASD (<i>n</i> =137)	HC (<i>n</i> =147)	<i>P</i> value
Age (years)	11.78±2.91	12.13±2.82	0.30 ^a
Sex (M/F)	122/15	119/28	0.06 ^b
FIQ	108.91±16.74	112.25±13.50	0.06 ^a
Mean FD	0.16±0.09	0.13±0.06	1.00×10 ^{-4a}
ADI-R			
Social score	18.91±5.49 (<i>n</i> =117)	-	-
Verbal score	14.81±4.74 (<i>n</i> =118)	-	-
RRB score	5.67±2.64 (<i>n</i> =118)	-	-

^a two-sample *t*-test; ^b chi-square test

F, female; M, male; FIQ, Full-Scale Intelligence Quotient; Mean FD, mean framewise displacement

mm³; (d) spatial smoothing using 6 mm full-width-half-maximum Gauss kernel; (e) detrending; (f) nuisance signals in white matter and cerebrospinal fluid were regressed and head movement parameters were adjusted using Friston 24. Global signal regression (GSR) remains controversial in rs-fMRI preprocessing [22, 23]. Therefore, we did not apply GSR in this study; (g) band-pass filtering (0.01~0.1 Hz).

Region of interest

The automated anatomical labeling atlas 3 (AAL3) brain template was selected for regions of interest (ROIs) definition due to its detailed division of thalamic nuclei and its precise delineation of the orbitofrontal cortex [24]. The AAL3 atlas segments the brain into 166 regions [25]. We resampled the original voxel sizes 1×1×1 mm³ to the sizes 3×3×3 mm³, with two small regions (label 133,134) were not defined. Therefore, 164 ROIs remained for subsequent brain network construction. More details about the ROIs label can be found in the Supplementary Materials.

The 164 ROIs were categorized into nine functional sub-networks using an approach that overlays the Yeo-7 network parcellation maps with the AAL3 template (Supplementary Materials), inspired by previous studies [26]. The nine functional networks identified are the visual network (VN), sensorimotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LN), frontal-parietal network (FPN), default mode network (DMN), subcortical network (SUB), and cerebellum network (CN). Figure 1 illustrates the distribution of ROIs across these subnetworks.

Dynamic functional connectivity network construction

For each subject, we adopted a non-overlapping sliding window correlation analysis to construct dFCN [27]. Based on the AAL3 atlas, we extracted averaged time series from 164 ROIs. To address site and head movement effects, these

signals were corrected before segmentation into *v* non-overlapping windows with length *l*. In each time window, we calculated the resting-state FC matrix F^i (164×164) using Pearson correlation analysis. Finally, these FC matrices in all time windows were constructed as dFCN. Finally, Fisher's Z-transformation was applied to normalize the FC matrices for further analysis.

Window length selection

Previous studies have shown that a window length of 30~60s can produce robust brain connectivity results and successfully estimate temporal fluctuations in rs-fMRI [28]. Inspired by the previous studies [18, 27], we selected window lengths of *l*=15, 16, 17,..., 30 volumes (i.e., 30, 32, 34,..., 60s) to avoid the choice of arbitrary time window lengths. Our primary goal was to investigate the temporal and spatial variability of dFCN. Therefore, we calculated the final variability by averaging across all 16 window lengths. Additionally, whole-brain spatial distribution maps of variability across all 16 window lengths, as well as the correlation of variability between different window lengths, are provided in the Supplementary Materials.

We applied the ComBat harmonization to correct site effects in ROI signals. Originally used to correct batch effects in genomic research, ComBat has been extended to adjust for site effects in diffusion tensor imaging and fMRI data from multiple sites [29, 30]. In this study, ComBat was performed with default parametric adjustments using the empirical Bayes procedure. Age, sex, group, IQ, and mean FD were included as regression variables in the ComBat model to retain biologically relevant variability and prevent overcorrection [31]. To further minimize the impact of head movement, we regressed the mean FD from the harmonized ROI signals [32].

Variabilities of dynamic functional connectivity network based on fuzzy entropy

We further employed fuzzy entropy to characterize regional-level temporal variability and spatial variability of dFCN. Figure 2 illustrates the calculation process for temporal and spatial variability. Detailed definitions, assumptions, and parameter settings for fuzzy entropy are provided in the Supplementary Materials. The specific definitions of temporal and spatial variability are outlined below:

Temporal variability

Given the dFCN, denoted as $dFCN = \{F^1, F^2, \dots, F^v\}$. For the temporal variability of specific brain *r*, we first extracted the functional architecture of ROI *r* within the *i*-th time

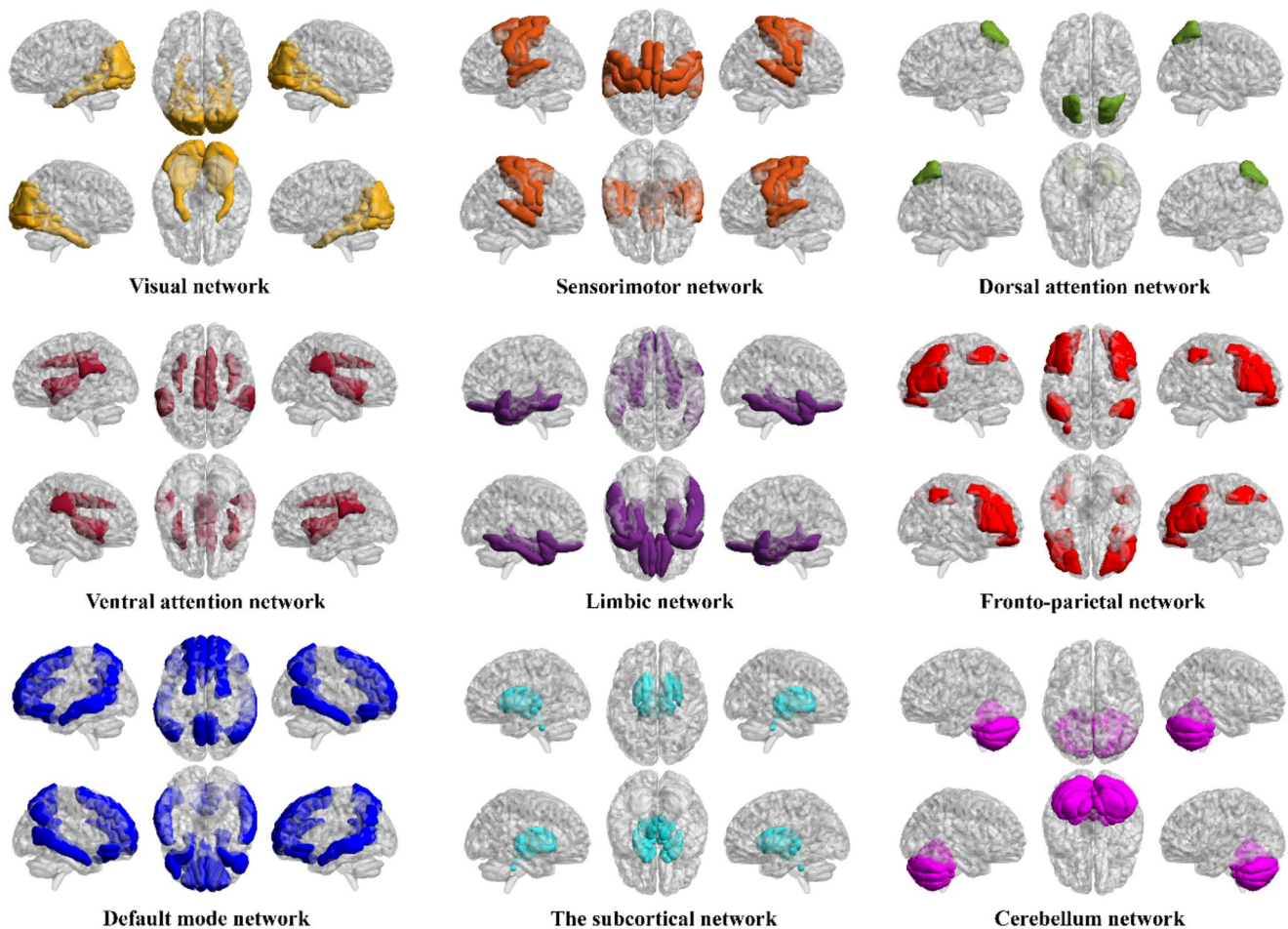


Fig. 1 The functional parcellation of 9 subnetworks based on the mapping between AAL3 atlas and Yeo 7-networks atlas

window as $F^i(r,:) = [F^i(r, 1), F^i(r, 2), \dots, F^i(r, n)]^T$ ($i = 1, 2, \dots, v$), where functional architecture refers to the overall FC profile of brain region r within the i -th time window. Then, we calculated the correlation coefficient between different functional architectures as.

$$Data_r = \text{corr}(F^i(r,:), F^j(r,:)), i, j = 1, \dots, v, i \neq j \quad (1)$$

Following this, fuzzy entropy was used to quantify the overall change among all $Data_r$ across different time windows. Finally, the temporal variability of an ROI r is defined as.

$$V_r = \text{FuzzyEn}(Data_r) \quad (2)$$

Here $Data_r$ is a 164×164 symmetric matrix.

Spatial variability

For the spatial variability of specific brain r , we first extracted the functional sequence between ROI r and ROI p as $F^{(i)}(r, p) = [F^{(1)}(r, p), F^{(2)}(r, p), \dots, F^{(v)}(r, p)]^T$, where

the functional sequence represents the changing profile of FC between a pair of specific brain regions across all time windows. Then, we calculated the correlation coefficients between different functional sequences associated with the ROI r , denoted as.

$$Data_{r,p} = \text{corr}(F^{(i)}(r, p), F^{(i)}(r, q)), p, q = 1, \dots, n, p \neq q \neq r \quad (3)$$

Based on $Data_{r,p}$, we calculated fuzzy entropy among all $Data_{r,p}$ associated with the ROI r across different brain regions. Finally, the spatial variability of an ROI r is defined as.

$$S_r = \text{FuzzyEn}(Data_{r,p}) \quad (4)$$

Here $Data_{r,p}$ is a $v \times v$ symmetric matrix.

To avoid repetition of features, we used only the lower triangular part of the symmetric matrix to calculate the value of fuzzy entropy.

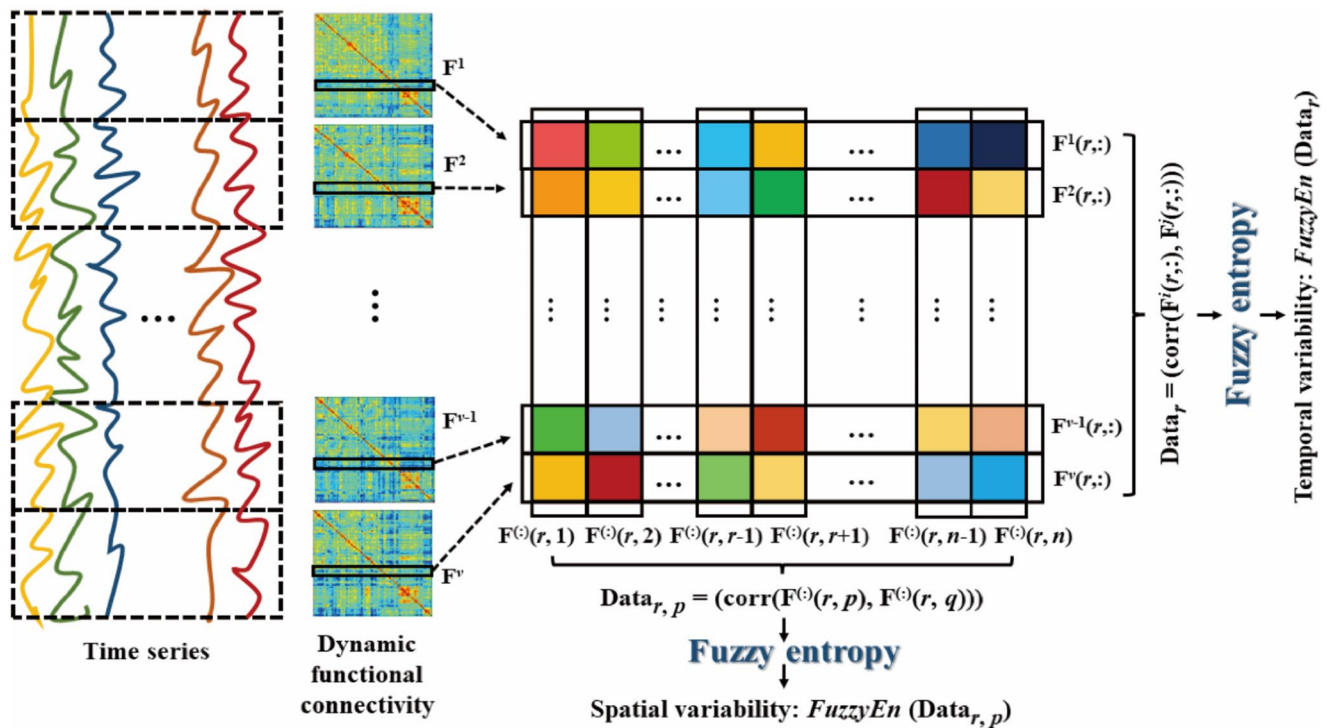


Fig. 2 Illustration of temporal variability and spatial variability algorithm based on fuzzy entropy for specific brain regions r

Correlation and statistical analysis

In this study, we used Spearman correlation analysis to investigate the relationship between regional temporal and spatial variability and clinical symptoms in ASDs, including ADI-R social, verbal, restricted, and repetitive behavior scores. The correlations with p -values below 0.05 were considered significant. To mitigate the influence of extreme values, we calculated the Mahalanobis distance for each sample point, removing the two points with the highest distances as outliers.

Two-sample t -tests (two-tailed) were performed to assess the between-group differences in temporal and spatial variability. The p -values obtained from these tests were then subjected to false discovery rate (FDR, $p < 0.01$) correction.

Classification of ASD based on temporal/spatial variability features

In this study, we used temporal and spatial variability of dFCN as features to identify ASD. Data from the SU I site were excluded given that it only contained data on ASDs, which could have led to bias in the classification task. We first extracted temporal (164-dimensional) and spatial (164-dimensional) variability of dFCN features for each subject. Furthermore, we integrated these two types of variability to form a new feature (328-dimensional) by simple concatenation. These features were normalized to -1 and 1.

Then we used a support vector machine (SVM) classifier with a radial basis function kernel and k -nearest neighbor (K-NN) classifier to predict ASD and HC. Details of the classifier setup and parameter optimization are provided in the Supplementary Materials.

To evaluate the performance of classifiers, we employed two across validation manners: (1) Leave-one-subject-out: one subject's data as the testing set and the remaining data as the training set, then repeated the process until each subject was used as the testing set once; (2) Leave-one-site-out: one site as the testing set and the remaining sites as the training set, then repeated the process until each site was used as a testing set once. In both strategies, the final classification accuracy is the average of the classification results from all iterations.

Results

Temporal and spatial variability patterns of brain network in ASD and HC groups

To provide an intuitive comparison of the temporal and spatial variability pattern of the whole brain, we keep the lowest 10% and highest 10% variability regions, respectively, to better demonstrate the temporal and spatial variability characteristics in ASD and HC groups, as shown in Figs. 3

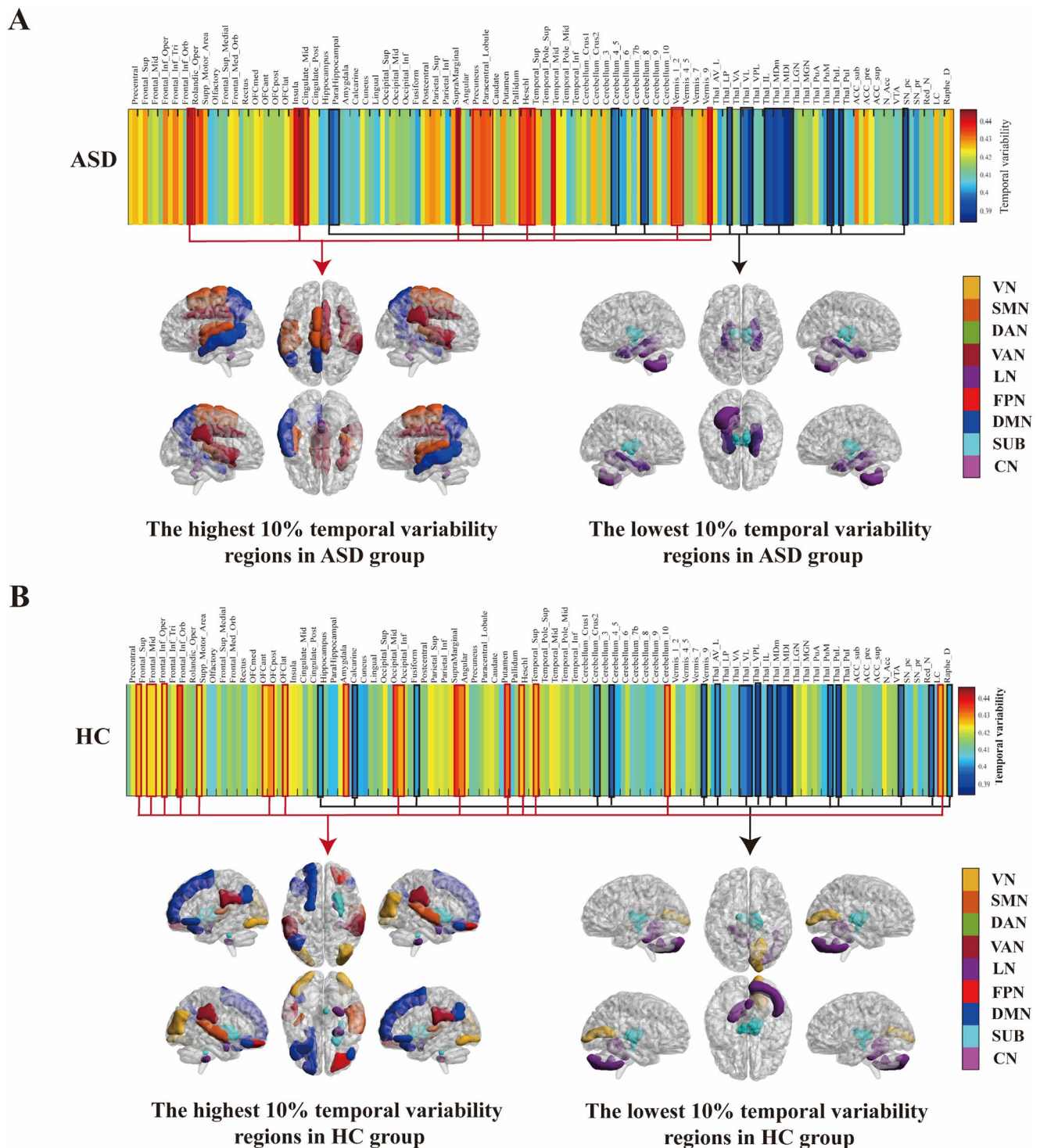


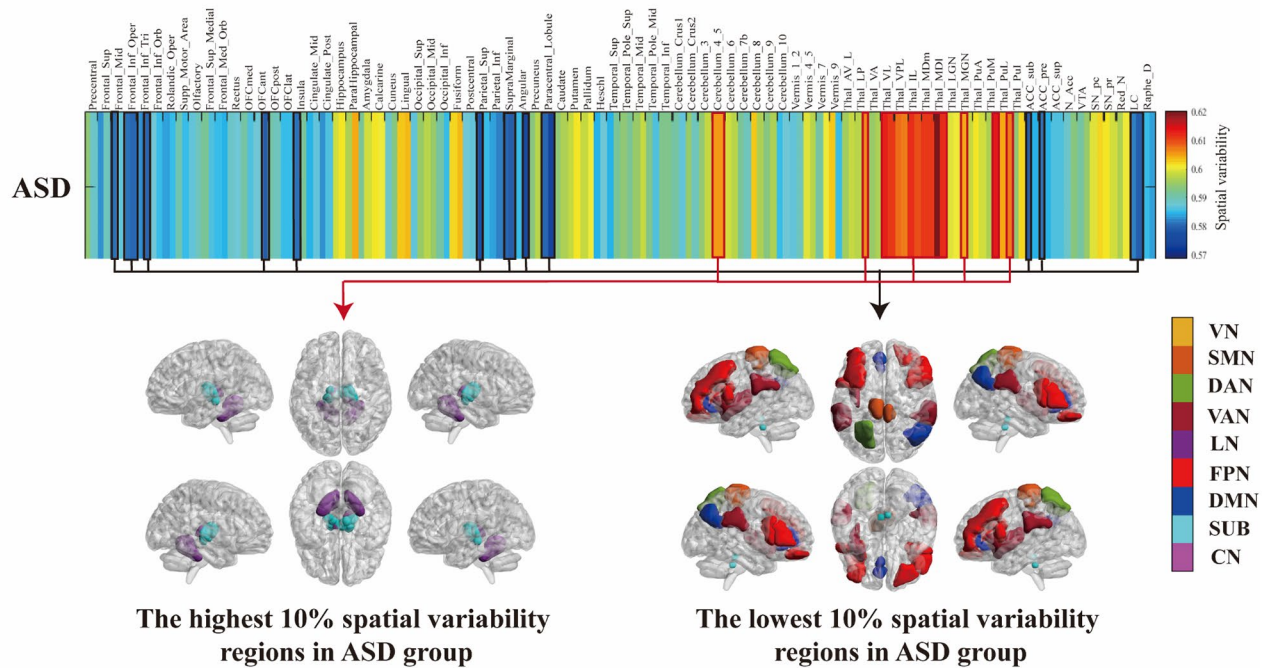
Fig. 3 Temporal variability distribution of different AAL3 regions in ASD and HC groups. **(A)** The brain regions with the highest and lowest 10% temporal variability in the ASD group. **(B)** The brain regions with the highest and lowest 10% temporal variability in the HC group

and 4. Figure S2 presents the whole-brain spatial distribution maps of temporal and spatial variability in ASD and HC groups.

For the ASD group, high temporal variability was mainly observed in SMN, VAN, DMN, and CN regions, while low

temporal variability was found in SUB, LN, and CN regions (Fig. 3A). For the HC group, high temporal variability was primarily located in LN, SMN, FPN, DMN, VAN, VN, and SUB regions, with low temporal variability in VN, SUB, and CN regions (Fig. 3B). For spatial variability, the ASD

A



B

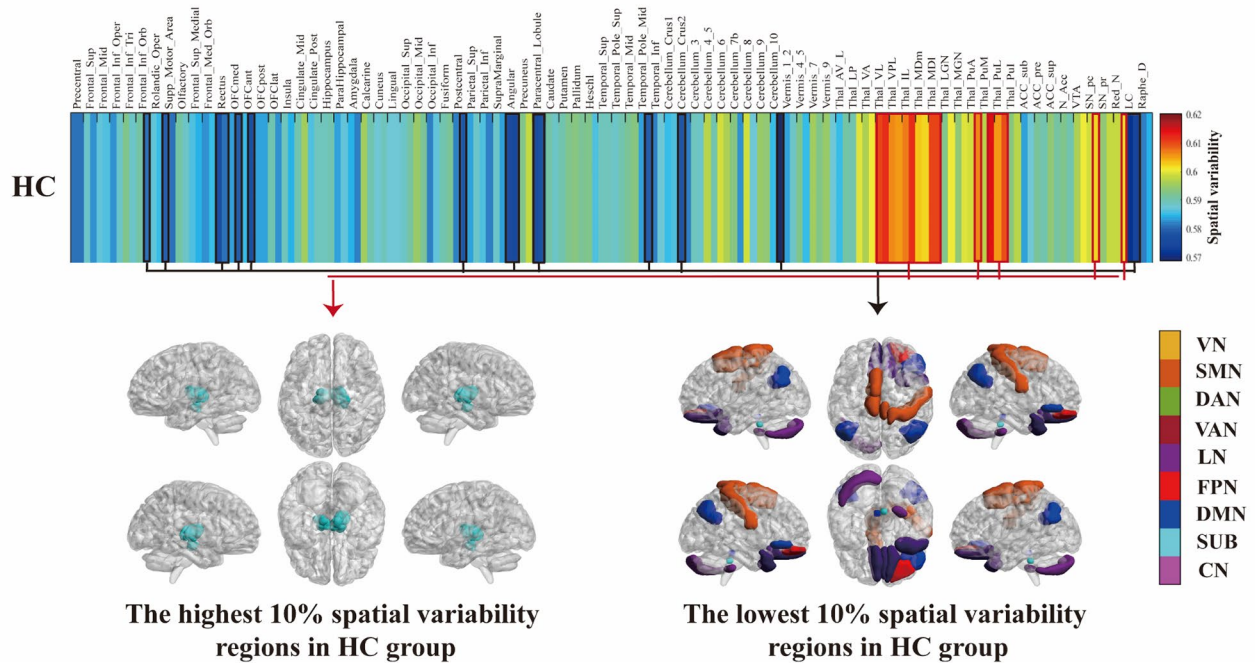


Fig. 4 Spatial variability distribution of different AAL3 regions in ASD and HC groups. **(A)** The brain regions with the highest and lowest 10% spatial variability in the ASD group. **(B)** The brain regions with the highest and lowest 10% spatial variability in the HC group

group showed high variability in the SUB and CN regions, while low variability was observed in the FPN, DMN, SMN, SUB, DAN, and VAN regions (Fig. 4A). For the HC group, high spatial variability was observed in SUB regions, while low spatial variability was found in SMN, LN, DMN, and CN regions (Fig. 4B). Detailed information regarding specific brain regions can be found in the Supplementary Materials.

Between-group difference in temporal/spatial variability of brain regions

Figure 5A displays the topological distribution of brain regions with significant differences in temporal variability between the two groups. For the temporal variability, we found a significant increase in most brain regions among ASDs compared with HCs, especially in SMN, SUB, and CN (Table S3). In contrast, the temporal variability in the right amygdala and right lateral posterior of the thalamus was significantly decreased in the ASD group. Among these regions with significant differences, we also found that the right amygdala was located in the highest 10% temporal variability regions in the HC group. In contrast, the right ventral posterolateral of the thalamus and lobule IX of cerebellar vermis were located in the lowest 10% temporal variability regions in the HC group.

Figure 5B shows the topological distribution of brain regions with significant differences in spatial variability between the two groups. Compared with HCs, we found that the spatial variability of most brain regions was significantly increased in ASD. The involved regions included SMN, VN, LN, SUB and CN (Table S4). In contrast, the spatial variability in DMN showed a significant decrease in the ASD group (Table S4). Of these regions with significant changes, we also found thalamic two subregions (the right mediodorsal medial magnocellular and left mediodorsal lateral parvocellular) were located in the highest 10% spatial variability regions in the HC group. In contrast, the left gyrus rectus and two cerebellar hemispheres (right lobule X of the cerebellar hemisphere and left crus II of the cerebellar hemisphere) were located in the 10% region with the lowest spatial variability in the HC group.

In addition, we found that the right amygdala and left thalamus, anteroventral nucleus show significant differences in both temporal and spatial variability.

Clinical correlation with temporal/spatial variability of brain regions

Figure 6 shows the correlation between temporal/spatial variability of dFCN and ASD symptoms. For the temporal variability, we found that the temporal variability of lobule

IX of vermis was negatively correlated with ADI-R social scores ($r = -0.2035$, $p = 0.0292$); the temporal variability of the right lateral posterior of the thalamus also had a significant negative correlation with ADI-R social scores ($r = -0.2305$, $p = 0.0132$) and ADI-R verbal scores ($r = -0.2012$, $p = 0.0303$).

For spatial variability, we found that spatial variability of the right lingual gyrus was positively correlated with the ADI-R verbal scores ($r = 0.1827$, $p = 0.0497$).

Classification performance based on temporal/spatial variability

Based on the temporal and spatial variability of dFCN features, we constructed the SVM and K-NN classification model with the same mode parameters for each validation method. For leave-one-subject-out cross-validation, we achieved the highest classification accuracy of 81.25% (75.20% for sensitivity, 86.39% for specificity) on a K-NN classifier with integrating variability features, shown in Table 2.

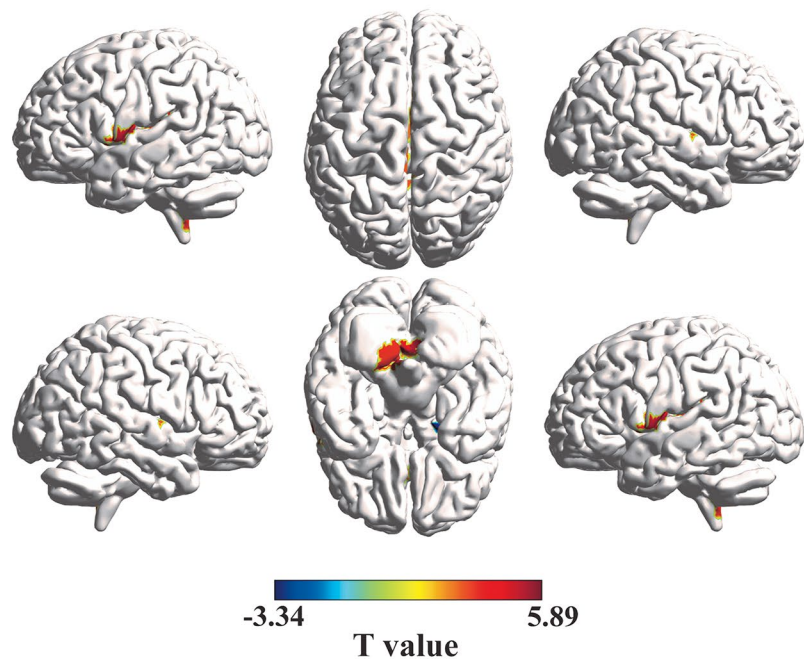
For leave-one-site-out cross validation, the top mean accuracy of 68.62% (77.55% for mean specificity, 70.40% for mean sensitivity) was achieved on the K-NN classifier with integrating variability features, shown in Table 2. Then, we further compared our multi-site classification results with other similar classification tasks. The comparative analysis is shown in Table 3. The integrated temporal and spatial variability features achieved superior classification performance compared with other features in previous multi-site classification studies of ASD. Additionally, to provide a more comprehensive evaluation of classification performance, we included receiver operating characteristic (ROC) curves for both classifiers in the Supplementary Materials.

Discussion

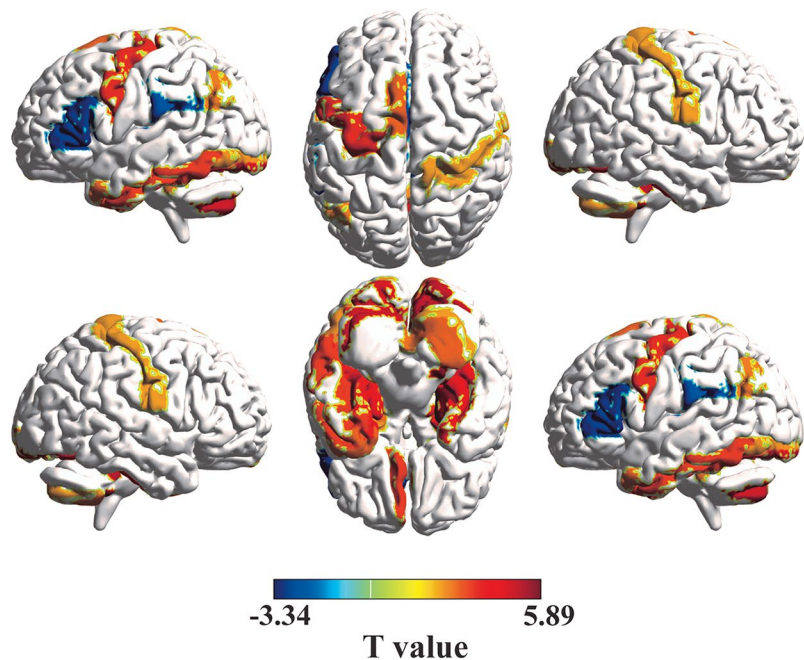
In this study, we utilized the fuzzy entropy technique to characterize the temporal and spatial properties of dFCN and explored the relationships between abnormal temporal and spatial variability patterns and clinical symptoms of ASD. We found that individuals with ASD exhibit widespread abnormalities in brain network variability, particularly in sensory, visual, limbic, cerebellar, and subcortical areas. Notably, abnormal temporal and spatial variability correlated significantly with clinical symptoms (i.e., ADI-R social scores). Our results also confirmed the utility of temporal and spatial variability features in distinguishing ASD from HC, with improved classification accuracy achieved through the integration of these features. Overall, our

Fig. 5 Topological distribution of brain regions with significant differences in both temporal and spatial variability between the ASD and HC groups. **(A)** The significant differences in regional-level temporal variability between the ASD and HC groups (FDR corrected, $P < 0.05$). The color scale represents t values. **(B)** The significant differences in regional-level spatial variability between the ASD and HC groups (FDR corrected, $P < 0.01$). The color scale represents t values

A Statistically significant regions for temporal variability



B Statistically significant regions for spatial variability



findings provide significant insights into the spatiotemporal dynamics of ASD-related brain function networks, offering a fresh perspective on ASD mechanisms and diagnostic pathways.

Brain network variability based on fuzzy entropy

The human brain exhibits complex spatiotemporal dynamics, with inter-regional connectivity evolving over time and across brain regions [41]. These dynamic patterns, characterized by fluctuating synchronization of brain network

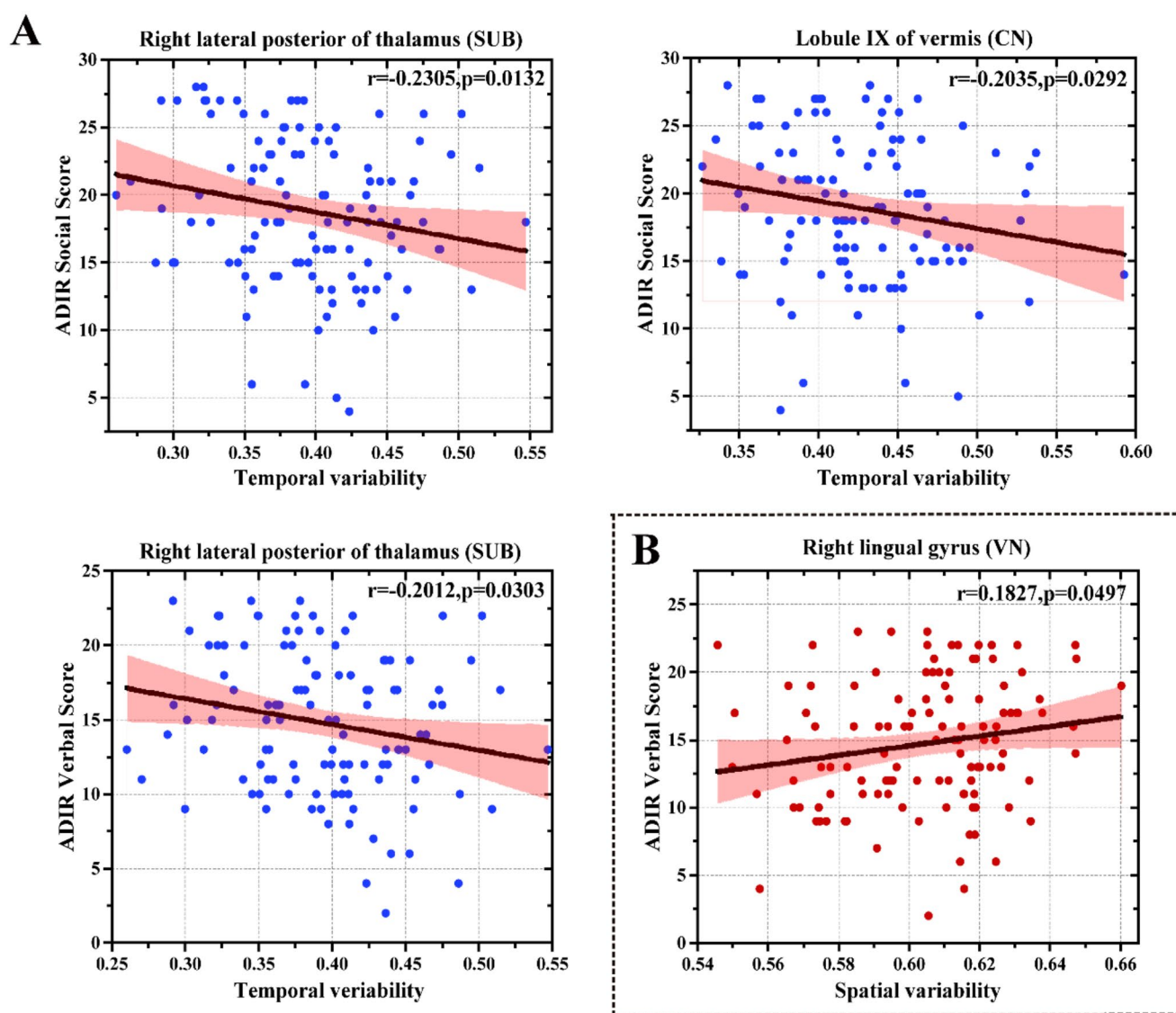


Fig. 6 The correlation between temporal/spatial variability and ASD clinical severity. **(A)** These blue scatter plots represent the correlation between regional-level temporal variability and the ASD clinical

symptom score scale; **(B)** These red scatter plots represent the correlation between regional-level spatial variability and the ADI-R verbal score

connectivity, can be quantified using entropy-based methods [42]. Among these, fuzzy entropy has been employed to assess the temporal variability of dynamic brain networks due to its simplicity, low data requirements, and resilience to noise [12]. In this work, we extend the application of fuzzy entropy to quantify both temporal and spatial variability in dFC. Regional-level temporal variability based on fuzzy entropy was used to characterize the synchronization changes of the connectivity patterns of overall FC between a specific region and other regions over time. Regional-level spatial variability based on fuzzy entropy was used to characterize the synchronization changes of the connectivity and interruption patterns of all FCs between a specific region and other regions across brain regions.

Temporal and spatial variability in HC and ASD

This study retained the top and bottom 10% of regions based on variability values, aiming to explore the unique temporal and spatial patterns of these regions of extreme variability. For the HC group, we observed significantly low temporal variability in early visual areas and partial nuclei of the thalamus and parts of the cerebellum, while the orbitofrontal areas involved in the DMN, FPN, and LN exhibited high temporal variability. The observed temporal variability pattern can be partly explained by the strength of FC. Previous research has demonstrated that early visual areas maintain strong FC with other visual cortical regions, which may contribute to their low temporal variability [43]. Other research

Table 2 The classification performance was obtained for all classifiers and features

Classifier	Features	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC (%)
Leave-one-subject-out cross-validation					
SVM	Temporal variability	71.32	67.20	74.83	78.91
	Spatial variability	77.21	69.60	83.67	85.52
	Integration variability	77.94	72.00	82.99	86.44
KNN	Temporal variability	76.84	65.60	86.39	76.00
	Spatial variability	79.41	78.40	80.27	79.41
	Integration variability	81.25	75.20	86.39	80.80
Leave-one-site-out cross-validation					
SVM	Temporal variability	53.12	64.80	53.06	66.69
	Spatial variability	62.38	60.00	66.67	69.96
	Integration variability	63.68	68.00	70.75	76.07
KNN	Temporal variability	61.89	61.60	73.47	72.93
	Spatial variability	66.63	67.20	78.23	79.28
	Integration variability	68.62	70.40	77.55	73.98

The highest metrics were marked as bold

has also shown that the primary sensory and unimodal association cortex exhibit low temporal variability, likely due to their involvement in neural circuits that support basic sensory processing [10]. The thalamus is believed to facilitate communication between multiple cortical regions [25]. The thalamus and cerebellum, have extensive connectivity with the cerebral cortex and maintain strong FC with many functional networks [44, 45], which may underlie the observed low temporal variability in these regions. Additionally, high temporal variability similar to that observed in the LN and orbitofrontal cortex has been reported in previous studies. Specifically, Roll et al. found that regions such as the amygdala, hippocampus, and orbitofrontal cortex exhibit weaker connectivity with other brain regions, leading to higher temporal variability [43].

Previous studies have demonstrated that FC networks also exhibit significant variability on spatial scales over time [46]. In this study, we observed that the HC group exhibited

very high spatial variability in subcortical regions, particularly the thalamus. As a critical component of the subcortical region, the thalamus not only integrates sensory information and projects it to relevant cortical areas, but also contributes to higher cognitive functions such as memory, attention, and awareness [47]. Higher-order nuclei of the thalamus may regulate cortical circuits by modulating the degree of synchrony among cortical neurons to meet behavioral demands in humans [48]. Furthermore, previous research has shown spatial heterogeneity in brain FC dynamics and suggested that such spatial heterogeneity may be related to differences in information processing in brain regions [49]. Studies also indicate that higher-level cognitive functions require the integration of distributed neural activities across large-scale brain networks [50]. Therefore, we speculate that the dynamic reorganization of large-scale FC in the spatial dimension over time, particularly the separation and integration of connectivity patterns between regions, may account for the observed high spatial variability.

Altered temporal and spatial variability in ASD associated with clinical symptoms

The higher temporal variability usually implies more “instability/flexibility” in FC interaction patterns (under-connected, but not broken) across time [13, 51]. Compared to the HC groups, we found significantly increased temporal variability in the SMN, SUB, and CN subnetworks in ASD. Such FC “instability/flexibly” in these subnetworks at the temporal scale may indicate that ASD requires more dynamic and adaptable connectivity patterns over time compared with HC. These flexible fluctuating connectivity patterns may compensate for the under-connectivity and support cognitive task performance similar to that of HC [52, 53]. Our findings observed that the ASD with slight symptoms (lower ADI-R social score) had higher temporal variability (instability/flexibility) in the SUB and CN

Table 3 Comparison with previous studies about multi-site classification accuracy for ASD (referencing [33–40])

Study	Data	Features	Site	Size	Classifier	Cross-subjects (%)	Cross-sites (%)
Chen et al. (2016)	rs-fMRI	FC	6	240	SVM	79.17	68.17
Tejwani et al. (2017)	rs-fMRI	Nodes variability	3	167	MLP	62.00	63.50
Spera et al. (2019)	rs-fMRI	FC	4	187	SVM	-	71.00
Dekhil et al. (2019)	sMRI	Delta matrices	18	1060	K-NN	75.00	-
	fMRI	Correlation matrices				79.00	-
Niu et al. (2020a)	rs-fMRI +PC	FC	12	809	DANN	73.20	68.89
Al-Hiyali et al. (2021)	rs-fMRI	Scalogram images (GoogLeNet)	3	82	K-NN	80.00	-
Tang et al. (2023)	rs-fMRI	3D volume	3	221	ADL	80.00	74.33
Our study	rs-fMRI	Integration variability	5	272	K-NN	81.25	68.62

The highest metrics were marked as bold

MLP, multilayer perceptron classifier; ADL, adversarial deep learning; PC, personal characteristic; DANN, multichannel deep attention neural network; sMRI, structural magnetic resonance imaging

subnetworks, supporting previous research linking “flexibility” and under-connectivity patterns in ASD [54, 55]. Beyond motor regulation, the cerebellum plays a crucial role in affective processing, cognition, and social behavior regulation [56]. A study found reduced FC between the left cerebellar dentate nucleus and brain regions involved in Theory of Mind (ToM), social cognition, and advanced emotional processing in ASD [57]. Recent research on ASD mouse models has shown that stimulating Purkinje neurons in the right cerebellar hemisphere improves social behavior deficits [58]. The SUB network mainly includes the thalamus and basal ganglia, which are involved in complex cognitive activities such as emotion, reward, and cognition [59]. A study on adults with ASD found that reduced intrinsic FC in the basal ganglia was negatively correlated with autism severity [60]. Moreover, brain networks involved in higher-order thinking in ASDs have been reported to exhibit reduced connectivity with subcortical areas [59]. These findings suggest that increased temporal variability in ASD reflects a more flexible FC pattern over time, supporting the aberrant brain underconnectivity theory as a potential mechanism underlying ASD.

In addition to temporal variability, spatial variability is an important indicator that captures the dynamic properties of brain networks. Unlike temporal variability, spatial variability mainly focuses on the separation or integration pattern of FC between brain regions/subnetworks across time [61]. In our study, we found that ASDs exhibited significantly increased spatial variability in the VN, LN, SUB, and CN subnetworks compared to HCs. Such spatial variability differentiation of these subnetworks may imply abnormalities in the FC integration of these networks/regions in ASD [62, 63]. Language and communication difficulties are core features of ASD, and an increasing body of research indicates that ASD language processing relies more on visual network areas [64]. For example, when the ASD group and the control group exhibited equivalent task performance, ASDs showed increased activation in the left lingual gyrus [65]. Moreover, previous studies have reported that children with ASD have difficulty integrating visual information effectively to guide skilled behaviors [66, 67]. In our study, we found a positive correlation between spatial variability of the right lingual gyrus (VN subnetwork) and ADI-R verbal scores, which suggested the higher spatial variability in this region, the more severe the symptoms related to communication in ASD. These studies suggested a greater reliance on visual processing regions for language tasks. Thus, we speculated that increased spatial variability in VN areas may reflect deficits in the functional integration of visual processing areas and, to some extent, communication deficits in individuals with ASD.

Prediction of ASD using temporal and spatial variability

Recent advances in large-scale datasets like ABIDE have enabled multicenter ASD classification. Previous rs-fMRI studies using ABIDE reported accuracies ranging from 62.00% to 80.00% [34, 37]. In our study, we employed temporal and spatial variability features with K-NN to identify ASD from HC, achieving 81.25% accuracy with the leave-one-subject-out cross-validation strategy and 68.62% accuracy with the leave-one-site-out cross-validation strategy. Compared to previous studies, our method showed enhanced classification performance on the overall dataset. The improved performance may be due to the integration of temporal and spatial variability features, which provide complementary information for ASD classification. Similar findings in brain disorder research have shown that combining temporal and spatial features improves classification accuracy [18]. Additionally, we used the ComBat method to harmonize site effects, which could have contributed to improved classification performance, as supported by previous research [68]. Overall, our study underscores the effectiveness of temporal and spatial variability features in ASD classification, particularly in multi-site applications.

Limitations

Several limitations should be addressed in the feature research. First, we acknowledge that different parcellation schemes may lead to varying results, future work should explore this issue more extensively to better understand how different templates may influence the findings. Additionally, the sampling size and consistent scanning parameters across sites may limit the generalizability of our findings. Future research should incorporate data with varying parameters and employ more sophisticated feature fusion techniques. Finally, expanding the age range and including ASD populations from different age groups and subtypes would deepen our understanding of temporal and spatial variability in ASD and provide insights into its heterogeneity.

Conclusion

In conclusion, this study investigated the dynamic brain network variability patterns in ASD and HC groups across temporal and spatial scales and explored multi-site ASD classification using these features. We found that individuals with ASD showed higher variability in most brain regions (SMN, VAN, VN, LN, SUB, and CN) compared to HCs, but lower variability in the amygdala, right lateral posterior of the thalamus (SUB), and the left anterior cingulate cortex,

pregenual regions (DMN). Furthermore, increased temporal variability in the right lateral posterior of the thalamus and lobule IX of the vermis, and increased spatial variability in the lingual gyrus, were correlated with ADI-R scores. Integrating temporal and spatial variability features improved classification performance in both cross-subject and cross-site tasks. These findings highlight the importance of spatiotemporal dynamics in understanding autism-related brain activity and provide new insights into the neurophysiological mechanisms of ASD.

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Author contributions SY designed the work, performed the data analysis and drafted the initial manuscript. SS, JL, YF, LZ, and KC were involved in data analysis and interpretation. JM, FX, DY, and PX contributed to the revisions and editing of the manuscript. XL and TZ were involved in funding acquisition, supervision, and manuscript revision. All authors read and approved the final manuscript.

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Data availability The image data used in this study can be found at http://www.fcon_1000.projects.nitrc.org/indi/abide.

Declarations

Ethical approval This study uses publicly available data from ABIDE. Ethical approval was obtained by the original data collectors, and no additional ethical approval was required for this study.

Competing interests The authors declare no competing interests.

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