The aberrant language network dynamics in autism ages 5–40 years

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Abstract

Background:

Language impairments, which affect both structural aspects of language and pragmatic use, are frequently observed in autism spectrum disorder (ASD). These impairments are often associated with atypical brain development and unusual network interaction patterns. However, a neurological framework remains elusive to explain them.

Methods:

In this study, we utilized the dynamic "meta-networking" framework of language—a theoretical model that describes the domain-segregation dynamics during resting states—to investigate cortical language network abnormalities in ASD aged 5–40 years.

Results:

Our findings revealed distinct developmental trajectories for three domain-specific language subnetworks in ASD, characterized by unique patterns of hypo- and hyper-connectivity that vary with age. Notably, these language network abnormalities proved to be strong predictors of verbal Intelligence Quotient and communication deficits, though they did not predict social abilities or stereotypical behaviors.

Limitations:

Due to the limited availability of linguistic data, our study was unable to assess the language deficit profiles of individuals with ASD.

Conclusions:

Collectively, these findings refined our understanding of the network mechanisms for language and communication deficits in ASD.

Keywords: autism spectrum disorder, language impairments, language network dynamics, verbal Intelligent Quotient

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by persistent difficulties in social communication and interaction, as well as restricted and repetitive patterns of behavior, interests, or activities. Language impairments, encompassing structural language aspects and pragmatics, frequently co-occur with ASD [1-6]. The profiles of language impairment in ASD exhibit significant heterogeneity, spanning domains such as phonology, syntax, semantics, lexical strength, and pragmatics [7, 8]. Three main language deficit profiles in individuals with ASD have been established: (i) minimally verbal autistic individuals , (ii) verbal autistic individuals with structural language impairments [1], and (iii) verbal autistic individuals without structural language impairments but with pragmatic impairment. Notably, pragmatic impairment is prevalent in the majority of individuals with ASD [1, 8-13] and often manifests as difficulties in social communication and interaction [14].

A wealth of evidence indicates that language and pragmatic impairments (the basic aspects of pragmatic language processing) in individuals with ASD are linked to untypical development and aberrant interaction within the language network [15-24]. The aberrant brain regions span bilaterally across language-related frontal, temporal and parietal cortices. Disruptions within the language network are bi-directional, with both hyper-connectivity and hypo-connectivity coexisting. However, several limitations of existing studies need consideration. First, while language network

abnormalities in these studies are found to be behavior- and clinical-related, there is a lack of a theoretical framework to explain these abnormalities. The language system comprises domain-specific subsystems [25-27], and domains of language can be affected differently in individuals with ASD [1]. Apart from effectively mapping aberrant language regions, a detailed illustration of domain-specific streamline disruption in individuals with ASD may offer more behaviorally relevant and translational information. Second, most of these studies focused on a single or mixed-age group, ignoring brain and language development [2, 6, 28-39]. Longitudinal studies have found that the brains of ASD undergo a complex developmental trajectory from overgrowth to undergrowth during adolescence [40-45]. However, how these abnormal developmental trajectories affect the development of language networks across different domains remains largely unknown. Third, most of these studies adopted static functional connectivity and ignored the time-varying patterns of the language network during resting state and tasks. The brain is an inherently dynamic system and reconfigures within a temporal range from milliseconds to years [25, 46-48]. Static functional connectivity is less sensitive and may underestimate the transient network disorganization in individuals with ASD [49-55].

To address these limitations, we utilized our recently developed dynamic "meta-networking" framework of language to explore the aberrant language network dynamics in children, adolescents, and adults with ASD. This framework offers a theoretical perspective on language network dynamics during resting state,

encompassing four temporally reoccurring states with distinct connectivity patterns, hub distribution, structural underpinnings, and cognitive relevance [25, 48]. The first three states are cognition-related and follow a domain-segregation manner. The first state, characterized by densely connected regions in the superior temporal gyrus (STG), is crucial for phoneme perception and lexical-phonological processing. The second state, with densely connected regions in the prefrontal cortex, is vital for speech production processing. The third state, marked by densely connected areas in the inferior parietal cortex, superior, and middle temporal gyrus (MTG), is essential for semantic processing. The fourth state, although dominant temporally, exhibits weak connectivity and serves as the baseline state. Together, these four states constitute the dynamic "meta-networking" framework of language. The concept of meta-networking denotes a network of networks, aligning with the "meta-networking" theory of cerebral functions [56]. According to this theory, complex cognition and behaviors, such as language, emerge from the spatiotemporal integration of distributed yet specialized sub-networks. Our dynamic "meta-networking" framework captures the domain-specific nature of language processing, aligning with the neurobiology of the dual-stream model of speech and language processing [26, 27, 57], and has demonstrated cognitive and clinical relevance [25, 48].

In this study, we analyzed resting-state fMRI data from 325 individuals with ASD (106 children, 121 adolescents, 98 adults) and 463 age-matched healthy controls (199 children, 143 adolescents, 121 adults) obtained from the Autism Brain Imaging Data

Exchange (ABIDE). We utilized the dynamic conditional correlation (DCC) approach [58] to construct the frame-wise connectivity matrices and k-means clustering to reveal the temporal-reoccurring states. Our study aimed to address two key questions: 1) Whether the language network dynamics in children, adolescents, and adults with ASD conform to the "meta-networking" framework of language, and how domain-specific language network dynamics are disrupted in individuals with ASD. 2) What are the developmental trajectories of domain-specific language streams, and how are these trajectories aberrant in relation to verbal language and communication deficits in individuals with ASD? By comparing the spatial and topological characteristics of language network dynamics in individuals with ASD, we sought to illuminate these questions and enhance our understanding of language development in individuals with ASD.

Materials and Methods

Participants

The ABIDE initiative is a multi-site open-data resource aimed at expediting research on the neural underpinnings of autism. It comprises two extensive collections: ABIDE I and ABIDE II. These collections include data from over 24 international brain imaging laboratories, totaling approximately 1026 individuals with ASD and 1130 age-matched Healthy Controls (HC). Each dataset includes resting-state fMRI data, along with corresponding structural MRI scans and detailed phenotypic information [59, 60].

We conducted our analysis on resting-state fMRI data from all sites. Within each site, we applied the following exclusion criteria to screen resting-state fMRI data: 1) Left-handedness; 2) Subjects with no Intelligence Quotient (IQ) or IQ < 70; 3) Maximum translation of head motion larger than 3 mm or rotation larger than 3°; 4) Images not covering the entire brain or temporal lobe; 5) Low spatial signal-to-noise ratio (lower three standard deviations of the group), especially in temporal, frontal, and parietal cortices. 6) Subjects with Autism Diagnostic Interview Revised (ADI-R) scores or no Autism Diagnostic Observation Schedule (ADOS) scores. Only subjects with ADOS-G were analyzed. Moreover, to eliminate the impact of using different ADOS versions, subjects assessed with ADOS-2nd were also excluded. 7) Subject whose IQ was not measured using the Wechsler Intelligence Scale (WASI, WISC and WAIS). Following these criteria, a total of 325 individuals with ASD (106 children aged 5–11 years, 121 adolescents aged 12–18 years, and 98 adults aged 19–40 years) and 463 age-matched healthy controls (199 children, 143 adolescents, and 121 adults) were included in the study. Demographic information, IQ scores (i.e., full scale IQ[FSIQ], verbal IQ[VIQ] and performance IQ[PIQ]), and Autism diagnostic and Observation Schedule (ADOS) scores were summarized in **Table 1**.

Data preprocessing

The resting-state fMRI data were preprocessed in the following steps: 1) delete the first 10 volumes; 2) slice timing; 3) head motion correction ; 4) co-register; 5) T1 segmentation and normalization into the MNI space using DARTEL; 6) functional

normalization using the deformation field of T1 images; 7) smoothing using a Gaussian kernel (full-width-at-half-maximum = 6 mm); 8) Linear detrend; 9) Nuisance signals regression (24 parameters, including the *x*, *y*, *z* translations, and rotations (6 parameters), plus their temporal derivatives (6 parameters) and the quadratic terms of 12 parameters); 10) Temporal band-pass filtering (0.01–0.1 Hz).

Table 1 Demographic information and clinical deficits

Characteristics Mean ± SD	Total			Children (5–11)			Adolescents (12–18)			Adults (19–40)		
	ASD *n* = 325	HC *n* = 463	*p*-value	ASD *n* = 106	HC *n* = 199	*p*-value	ASD *n* = 121	HC *n* = 143	*p*-value	ASD *n* = 98	HC *n* = 121	*p*-value
Gender (Female/Male)	41 / 284	120 / 343	< **0.01**[a]	18 / 88	76 / 123	< **0.01**[a]	14 / 107	27 / 116	0.10	9 / 89	17 / 104	0.27
Age, Years [MIN, MAX]	16.44 ± 6.99 [5.22, 39.20]	15.29 ± 6.74 [6.36, 39.39]	**0.02**[b]	9.69 ± 1.56 [5.22, 11.99]	9.89 ± 1.23 [6.36, 11.95]	0.25	15.14 ± 2.02 [12.02, 18.92]	14.67 ± 1.96 [12, 18.08]	0.06	25.17 ± 5.18 [19.09, 39.20]	24.93 ± 5.02 [19.08, 39.39]	0.73
FSIQ	107.47 ± 16.54 *n* = 260	113.97 ± 12.94 *n* = 419	< **0.01**[b]	105.86 ± 18.29 *n* = 80	115.47 ± 13.63 *n* = 175	< **0.01**[b]	105.87 ± 17.02 *n* = 100	110.92 ± 12.92 *n* = 143	**0.01**[b]	110.05 ± 13.73 *n* = 80	115.67 ± 10.93 *n* = 101	< **0.01**[b]
VIQ	106.47 ± 16.74 *n* = 261	114.26 ± 14.09 *n* = 419	< **0.01**[b]	106.16 ± 17.77 *n* = 81	116.89 ± 15.35 *n* = 175	< **0.01**[b]	104.73 ± 17.06 *n* = 100	111.32 ± 13.09 *n* = 143	< **0.01**[b]	108.96 ± 15.09 *n* = 80	113.88 ± 12.33 *n* = 101	**0.02**[b]
ADOS Social	7.48 ± 2.72 *n* = 200	—	—	7.24 ± 2.49 *n* = 58	—	—	7.72 ± 2.90 *n* = 69	—	—	7.42 ± 2.74 *n* = 73	—	—
ADOS Comm	3.54 ± 1.60 *n* = 196	—	—	3.19 ± 1.43 *n* = 57	—	—	3.66 ± 1.83 *n* = 68	—	—	3.69 ± 1.47 *n* = 71	—	—
ADOS RRB	2.25 ± 1.34 *n* = 149	—	—	2.49 ± 1.33 *n* = 43	—	—	2.26 ± 1.35 *n* = 53	—	—	2.04 ± 1.32 *n* = 53	—	—

[a] *P*-value obtained using Pearson's chi-square test.

[b] *P*-value obtained using a two-sample t-test.

ASD, Autism spectrum disorder; HC, Health control; SD, Standard deviation; FSIQ, full scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; ADOS, Autism Diagnostic Observation Schedule; ADOS Comm, ADOS Communication; ADOS RRB, ADOS Restricted interests and repetitive behavior.

Language network definition

The putative language network was defined in the Human Brainnetome Atlas [61]. We extracted all parcels that exhibited significant activation in language-related behavioral domains (i.e., language or speech) or paradigm classes (e.g., semantic, word generation, reading, or comprehension). Thirty-three cortical parcels in the left hemisphere and 15 cortical parcels in the right hemisphere were selected. Their extents are highly similar to those identified by other researchers [62-66]. Considering bilateral language processing [67-72] and the recruitment of right hemisphere language regions for compensation, 19 parcels of homologs in the right hemisphere and 1 parcel of homologs in the left hemisphere were also selected. Altogether, a symmetric language network (BNL68, Supplementary Fig.1) including 68 cortical ROIs (34 ROIs in each hemisphere) was defined [73, 74], including the superior, middle, and inferior frontal gyrus (SFG, MFG, and IFG, respectively), the ventral parts of the precentral gyrus (PrG) and postcentral gyrus (PoG), the STG, MTG and inferior temporal gyrus (ITG), the fusiform gyrus (FuG), the Para hippocampus gyrus (PhG) and the posterior superior temporal sulcus (pSTS). The coordinates (in Montreal Neurologic Institute space) and meta results of each parcel are summarized in Supplementary Table 1.

Frame-wise time-varying language network construction using DCC

To identify the temporal reoccurring states of language network, the dynamic conditional correlation (DCC) approach was adopted to construct the framewise time-varying language network [58]

(https://github.com/caWApab/Lindquist_Dynamic_Correlation/tree/master/DCC_toolbox). It has been shown that DCC outperformed the standard sliding-window approach in tracking the network dynamics [58, 75].

DCC is a variant of the multivariate GARCH (generalized autoregressive conditional heteroscedastic) model [76, 77], which has been shown to be particularly effective for estimating both time-varying variances and correlations. GARCH models express the conditional variance of a single time series at time *t* as a linear combination of the past values of the conditional variance and of the squared process itself. All the parameters of DCC are estimated through quasi-maximum likelihood methods and require no ad hoc parameter settings.

The DCC algorithm consists of two steps. To illustrate, let us assume that there is a pair of time series from two ROIs, x_t and y_t. In the first step, standardized residuals of each time series are estimated using a univariate GARCH (1,1) process. In the second step, an exponentially weighted moving average (EWMA) window is applied to the standardized residuals to compute a non-normalized version of the time-varying correlation matrix between x_t and y_t. The mathematical expressions of the GARCH (1,1) model, DCC model, and EWMA, and the estimations of the model parameters were provided by Lindquist et al. [58].

K-means clustering was adopted to decompose the dFC matrices into several

reoccurring connectivity states. The optimal number of clusters *k* was estimated based on the elbow criterion, i.e., the ratio between the within-cluster distance to between-cluster distances [78]. L1 distance function ('Manhattan distance') was implemented to assess the point-to-centroid distance. Each time window was finally assigned to one of these connectivity states.

Topological properties of dFC states

For each subject, a state-specific connectivity matrix was estimated by calculating the median of all connectivity matrices that were assigned to the same state label [79]. Before calculation, a correlation threshold ($r > 0.2$) was used to eliminate weak connections that might have arisen from noise. Due to the nature of negative connections being debatable [80], only positive connections were considered in this work. In the current study, we used a weighted network rather than a binarized network to conserve all connectivity information. Considering the heterogeneous lesion locations, we only focused on the changes in nodal and global topological properties, but not each connection.

Global topological metrics: for each state-specific matrix, three network topological properties were calculated: 1) Total connectivity strength (FC strength). The FC strength of a network was calculated by summing functional connectivity strengths of all suprathreshold connections into one value [81]; 2) Global network efficiency (gE). The gE reflects the capability for parallel information transfer and functional

integration. It is defined as the average of the inverses for all weighted shortest path lengths (the minimal number of edges that one node must traverse to reach another) in the thresholded matrix [82]; 3) Local network efficiency (lE). The lE reflects the relative functional segregation and is defined as the average of the global efficiency of each node's neighborhood sub-graph; 4) Rich-club organization. Rich-club organization in a network refers to a phenomenon that the hub nodes are more densely connected among themselves than non-hub nodes. The presence of a rich-club organization provides important information on the higher-order structure of a network and indicates the functional specialization [83].

Nodal topological metrics: We calculated nodal strength, gE, and lE for each node. We also calculated betweenness centrality (BC), an index indicating whether a particular node lies on the shortest paths between all pairs of nodes in the network.

As a complementary analysis, we also calculated the static functional connectivity (sFC) matrix using the Pearson correlation coefficient. We then calculated the three topological properties of sFC and investigated the alterations in the two patient groups.

Functional relevance of state-dependent hub distributions

To assess the functional relevance of hubs in each state, we performed term-based meta-analyses on the platform NeuroQuery (https://neuroquery.org/) [84]. NeuroQuery predicts the spatial distribution of activity from 418,772 activation

locations associated with 7647 terms in the full texts of 13,459 neuroimaging articles. To verify the functional specificity, language-related terms (speech perception, inner speech, phonological processing, speech production, and semantic processing) were analyzed. The functional relevance was assessed by calculating the dice coefficients between binary images of hub nodes and meta results (dice = 2* (hub * meta)/(hub + meta)). Given the left-lateralized activations observed in the meta-analysis, the Dice coefficients were calculated for both the whole brain and the left hemisphere.

Statistical analysis

Age, FIQ, VIQ, and PIQ were analyzed by two-sample t-tests. Sex data were analyzed by Pearson's chi-square test.

For each state, edge strength, nodal and global topological properties were compared by performing two-sample t-tests. The results of edge strength were corrected using network-based statistic (NBS) [85] with an edge *p*-value of 0.01 and a component *p* value of 0.05. The results of nodal and global topological properties were corrected using False Discovery Rate (FDR) with a corrected *p*-value of 0.05.

The associations between edge strength and language deficits of individuals with ASD (i.e., VIQ and ADOS communication scores) were assessed by calculating the partial Pearson correlation coefficient after regressing out their sex, age, and FSIQ. The results were corrected using NBS with a component *p*-value of 0.05.

Machine learning-based dFC-behavior prediction model

To investigate whether the reorganized dFCs were associated with autistic language deficits, we constructed multivariate machine learning-based dFC-deficits prediction models. The relevance vector regression (RVR) algorithm and linear kernel function were adopted [86, 87]. RVR has no algorithm-specific parameter and thus does not require extra computational resources to estimate the optimal algorithm-specific parameters [88].

Linear relevance vector regression (RVR). RVR is a Bayesian framework for learning sparse regression models. In RVR, only some samples (smaller than the training sample size), termed the 'relevance vectors', are used to fit the model:

$$y(x) = \sum_{i=1}^{m} w_i \tau_i + \in \quad (1)$$

where τ_i are basis functions, $\in$ is normally distributed with mean 0 and variance β. RVR uses training data to build a regression model:

$$y = \theta\omega + \in \quad (2)$$

where $y = [y_1, y_2, \dots y_n]^T$, $\theta = [\theta_1, \theta_2, \dots \theta_n]$, $\theta_i = [\tau_i(x_1), \tau_i(x_1), \dots \tau_i(x_n)]^T$. Each vector θ_i, consisting of the values of the basis function τ_i for the input vectors, is a relevance vector.

The model parameters β were found by using the maximum likelihood estimates from the conditional distribution: $p(y \mid \alpha, \beta) = \mathcal{N}(y \mid 0, \mathcal{C})$, where the $\mathcal{C} = \beta I_n +$

$\Phi A^{-1}\Phi^T$. To make the RVM favor sparse regression models, prior distributions were assumed for both w_i and β^{-1}, i.e., $p(w_i \mid \alpha_i) = \mathcal{N}(0, \alpha_i^{-1})$. The ways of treating priors, however, lead to the same relevance vector machine construction.

Prediction accuracy and significance. Leave-one-out-cross-validation (LOOCV) was used to calculate the prediction accuracy (the Pearson correlation coefficient between the predicted and actual labels). In each turn of the LOOCV, one patient was designated as the test sample, and the remaining patients were used to train the lesion model. The predicted score was then obtained by the feature matrix of the tested sample.

The significance level was computed based on 1000 permutation tests. For each permutation test, the prediction labels (e.g., verbal IQ) were randomized, and the same RVR prediction process as used in the actual data was carried out. After 1000 permutations, a random distribution of accuracies was obtained and the P value was correspondingly calculated: $P = \frac{number\ of\ permutaion\ tests < actual\ accuracy + 1}{number\ of\ permutaion\ tests + 1}$.

Features of each prediction model were the subject's median matric of all states. As a complementary analysis, we also constructed sFC-behavior prediction model.

Results

Demographic and clinical characteristics

Table 1 summarizes the demographic, language, and clinical information of the participants. Males with ASD were dominant in all three groups. The FSIQ and VIQ were significantly lower in ASD in all three groups.

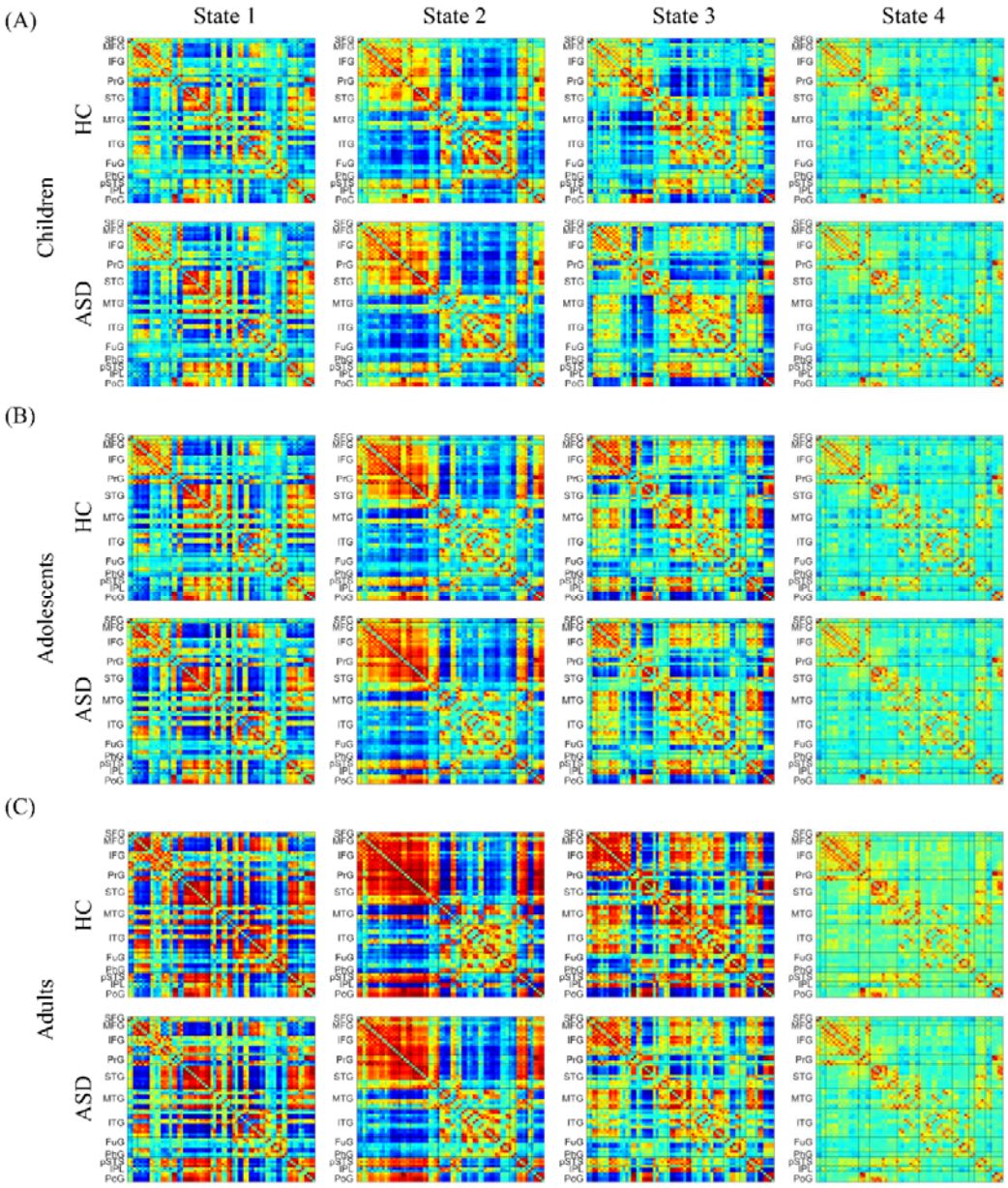

Figure 1. Cortical language network dynamics in HCs and ASDs. Four temporally recurring states with distinct functional connectivity patterns were identified in each group. Based on the

dynamic meta-networking framework of language proposed by Yuan et al. (2023), K for K-means clustering was set to 4 for each subject group, with state numbering reflecting the spatial similarity of each state to the dynamic meta-networking framework of language.

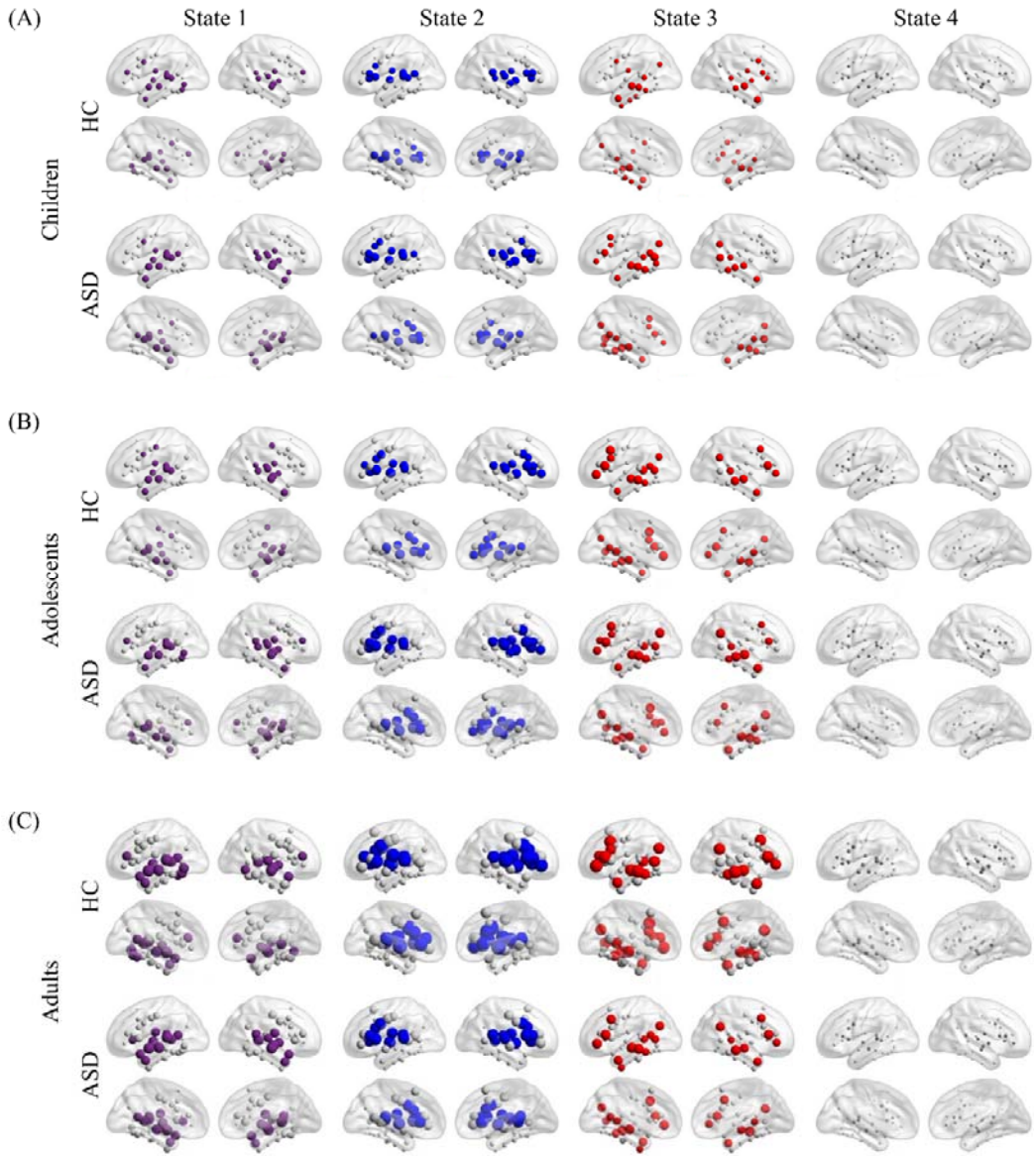

Figure 2. State-dependent hub distributions in HCs and ASDs. For each state, we calculated the nodal strength distribution and found that the distributions for all states were best fitted to the probability of an exponentially truncated power-law, suggesting the existence of hubs.

Referencing Yuan et al. (2023), in the first three states, the first 20 nodes with the highest nodal strength were colored and defined as hubs. Given that state 4 represents a weak connection state, we did not compute the nodal hub properties.

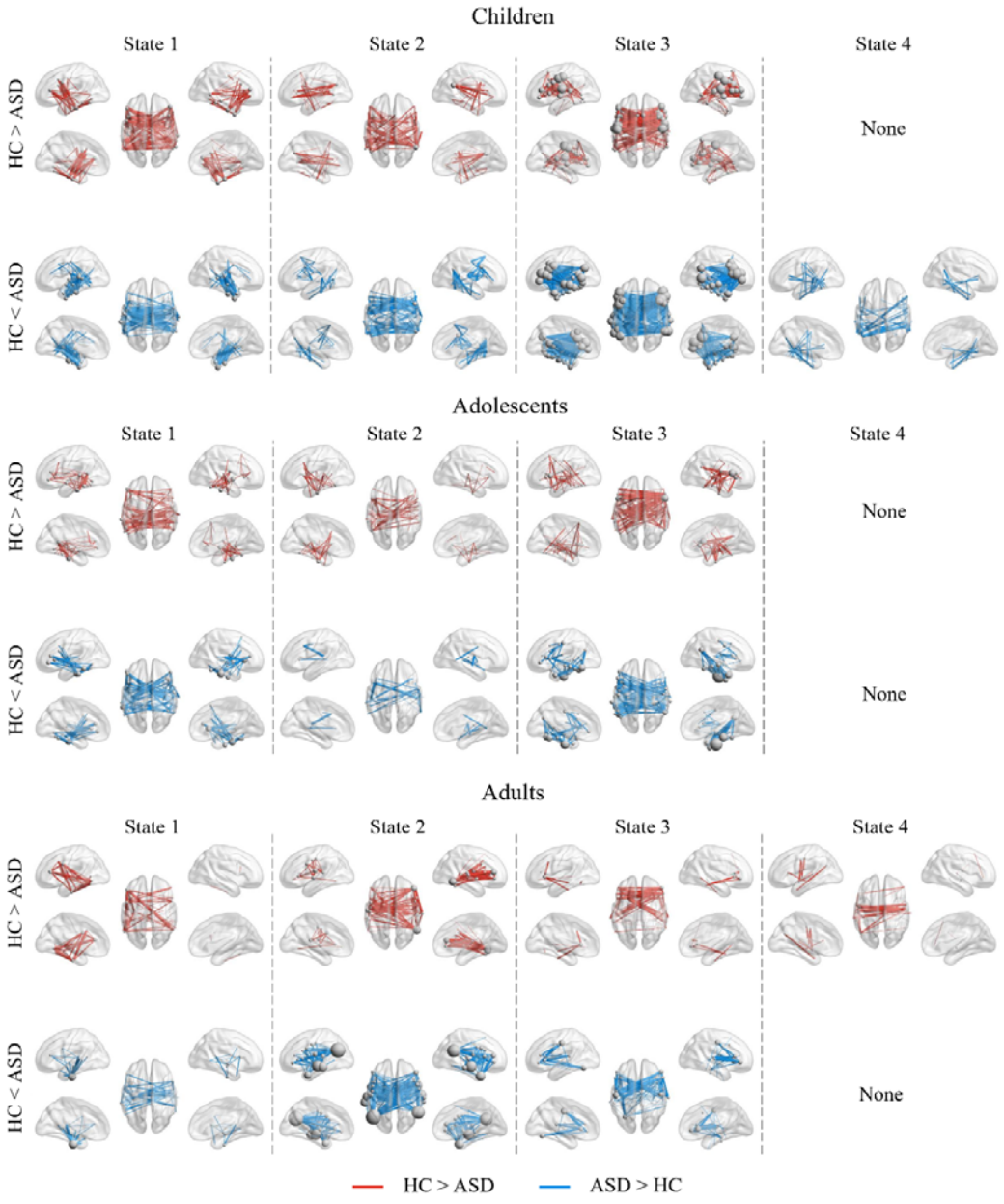

Figure 3. The domain-specific and age-dependent hyper- and hypo-connectivity in individuals with ASD. For each state, between-group differences of edges were corrected using NBS with an edge *P* value of 0.01 and a component *P* value of 0.05.

The temporal reoccurring states of language network in resting state

In the six groups of HCs and ASDs, four temporal reoccurring states were identified (**Figs. 1, 2**). Consistent with the dynamic "meta-networking" framework of language, these four states exhibited distinct functional connectivity patterns and hub distributions. State 1 was characterized by moderate to high positive connectivity between nodes in the bilateral STG, PrG, and PoG, but weak or moderate negative connectivity between the prefrontal nodes and temporal nodes. In state 2, strong positive connectivity among the prefrontal nodes was observed. State 3 distinguished itself from states 1 and 2 to strong connectivity among temporal nodes. State 4 showed an overall weak connectivity pattern.

All states demonstrated rich-club organizations

The normalized rich-club curves were calculated respectively on the weighted network thresholded with a correlation coefficient of 0.2. The normalized rich-club coefficients $\varphi_{norm}(k)$ were larger than 1 over a range of values of *K* for all states (**Supplementary Fig. 13**).

State-dependent hub distributions followed a domain-segregation pattern

We found that the nodal strength distributions of all states were best fitted by the exponentially truncated power-law form (**Supplementary Fig. 2**), indicating the presence of a small set of highly connected hub nodes. In each state, the first 20 nodes with the highest nodal strength were defined as hubs. In the first three states, non-random hub distributions were observed (**Figs. 1, 2**). In state 1, hubs were mainly distributed in STG. In state 2, hubs were mainly distributed in the prefrontal cortex and posterior temporal cortex. In state 3, hubs were mainly distributed in the temporal cortex, posterior parietal cortex, and IFG. We did not consider the hubs in state 4 due to the weak connectivity strength.

To assess the functional relevance of hubs in the first three states, we performed term-based meta-analyses on the platform NeuroQuery. According to the hub distributions, five terms, speech perception, inner speech, phonological processing, speech production, and semantic processing were analyzed. The dice coefficients between hubs and meta results were term- and state-specific (**Supplementary Fig. 3**). For example, in HCs of adolescents, the dice coefficients were: 1) state 1: speech perception, 0.44; inner speech, 0.47; phonological processing, 0.46; speech production, 0.44; semantic, 0.22. State 2: speech perception, 0.36; inner speech, 0.38; phonological processing, 0.46; speech production, 0.37; semantic, 0.21. State 3: speech perception, 0.45; inner speech, 0.47; phonological processing, 0.53; speech production, 0.44; semantic, 0.26.

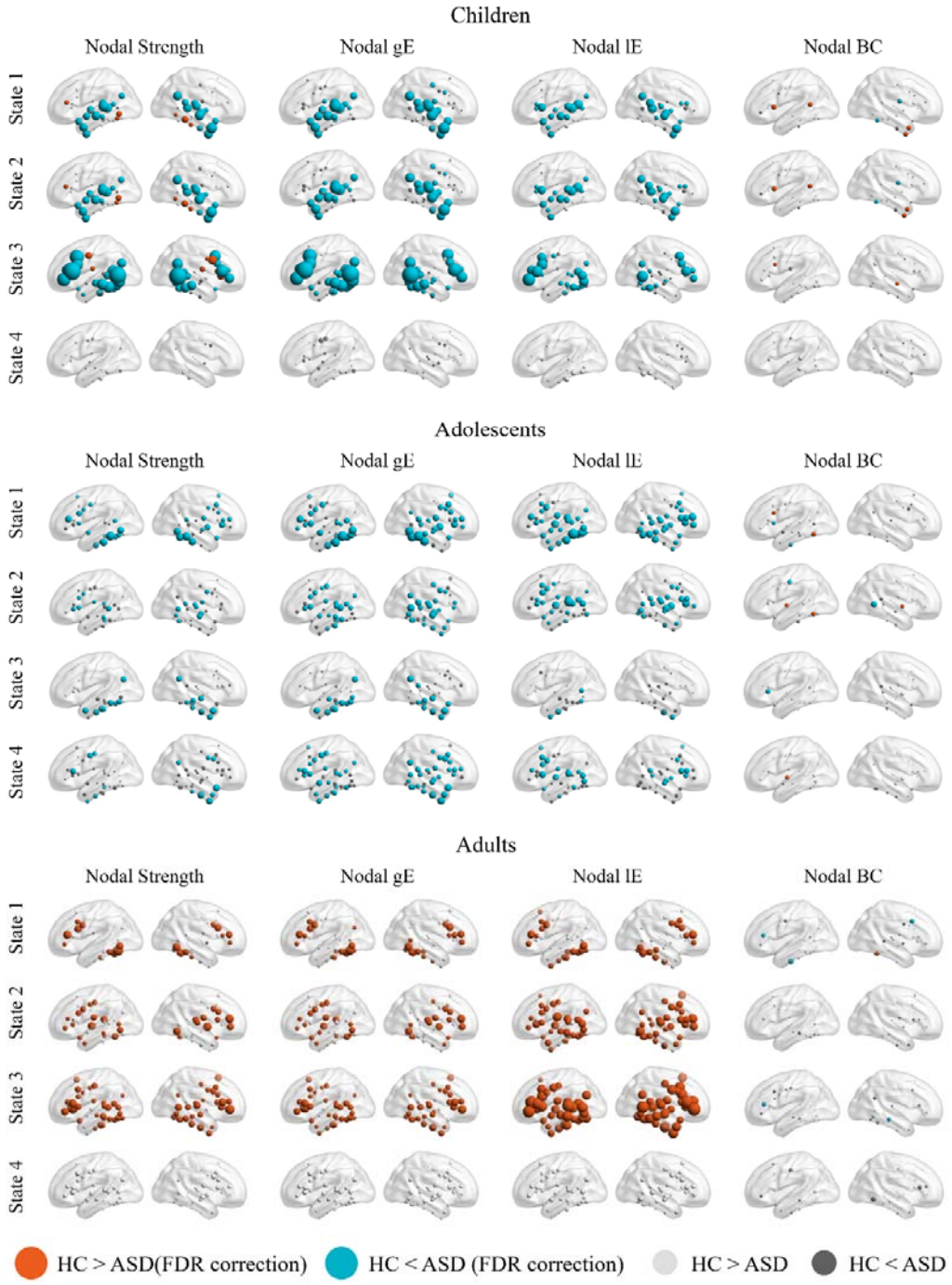

Figure 4. Changes of nodal topological characteristics. Four nodal topological properties, the nodal strength, the nodal global efficiencies (gE), and local efficiencies (lE), and the nodal betweenness centrality (BC), were calculated for each subject median of state dFCs. Between-group statistical comparisons were performed by using two-sample t-tests (FDR correction, $p < 0.05$).

Given the critical role of STG in speech perception and phonological processing, we speculated that hubs in state 1 were mainly implicated in speech perception and phonological processing. Additionally, hubs in state 2 showed significant overlap with regions implicated in phonological processing. Given the critical role of IFG and the ventral part of PrG in speech production [89], we speculated that hubs in state 2 were primarily involved in speech production. Moreover, hubs in state 3 exhibited substantial overlap with regions associated with all five terms. Considering the critical role of IPL, ATL, and orbitofrontal cortex in semantic processing [90], we hypothesized that hubs in state 3 were primarily implicated in semantic processing. Similar observations were made in the other groups, indicating a domain-separation pattern of language network dynamics in resting state across all three groups.

The hypo- and hyper-connectivity of language network in individuals with ASD

Language network disruptions in individuals with ASD were found in the first three states (**Fig. 3**). The hypo- and hyper-connectivity of language network in ASD were state-specific and age-dependent. Inter-hemispheric hypo- and hyper-connectivity were dominant. The brain regions exhibiting hypo- and hyper-connectivity include not only the hub regions in each state but also the connections between hub regions and non-hub regions in each state.

Those hypo- and hyper-connectivity were significantly correlated with VIQ, ADOS communication and social scores (**Supplementary Table 4, 5, 6**). These significantly

correlated brain regions are distributed across the frontal, temporal, and parietal lobes. For VIQ, hypo-connectivity and hyper-connectivity are negatively and positively correlated, respectively. However, for ADOS communication and social scores, hypo-connectivity and hyper-connectivity are positively and negatively correlated, respectively. Additionally, we found that the hypo-connectivity and hyper-connectivity in certain brain regions are significantly correlated with ADOS stereotypical scores. The regions and directions of these correlations are also associated with age.

The global and nodal topological properties of language network dynamics in individuals with ASD

In children and adolescents with ASDs, we observed significant increases of global and nodal properties of the first three states when compared with HCs (**Figs. 4 and 5**). However, in adults with ASDs, significant decreases in these properties were observed.

In children with ASD, the global (r = -0.31, p < 0.01) and local efficiency (r = -0.28, p = 0.01) of state 2 were negatively correlated with VIQ, the total functional connectivity strength of state 2 were negatively correlated with ADOS social scores (r = -0.3, p = 0.03). Interestingly, the negative correlation observed in the child group reversed to a positive correlation in the adult group. In adults with ASD, the global (state 3: r = 0.25, p = 0.03; state 4: r = 0.25, p = 0.03) and local efficiency (state 3: r = 0.24, p = 0.03; state 4: r = 0.23, p = 0.04) of states 3 and 4 were positively correlated

with VIQ, the total functional connectivity strength of state 3 was positively correlated with VIQ (r = 0.23, p = 0.04). No significant correlation was observed in the adolescent group.(**Fig. 6 and Supplementary Table 9**)

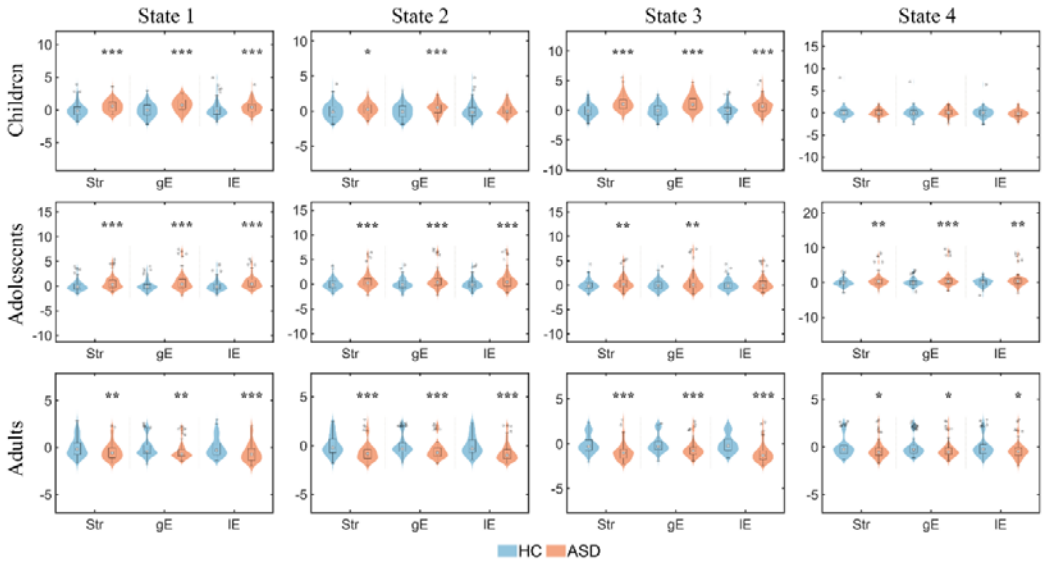

Figure 5. Global topological characteristics of each state in individuals with ASD. Three network topological properties, the total functional connectivity strength (Str), the network global (gE), and local efficiencies (lE) were calculated for each subject's median of state dFCs. For illustration purposes, the topological values were z-scaled. The "*" symbol denotes the statistical comparisons between HC and ASD reach an uncorrected p-value of 0.05. *, uncorrected $p < 0.05$; **, uncorrected $p < 0.01$; ***, uncorrected $p < 0.001$.

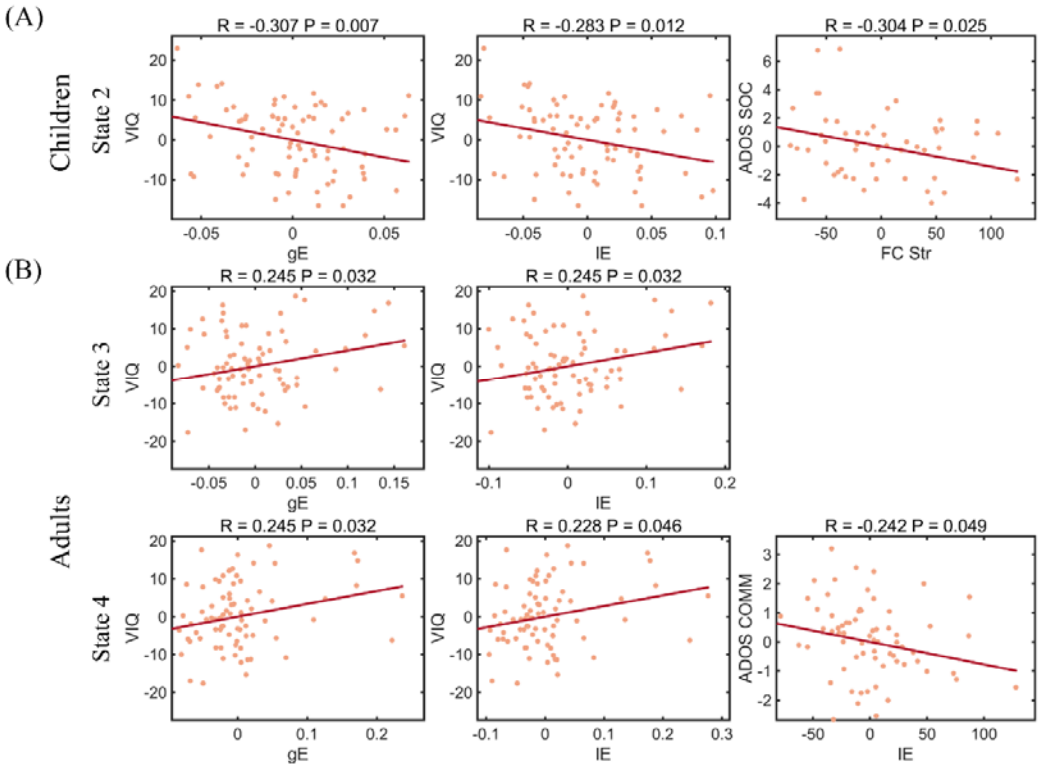

Figure 6. **Partial Pearson correlation between behavioral scores and global topological characteristics in individuals with ASD.** We conducted a partial correlation analysis between three global topological features and behavioral scores. In children and adults with ASDs, the global topological properties and VIQ were significantly correlated, yet in opposite directions.

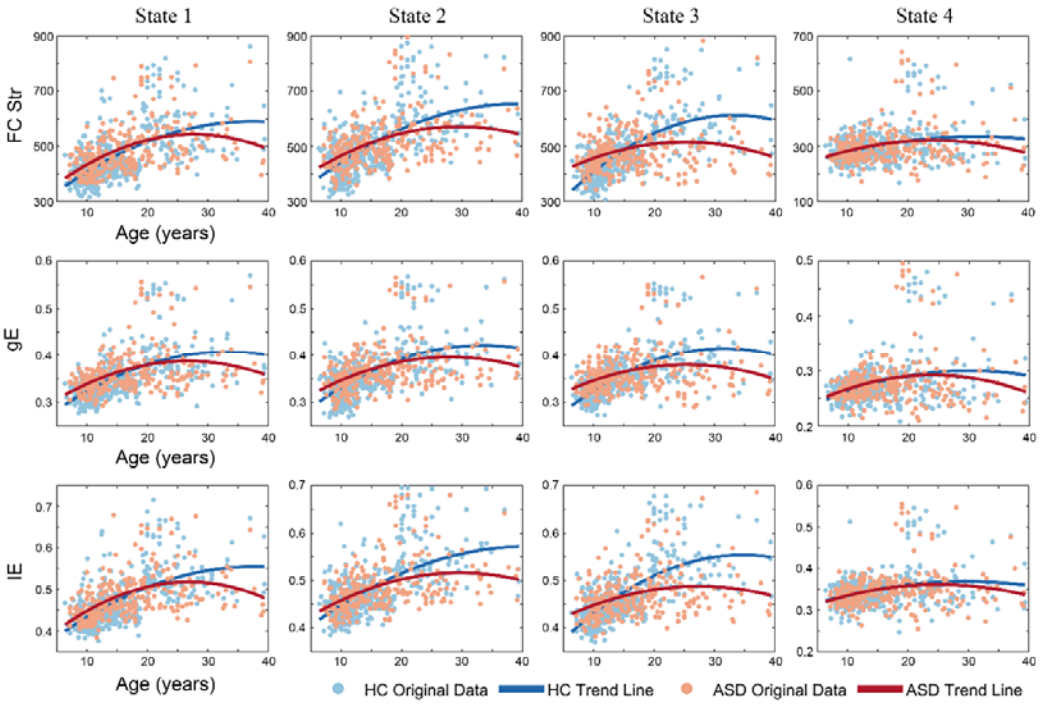

Figure 7. Domain-specific development trajectories of language networks fitted using polynomial functions. The developmental trajectories of the three topological properties in state 1 indicated that, compared to HCs, the developmental inflection points for ASD occur around the age of 20. Abnormal increases in topological properties are observed before 20 years old, followed by a decrease in abnormalities after20 years old. In contrast, the developmental trajectories for states 2 and 3 suggested that the inflection points for higher-order language domains occur earlier, approximately around the age of 15.

The dFCs significantly predicted VIQ and communication scores of individuals with ASD

RVR-based dFC-deficits prediction analyses revealed that dFCs of the four states significantly predicted VIQ of individuals with ASD for all the three groups (predicted vs. real, permutation tests, children, r= 0.41, p = 0.01; adolescents, r= 0.31,

p = 0.023; adults, r= 0.36, p = 0.01). The dFCs of the four states also significantly predicted ADOS communication scores of adolescents (r= 0.47, p = 0.005) and adult with ASD (r= 0.42, p = 0.006). The dFCs could not predict ADOS social and stereotypic scores (**Fig. 8**).

We then constructed prediction models for all ASD samples and found that dFCs of the four states still significantly predicted verbal IQ (r= 0.36, p = 0.001) and ADOS communication scores (r = 0.33, p = 0.004).

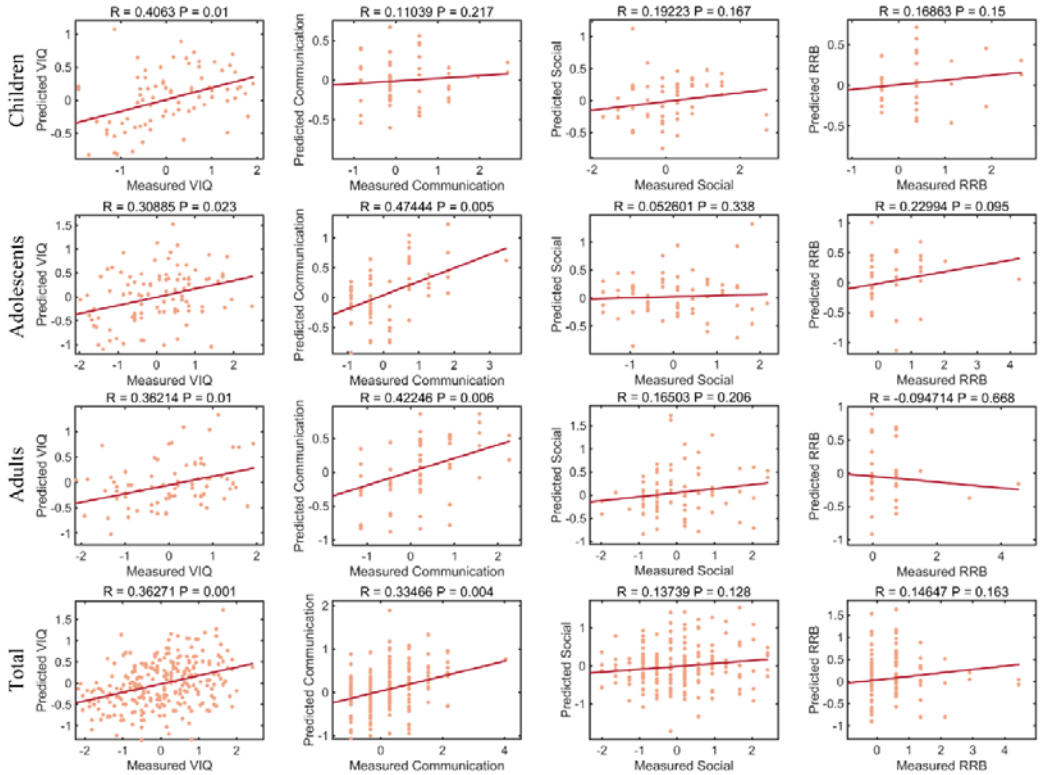

Figure 8. The dFC-deficits model accuracies and significance. A. The dFCs of the four states significantly predicted individual patients' behavior scores. B. The scatter plots showed real (normalized within each group) and predicted scores and the corresponding linear fitted lines. The R value was the Pearson correlation coefficient between the predicted values and the actual values,

and the model significance and the *P* values were based on 1000 permutation tests.

Between-group comparisons of sFC

For sFC, inter-hemisphere hypo-connectivity were observed in the three ASD groups (**Supplementary Fig. 8**). Hyper-connectivity was only observed in children with ASD. Several hypo- and hyper-connectivity were correlated with VIQ scores (Supplementary Fig. 9). There was no significant group-difference for either nodal or global topological properties (**Supplementary Figs. 10 and 11**).

In addition, sFC-deficits prediction analyses revealed that sFC significantly predicted ASD's verbal IQ (children, $r = 0.46$, $p = 0.002$; adolescents, $r = 0.35$, $p = 0.009$; adults, $r = 0.33$, $p = 0.04$; total, $r = 0.34$, $p < 0.001$) and ADOS communication scores (adolescents, $r = 0.32$, $p = 0.018$; adults, $r = 0.45$, $p = 0.001$; total, $r = 0.27$, $p = 0.046$) (**Supplementary Fig. 12**).

Discussion

In this study, we analyzed resting-state fMRI data from the ABIDE datasets to examine the aberrant dynamics of the language network in children, adolescents, and adults with ASD. Unlike previous studies that focused solely on network dynamics, we employed the dynamic "meta-networking" model of language during resting state, as proposed by Yuan et al. [25]. This framework enabled us to scrutinize domain-specific alterations in individuals with ASD.

We demonstrated that the language network dynamics in healthy children, adolescents, and adults exhibited domain-segregation patterns. Domain segregation, which delineates the division of labor between dorsal and ventral processing, serves as a fundamental functional framework in the human brain [91]. This framework is evident across various cognitive domains, such as vision (what vs. how), audition (what vs. where), control [92], memory [93], and speech (phonological vs. semantic) [26, 94, 95], phonological processing . The dynamic "meta-networking" framework of language, as proposed by Yuan et al. (2023), comprises three domain-related states: state 1 for speech perception and phonological representation, state 2 for speech production, and state 3 for semantic processing, along with one baseline state 4. This framework offers a dynamic and connectional account of the dual-stream model of language [26]. The observation of domain-separation language network dynamics in healthy children suggests that the functional segregation and specialization of domain-related language processing mature during preschool-age [39, 96-99].

Our results underscored the efficacy of the dynamic "meta-networking" framework of language in capturing the abnormal language network dynamics in individuals with ASD, shedding light on domain- and state-specific changes that vary across age groups. A recent literature review noted that individuals with ASD exhibit under-connectivity of inter-hemispheric language regions [15]. However, we found that the language network changes in individuals with ASDs were complex. We found that the

domain-segregation language network dynamics of individuals with ASD were sub-optimal, and domain- and state-specific hyper- and hypo-connectivity were observed for various critical language areas. Specifically, in children with ASD, we observed hypo- and hyper-connectivity among IFG, PrG, PoG and temporal cortex in states 2 and 3. In adolescents with ASD, hypo- and hyper-connectivity among IFG, STG, and MTG were observed in states 1 and 2. Similarly, in adults with ASD, hypo- and hyper-connectivity among IFG, STG, and ITG were observed in state 1. These language network changes were also associated with and predictable for VIQ and ADOS communication scores, but not stereotyped behavior scores, suggesting their language specificity [1, 16, 31, 63, 100-103].

The most significant characteristic of brain development in individuals with ASD is overgrowth from infancy to early adolescence, followed by undergrowth from late adolescence into adulthood [40, 42, 44, 104-106]. A more detailed analysis of brain regions and networks revealed that the developmental trajectories of network properties differ across various brain regions [107] and networks [108]. In our cross-sectional samples, we found that the developmental trajectories of the topological properties in the first three states in the ASD group align with the aforementioned pattern compared to the control group. Interestingly, however, the crossover points between the developmental trajectories of state 2 and state 3 with state 1 differed between the ASD and control groups. The crossover point for state 1 is around 20 years of age. In contrast, the crossover points for states 2 and 3 are around 15 years of

age. The hub regions of state 1 are primarily located in the STG and the ventral part of the sensorimotor network. These regions are involved in speech sound perception and representation, as the critical interface between auditory and language systems [109]. A substantial body of research has reported overgrowth of the bilateral STG in individuals with ASD [103, 110-113], with this anomaly persisting from infancy [104, 114, 115] into young adulthood. The hypoactivation of STG has been demonstrated to be a neural signature of later poor language outcomes in individuals with ASD [16, 114, 115]. In addition to the critical role of the STG in language development, some studies have suggested that functional connectivity disruptions in STG and superior temporal sulcus are also associated with emotional disturbances in individuals with ASD [116]. These findings imply that persistent anomalies in speech perception and representation may underpin the atypical language development associated with ASD, as well as its more complex emotional and social dysfunctions.

Limitations

There are several limitations in this study. Firstly, this study did not include structured linguistic assessments for ASD, such as those related to phonology, semantics, and syntax, nor did it cover lexicon and pragmatics. Although we identified state-specific differences, we could not further explore whether these differences are associated with domain-specific deficits. In fact, both VIQ and ADOS communication are highly complex tests that encompass various aspects of both linguistic and non-linguistic abilities. This complexity may explain why the functional connectivity observed in

this study, as well as in other related studies, shows only weak correlations with these measures. Secondly, while our study contributes to a theoretical framework of aberrant language network dynamics, the clinical relevance in terms of diagnosis and intervention remains unclear. Based on our findings, a reasonable hypothesis is that the dynamic "meta-networking" framework of language could potentially serve as a reference to assess the degree of abnormality in the language network of individuals with ASD or the extent of reorganization of the language network after intervention. Thirdly, due to the age range limitations of the ABIDE dataset (participants aged five and above), we were unable to explore language network abnormal patterns before the age of five. The period before five years old is crucial for language development. Understanding the dynamic interaction and separation between language-related brain areas, particularly in the frontal and temporal lobes during this period, is not only a significant scientific question but also essential for comprehending language developmental abnormalities in ASD.

Conclusions

In our study, we refined the hypo- and hyper-connectivity patterns within the language network in children, adolescents, and adults with ASD by adopting the dynamic "meta-networking" framework of language. The atypical brain and language development observed in individuals with ASD led to a sub-optimal domain-segregation patterns of language network dynamics during resting state. We found that the aberrant language network dynamics in individuals with ASD were domain-

and state-specific, meaning they varied depending on the specific language processing domain and the state of the dynamic "meta-networking" framework. Additionally, these alterations were age-dependent, highlighting the dynamic nature of language development in individuals with ASD.

Furthermore, our findings demonstrated that these aberrant language network dynamics were predictive of individual VIQ, ADOS communication scores. Collectively, these findings refined our understanding of the network mechanisms for language and communication deficits in individuals with ASD.

Data/code availability statement

Behavioral and fMRI data are available on at https://fcon_1000.projects.nitrc.org/indi/abide/. The DCC toolbox was available at https://github.com/canlab/Lindquist_Dynamic_Correlation/tree/master/DCC_toolbox. Other software used in the study was based on DPABI (http://rfmri.org/dpabi), SPM (http://www.fl.ion.ucl.ac.uk/spm), GRETNA (https://www.nitrc.org/projects/gretna/) and BrainNetViewer (https://www.nitrc.org/projects/bnv/).

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Conflict of Interest Statement

The authors declare no competing financial interests.

Contributions

Zhe Hu contributed to fMRI data analysis, results visualization and interpretation, the revision of the manuscript, the quality control of phenotypic data. Xiaolin Guo contributed to fMRI data analysis, interpretation of results, the quality control of phenotypic and imaging data. Junjie Yang contributed to data analysis, computer programming. Zhiheng Qu and Zhongqi Li contributed to the quality control of phenotypic and imaging data. Junjing Li contributed to fMRI data analysis. Xiaowei Gao, Jiaxuan Liu, Yaling Wang, Wanchun Li, Wanjing Li, Yien Huang, Jiali Chen contributed to interpretation of results. Binke Yuan conceptualised the study design, gained funding, supervised the data analysis, interpretated the results, wrote the draft, critically reviewed and revised the manuscript. Xin Wang gained funding, interpretated the results, critically reviewed and revised the manuscript. All authors reviewed the manuscript, participated in revision, and approved of the final version.

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Captions to figures

Figure 1.

Figure 4. The domain-separation manner of language network dynamics in resting state. The functional hubs of the first three states and their spatial similarities with the meta-analytic results of auditory, phonological, and semantic processing. A: in each group, nodes with strength larger than the mean value of the four states are defined as network hubs. B: the dice coefficients between binary images of hub nodes and meta results (dice = 2* (hub * meta)/(hub + meta)). Considering the left-lateralized activations of meta results, the dice coefficients were calculated in the left hemisphere. C: the meta-results of auditory processing (1252 studies, 46557 activations), phonological processing (377 studies, 17844 activations), and semantic processing (1031 studies, 40030 activations), which are from term-based meta-analyses of association tests with FDR correction (corrected $P < 0.01$, https://www.neurosynth.org/).

Figure 7. Changes of nodal topological characteristics between. Between-group statistical comparisons were performed by using two-sample t-tests (FDR correction, $P < 0.05$).

Figure 8. The dFC-linguistics model accuracies and significance. The dFCs of the four states significantly predicted individual patients' language deficits. The scatter plots showed real (normalized within each group) and predicted AQ scores and the corresponding linear fitted lines. The R value was the Pearson correlation coefficient between the predicted values and the actual values, and the model significance and the P values were based on 1000 permutation tests.