General Psychiatry

Diminished functional segregation and resilience are associated with symptomatic severity and cognitive impairments in schizophrenia: a large-scale study

Haohao Yan,[1] Yiding Han,[1] Xijia Xu,[2] Hongxing Zhang,[3,4] Yiqun He,[5] Guojun Xie,[6] Huabing Li,[7] Feng Liu,[8] Ping Li,[9] Jingping Zhao,[1] Wenbin Guo [1]

To cite: Yan H, Han Y, Xu X, *et al*. Diminished functional segregation and resilience are associated with symptomatic severity and cognitive impairments in schizophrenia: a large-scale study. *General Psychiatry* 2024;**37**:e101613. doi:10.1136/gpsych-2024-101613

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gpsych-2024-101613).

HY and YH are joint first authors.

Received 08 March 2024
Accepted 25 June 2024

For numbered affiliations see end of article.

Correspondence to
Dr Wenbin Guo;
guowenbin76@csu.edu.cn

ABSTRACT

Background The research findings on the topological properties of functional connectomes (TP-FCs) in patients with schizophrenia (SZPs) exhibit inconsistencies and contradictions, which can be attributed to limitations such as small sample sizes and heterogeneous data processing techniques.

Aims To address these limitations, we conducted a large-scale study. Uniform data processing flows were employed to investigate the aberrant TP-FCs and the associations between TP-FCs and symptoms or cognitions (A-TP-SCs) in SZPs.

Methods The large-scale study included six datasets from four sites, involving 497 SZPs and 374 healthy controls (HCs). A uniform process for imaging data preprocessing and functional connectivity matrix configuration was used. ComBat was employed for data harmonisation, and various TPs were calculated. We explored between-group differences in brain functional integration (FI) and functional segregation (FS) measured with TP-FCs, and conducted partial correlation analyses, with adjustments for age, gender and educational level, to identify A-TP-SCs.

Results Compared with random networks and HCs, SZPs maintained small-worldness and global FI capacity despite their compromised global FS capacity and resilience. A decline in nodal FI and FS capacity was observed in sensory areas, whereas an increase in nodal FI capacity was found in regions associated with cognition and information integration. In addition, associations between TP-FCs and positive symptoms, negative symptoms or cognitive functions including speed of processing, visual learning and the ability to inhibit cognitive interference were identified in SZPs.

Conclusions The identified A-TP-SCs verified that reductions in FS and resilience indicated pathological impairments in schizophrenia. The A-TP-SCs or TP-FCs, which measured the same attributes of the functional connectomes, exhibited high internal consistency, robustly reinforcing these findings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ An emerging hypothesis links the onset of schizophrenia to disruptions in the topology of large-scale brain networks. Findings on topological properties of the functional connectomes (TP-FCs) of patients with schizophrenia (SZPs) have been inconsistent or contradictory. A recent meta-analysis emphasised the effect of small sample sizes and heterogeneous data processing flows on the low reproducibility of TP-FC findings in SZPs.

WHAT THIS STUDY ADDS

⇒ The large-scale study with uniform data processing flows revealed that SZPs maintained small-worldness and global functional integration capacity despite the presence of compromised global functional segregation (FS) capacity and resilience against insults. Associations between TP-FCs and symptoms or cognitive functions were identified, verifying that diminished global FS and resilience are pathological impairments in schizophrenia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This large-scale study addressed crucial factors contributing to the low reproducibility of findings related to the TP-FCs in SZPs. With robust results, the study indicates that diminished global FS and resilience represent pathological impairments in schizophrenia. These findings provide invaluable insights into the pathological mechanisms underlying schizophrenia.

INTRODUCTION

Investigating brain networks and revealing their organisational principles is crucial for elucidating brain architecture. Brain networks represent real-life complex systems, exhibiting neither uniformly random nor strictly ordered organisational features. Functional brain networks are guided by two primary organisational principles: functional segregation (FS) and functional integration (FI).[1] FS involves specialised processing within closely connected groups of brain regions, and FI denotes the ability of the brain to swiftly combine specified information from dispersed regions. Brain networks consist of nodes and edges. Graph theory,

a mathematical discipline focused on studying graphs as structures for modelling pairwise relations between objects, can thus be used to reveal the relationships among these nodes and edges. Furthermore, based on graph theoretical approaches, topological properties of the functional connectomes (TP-FCs) have been demonstrated as robust metrics with high test–retest reliability to quantitatively characterise the organisational principles of the functional architectures of the brain.[2] Thus, the examination of TP-FCs offers invaluable insights into typical brain architecture and the pathological mechanisms underlying disorders related to structural and functional brain impairments.

Schizophrenia, a progressive brain disease characterised by extensive brain structural and functional abnormalities, suggests that TPs hold potential as measures for understanding its pathogenesis. An emerging hypothesis links the onset of schizophrenia to disturbances in the topology of large-scale brain networks, resulting from pathological damage rather than isolated lesions in specific brain regions.[3 4] This hypothesis is substantiated by consistent findings (online supplemental appendix p. 1–2) of abnormal TP-FCs in patients with schizophrenia (SZPs) and the associations between TP-FCs and symptoms or cognitions (A-TP-SCs) in SZPs.[5–9]

Nonetheless, findings on the TP-FCs in SZPs exhibit inconsistencies and contradictions (online supplemental appendix p. 1–2). With these disparities considered, two meta-analyses were conducted to synthesise findings and explore potential factors influencing the TPs of SZPs.[3 4] In the earlier meta-analysis, reduced Sigma, clustering coefficients (Cp), and network local efficiency (Eloc) were observed in TP-FCs for SZPs relative to healthy controls (HCs), with no significant differences in characteristic path length (Lp) and network global efficiency (Eg).[3] However, a meta-analysis published in 2023 yielded contradicting results. Except for higher Gamma in SZPs, no significant differences were found in TP-FCs compared with HCs.[4] Moreover, the meta-analysis in 2023 emphasised the effect of small sample sizes and heterogeneous data processing flows on low reproducibility in TP-FC findings for SZPs.[4] Relying on the quality of original studies, meta-analyses adhere to the principle of 'garbage in, garbage out', posing a potential deviation from the truth when low-quality studies are incorporated. Based on our systematic search (online supplemental appendix p. 1–2), only one original study included over 100 SZPs,[10] and over half of the original studies exploring TP-FCs in SZP involved fewer than 40 SZPs. Small studies are susceptible to sampling variability, which decreases with increasing sample sizes at a rate of $\sqrt{n}$.[11] Marek *et al* suggested that a substantial sample size of thousands of individuals is required to achieve reproducible studies on the associations between inter-individual variability in human brain function/structure and psychiatric symptomatology or cognition.[11] Nonetheless, DeYoung *et al* suggested that a minimum sample size of 200 could be adequate for these correlational studies if the expected effect size is not less than 0.2.[12] Given the small sample size in previous studies investigating A-TP-SCs in SZPs,[5–9 13] the low reproducibility of findings in studies on TP-FCs in SZPs and the resulting inability of meta-analysis to precisely elucidate TP-FCs and A-TP-SCs in SZPs, it is essential to perform an original study on TP-FCs and A-TP-SCs in SZPs with a large sample size and a unified data process workflow.

Large-scale studies differ from small-sample studies in that they enhance statistical power, enabling the detection of reliable yet subtle differences.[14] Conducting big-data functional magnetic resonance imaging (fMRI) studies requires addressing site effects through methods like data harmonisation.[14 15] Wang *et al* performed a comprehensive evaluation of harmonisation approaches and found that methods including ComBat, effectively alleviate site effects while preserving the between-subject biological variability.[14] ComBat has been widely used in studies on diffusion tensor imaging data, cortical thickness, functional connectivity (FC) in resting-state fMRI (rs-fMRI), and TP-FCs.[16] In the current study, we employed ComBat for data harmonisation. A detailed introduction to ComBat is provided at https://github.com/Jfortin1/ComBatHarmonization (accessed on 10 December 2023).

We conducted a large-scale study, using samples from multiple sites and employing ComBat for data harmonisation, to investigate TP-FCs and A-TP-SCs in SZPs. This research sought to reveal the architecture of the functional connectomes in SZPs, offering invaluable insights into the pathological mechanisms underlying the disorder.

METHODS

Sites and participants

This study used data from six datasets obtained from four sites (online supplemental table S1). Datasets A, B and C included drug-naive SZPs, whereas datasets D and F included both drug-naive and drug-exposed SZPs. Moreover, dataset E included both treatment-resistant and non-treatment-resistant SZPs. A standardised set of inclusion and exclusion criteria was uniformly applied across all study sites for the selection of SZPs. The inclusion criteria included: (1) diagnosis of schizophrenia confirmed by two experienced psychiatrists using the Structured Clinical Interview according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-V) criteria; (2) right-handedness; and (3) minimum of 6 years of formal education. The exclusion criteria were: (1) neurological disorders; (2) severe physical illness; (3) history of substance use; (4) contraindications for MRI scan; and (5) pregnancy. Detailed criteria for selecting SZPs and HCs are presented in the following studies: Wang *et al* for dataset A,[17] Guo *et al* for dataset B,[18] Shan *et al* for dataset C,[19] Shan *et al* for dataset D,[20] Gao *et al* for dataset E[21] and Jing *et al* for dataset F.[22] The study procedure is presented in figure 1.

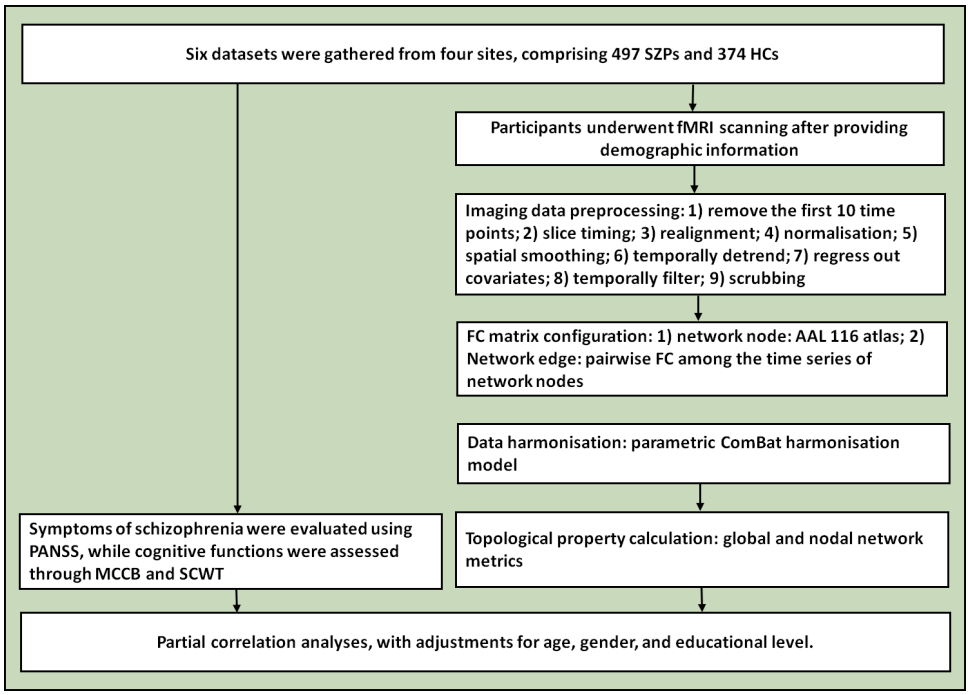

Figure 1 Flowchart. AAL 116 atlas, Anatomical Automatic Labelling 116 atlas; FC, functional connectivity; fMRI, functional magnetic resonance imaging; HCs, healthy controls; MCCB, MATRICS Consensus Cognitive Battery; PANSS, Positive and Negative Syndrome Scale; SCWT, Stroop Colour and Word Test; SZPs, patients with schizophrenia.

Schizophrenia severity and cognitive assessments

We used the Chinese version of the Positive and Negative Syndrome Scale (PANSS) to assess the severity of schizophrenia (online supplemental appendix p. 3). PANSS consists of three subscales: Positive Scale, Negative Scale and General Psychopathology Scale. These scales are designed to evaluate positive and negative symptoms of schizophrenia, together with general psychopathology. Moreover, we employed the Chinese version of the MATRICS Consensus Cognitive Battery (MCCB) and the Stroop Colour and Word Test (SCWT) to assess the cognitive performance of these patients (online supplemental appendix p. 3). The MCCB includes nine tests across seven cognitive domains, and the SCWT comprises three tests measuring the ability to inhibit cognitive interference (Stroop Effect).

Imaging data acquisition and preprocessing

Siemens scanners were used for four datasets, a Philips scanner for one dataset, and a GE scanner for another. The scan parameters for rs-fMRI were largely consistent across all datasets (online supplemental table S1). We employed GRETNA (V.2.0) for preprocessing imaging data at all sites, following uniform steps across datasets (figure 1 and online supplemental appendix p. 3).

Functional connectivity matrix configuration and data harmonisation

The FC matrix was configured using GRETNA (V.2.0) and involved two steps: node definition and edge definition. In node definition, the Anatomical Automatic Labelling 116 atlas was used, and pairwise functional connectivity was determined among the time series of the nodes by calculating Pearson correlation coefficients for edge definition. We further performed Fisher's r-to-z transformation to enhance the normality of the correlations. After the 116×116 FC matrix was configured, the parametric ComBat model was used for data harmonisation to eliminate site effects. Detailed procedures for implementing ComBat were provided in previous studies.[15]

Calculation of topological properties

After applying ComBat harmonisation, we used a sparsity threshold (0.05–0.40, with an interval of 0.01) to generate the binary FC matrix. We subsequently calculated global and nodal network metrics across 36 sparsity networks and determined the area under the curve (AUC) for these metrics. We further generated 100 random networks to assess whether brain networks exhibit a significantly non-random topology.[1] Global network metrics encompass Sigma, Gamma, Lambda, Cp, Lp, Eg, Eloc, assortativity, synchronisation, hierarchy and modularity. Nodal network metrics include betweenness centrality (Bc), degree centrality (Dc), nodal efficiency (Ne), nodal local efficiency (NLe), nodal Cp (NCp) and nodal Lp (NLp). Detailed metric annotations are presented in the supplementary material (online supplemental appendix p. 4). Calculation formulas for these metrics are presented in previous publications.[1 2]

Statistical analysis

Demographic information and cognitive assessments were statistically analysed using SPSS V.25.0. Disparities in gender distribution between SZPs and HCs were assessed

using a χ^2 test. Age, educational level and cognitive comparisons were conducted using independent-samples t-tests or Mann-Whitney U tests, depending on the results of normality tests (Shapiro-Wilk or Kolmogorov-Smirnov tests).

We used GRETNA (V.2.0) to compare the TP-FCs between SZPs and HCs. A one-sample t-test was employed to investigate whether the brain networks of SZPs or HCs exhibited small-worldness by comparing Sigma value with 1.1. Independent-samples t-tests were used to compare the AUC for global network metrics and these metrics in each of the 36 sparsity networks between SZPs and HCs, with age, gender and years of education as covariates. The significance level was set at p=0.05. However, the significance level for the comparisons of these metrics in each of the 36 sparsity networks was adjusted for multiple comparisons using Bonferroni's correction (p=0.0014 for the simultaneous conduct of 36 tests). Moreover, independent-samples t-tests were conducted to compare the AUC for nodal network metrics in each of the 116 nodes between SZPs and HCs, with age, gender and years of education as covariates. The significance level was set at p=0.05 but adjusted for multiple comparisons using Bonferroni's correction (p=0.0004 for the simultaneous conduct of 116 tests).

Partial correlation analyses were conducted, with adjustments for age, gender and educational level to identify the A-TP-SCs in SZPs. The significance level was set at p=0.05, and the threshold for significance in correlations between nodal network metrics and schizophrenia severity or cognitive assessments was adjusted for multiple comparisons by using Bonferroni's correction (p=0.0004 for the simultaneous conduct of 116 tests).

RESULTS

Demographic information

The study included six datasets from four sites, involving 497 SZPs (aged 12–60 years) and 374 HCs (aged 12–59 years). SZPs and HCs were matched in gender and age across the entire sample, but SZPs had a lower educational level than HCs. The demographic details of the entire sample and each dataset are listed in online supplemental table S2. Additional illustrations are presented in the online supplemental figures S1,S2.

Schizophrenia severity

In the entire sample, PANSS scale data were available for 490 of 497 SZPs. PANSS scale data were missing for three patients in dataset B, three in dataset D, and one in dataset F. All datasets showed varying degrees of schizophrenia severity (online supplemental figures S3,S4 and online supplemental table S3).

Between-group differences in cognitive functions

Cognitive functions were assessed across datasets A, C and E; other datasets lacked cognitive assessment data. SZPs demonstrated cognitive impairments across various domains, regardless of whether datasets (datasets A, C or E) were analysed individually or collectively (online supplemental figures S5–S8 and online supplemental tables S4–S7).

Between-group differences in global network metrics

The statistical results for the AUC of global network metrics are presented in figure 2 and online supplemental table S8. Sigma exceeded 1.1 for both SZPs and HCs across all sparsity networks (online supplemental figure S9). No significant differences were found

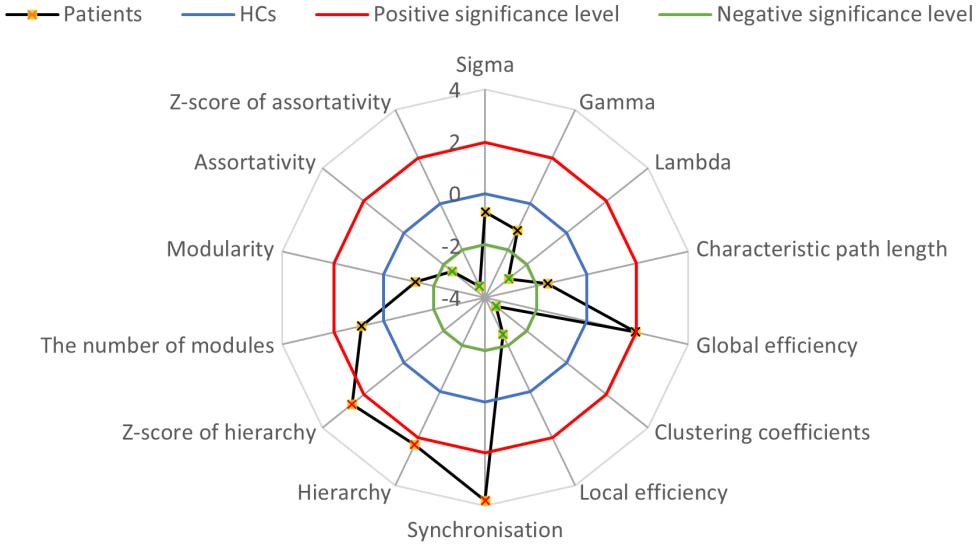

Figure 2 Radar map illustrating the statistical results for the AUC of global network metrics. Positive and negative significance levels at 1.96 and –1.96 of t values, respectively. The coordinate axis, ranging from –4 to 4, represents the t values from independent sample t-tests conducted between patients with schizophrenia and HCs. Red crosses denote patients with a higher AUC, green crosses indicate a lower AUC in this global network metric and black crosses represent no significant difference between the two groups. AUC, area under the curve; HCs, healthy controls.

in the AUC for Sigma (online supplemental figure S9), Gamma (online supplemental figure S9), Lp (online supplemental figure S10), Eg (online supplemental figure S10), the number of modules (online supplemental figure S11) and modularity (online supplemental figure S11), as well as these metrics at each sparsity network (online supplemental figures S9-S11). No significant differences were found in the Eloc (online supplemental figure S10), assortativity (online supplemental figure S11), hierarchy (online supplemental figure S12) and Z-score of hierarchy (online supplemental figure S12) at each sparsity network. However, compared with HCs, SZPs exhibited a lower AUC for Lambda (online supplemental figure S9), Cp (online supplemental figure S10), Eloc (online supplemental figure S10), assortativity (online supplemental figure S11) and Z-score of assortativity (online supplemental figure S11), and a higher AUC (online supplemental figure S12) for synchronisation, hierarchy and Z-score of hierarchy. Also, SZPs showed lower Lambda (online supplemental figure S9), Cp (online supplemental figure S10), Z-score of assortativity (online supplemental figure S11), as well as higher synchronisation (online supplemental figure S12) in specific sparsity networks compared with HCs (online supplemental table S9).

Between-group differences in nodal network metrics

SZPs showed an altered AUC for Dc and Ne in similar brain regions (figure 3). Notably, decreased AUC was observed in the Rolandic operculum, parahippocampal gyrus, lingual gyrus, fusiform gyrus, Heschl's gyrus and temporal gyrus. In contrast, increased AUC was found in the frontal gyrus, cingulate gyrus, angular gyrus, caudate and thalamus. Furthermore, SZPs exhibited decreased AUC for NCp and NLe in overlapping brain regions (figure 4), including the olfactory cortex, insula, occipital gyrus, postcentral gyrus, Heschl's gyrus and temporal gyrus. Moreover, changes in AUC for Bc were observed in specific nodes (figure 4), with increased AUC in the thalamus and decreased AUC in the temporal gyrus. Moreover, compared with HCs, SZPs showed increased AUC for NLp in the temporal gyrus (figure 3). Detailed statistical results of nodal network metrics are given in the (online supplemental table S10).

Verify the robustness of between-group differences in global and nodal network metrics

To verify whether including patients in the rapid developmental phase of adolescence, specifically those aged 12–16, impacted the between-group differences in global and nodal network metrics, we excluded patients and HCs in this age group (43 SZPs and 31 HCs). The between-group differences in global network metrics (online supplemental figures S13–S17; online supplemental tables S11,S12) and nodal network metrics (online supplemental figures S18–S19; online supplemental table S13) remained consistent with those of all subjects.

Associations between TP-FCS and symptoms or cognitions

In SZPs, following adjustments for age, gender and educational level, partial correlation analysis revealed associations between residual AUC for specific TP-FCs and residual scores of positive and negative symptoms (table 1 and online supplemental figure S20), as well as cognitive assessments in speed of processing, visual learning and the ability to inhibit cognitive interference (table 1 and online supplemental figures S21–S23).

DISCUSSION

Main findings

This large-scale study, conducted across four sites with six datasets, included 497 SZPs and 374 HCs. The groups were age-matched and gender-matched, but SZPs had lower educational levels. The majority of SZPs presented mild-to-moderate severity of schizophrenia symptoms, accompanied by cognitive impairments across various domains. Notably, abnormal TP-FCs and A-TP-SCs were identified in SZPs.

Global network metrics

Sigma, Gamma and Lambda are metrics related to random networks (Sigma=Gamma/Lambda, Gamma=Cp of real brain networks/Cp of random networks and Lambda=Lp of real brain networks/Lp of random networks).[1] Random networks mirror the same number of nodes, edges and degree distribution as actual brain networks.[1] Our investigation indicates that SZPs maintain small-worldness (Sigma>1.1) compared with randomly generated networks and show no significant difference from HCs in small-worldness.[1] Moreover, SZPs exhibited no significant difference from HCs in AUC for Gamma and Gamma within each sparsity network; however, a lower AUC for Lambda and lower Lambda in certain sparsity networks were observed. Gamma and Lambda represent the efficiency of FS and FI, respectively, in actual brain networks based on existing nodes, edges and degree distribution according to the formula.[1] Therefore, patients exhibited no difference with HCs in the efficiency of FS but had higher efficiency in FI. This observation suggests a compensatory increase in the efficiency of FS under pathological conditions.

Furthermore, compared with HCs, SZPs showed no significant difference in AUC for Lp and Eg, as well as these metrics across all sparsity networks. Lp and Eg represent measures of global FI.[1] Thus, SZPs demonstrated equivalent global FI capabilities with HCs, and the measurement methods confirmed each other. However, SZPs exhibited decreased AUC for Cp and Eloc, as well as Cp in some sparsity networks. Cp and Eloc represent measures of global FS.[1] Thus, relative to HCs, SZPs showed a reduced ability for global FS, and the measurement methods confirmed each other. However, SZPs and HCs exhibited no difference in AUC for the number of modules and modularity, as well as these metrics across all sparsity networks. Modular architecture, also a measure of

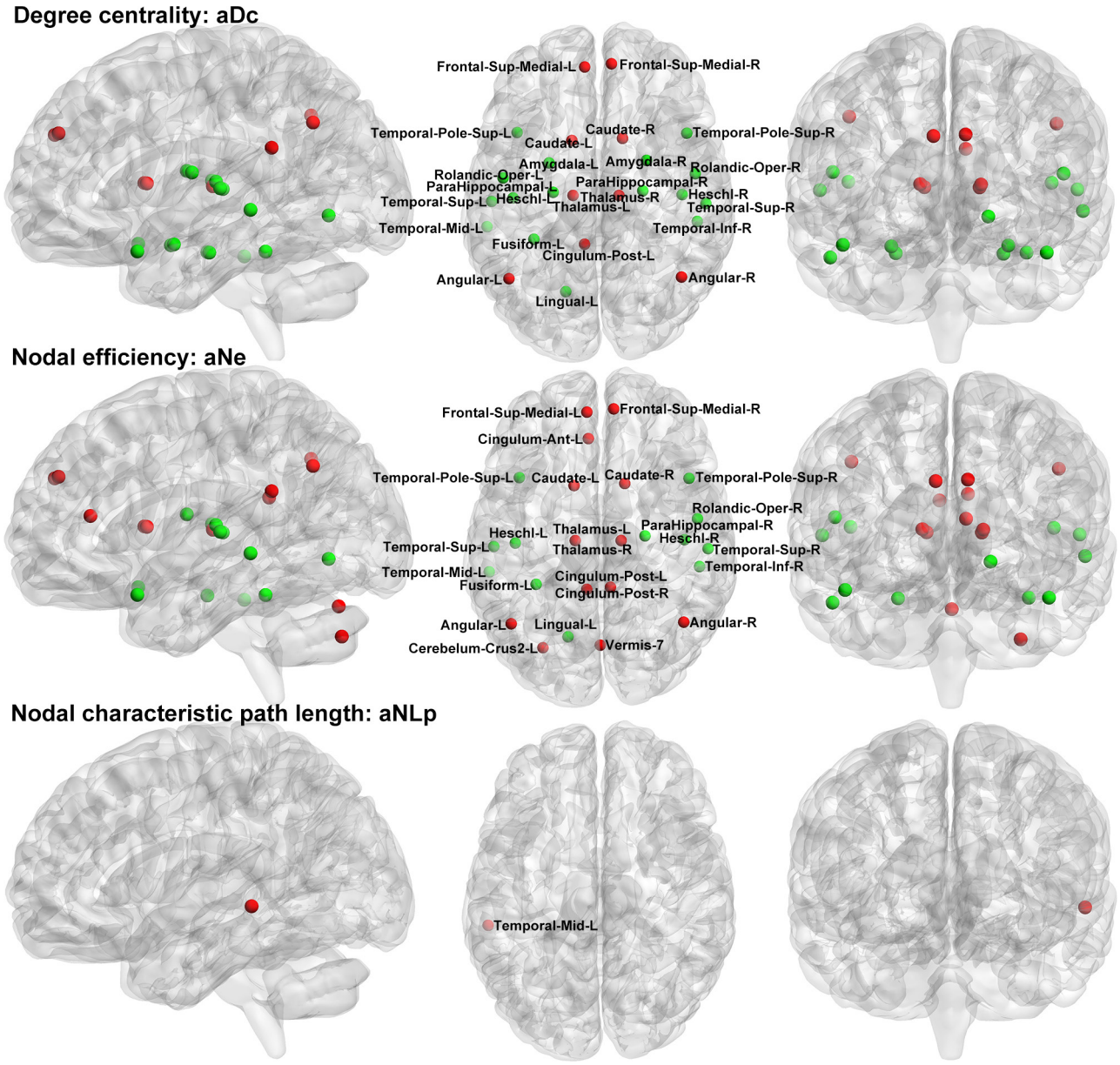

Figure 3 Patients with schizophrenia exhibit the altered area under the curve (AUC) for degree centrality and nodal efficiency in almost the same brain regions. Patients show an increased AUC for nodal characteristic path length in the temporal gyrus compared with healthy controls. aDc = area under the curve for degree centrality; aNe = area under the curve for nodal efficiency; aNLp = area under the curve for nodal characteristic path length.

FS,[8] was retained by SZPs. However, despite maintaining a functional network modular architecture, SZPs demonstrated lower clustering and local information communication. Moreover, SZPs exhibited increased AUC for synchronisation, hierarchy and Z-score of hierarchy, as well as synchronisation in certain sparsity networks. These metrics assess the tendency of all nodes to fluctuate or oscillate in the same wave pattern.[2] Therefore, nodes in SZPs are more prone to fluctuations or oscillation within the same wave pattern than those in HCs, suggesting a decreased capacity for specialised processes.[13] FS refers to the specialised processing capacity within closely connected groups of brain regions.[1] Therefore, the decreased Cp and Eloc, accompanied by increased synchronisation and hierarchy, consistently highlight the presence of reduced global FS in SZPs. Compared with HCs, SZPs exhibited lower assortativity and Z-score of assortativity, as well as Z-score of assortativity in certain sparsity networks. Assortativity, which assesses the correlation between the degrees of nodes at opposite ends of an edge, serves as a metric for evaluating the resilience of functional networks.[1 2] Thus, SZPs demonstrated reduced resilience in functional networks, rendering them more susceptible to insult.[1]

In summarising the global network perspective findings, SZPs exhibited preserved small-worldness and global FI capabilities. However, a notable impairment was observed in the ability of global FS and resilience against external perturbations.

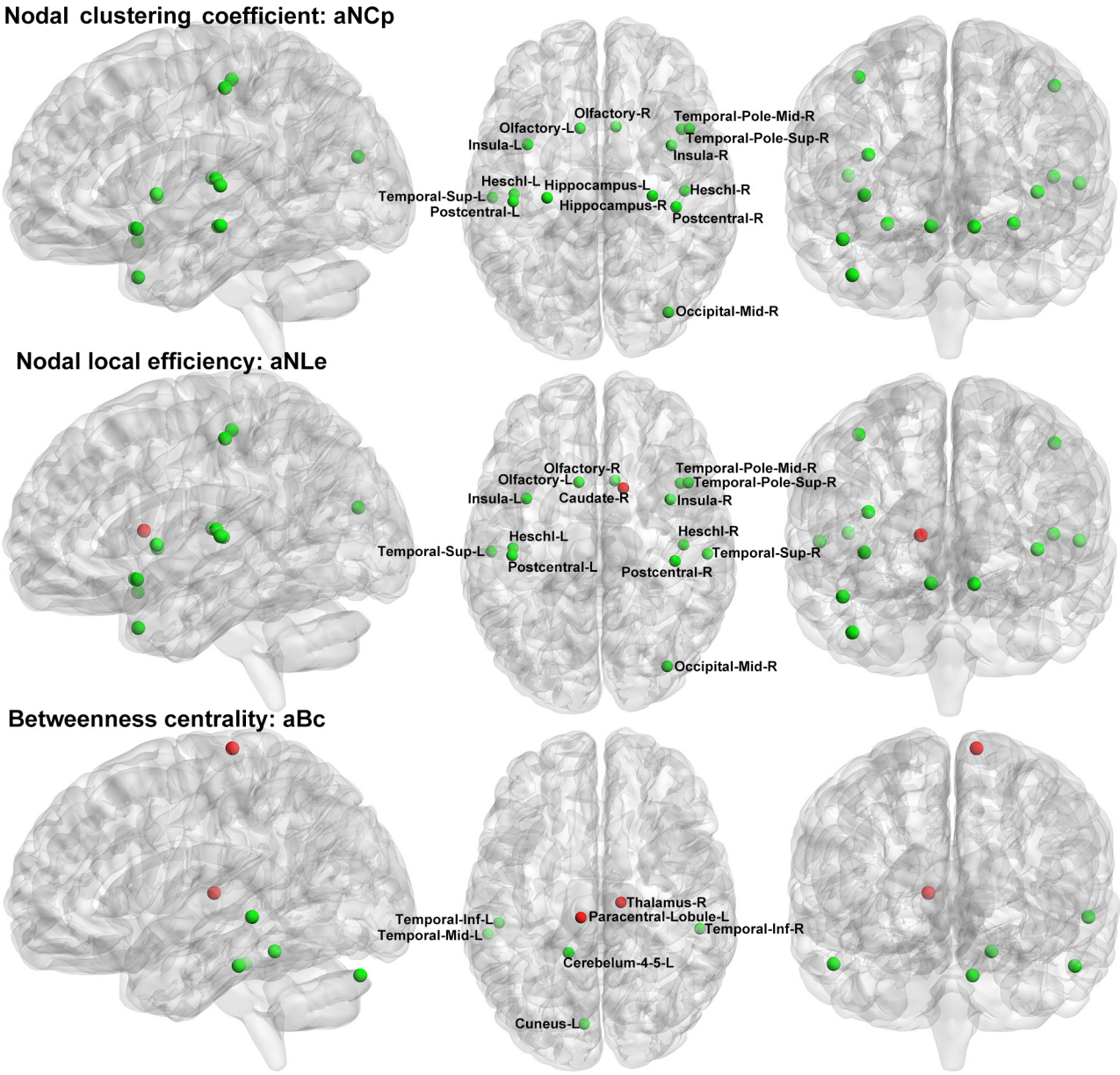

Figure 4 Patients with schizophrenia show a decreased area under the curve (AUC) for nodal clustering coefficient and nodal local efficiency in almost the same brain regions. Patients exhibit altered AUC for betweenness centrality. aBc = area under the curve for betweenness centrality; aNCp = area under the curve for nodal clustering coefficient; aNLe = area under the curve for nodal local efficiency.

Nodal network metrics

Both Dc and Ne assess nodal capacity for FI.[1] SZPs showed altered AUC for Dc and Ne in nearly the same brain areas. Consequently, these metrics mutually supported each other, suggesting a decreased nodal capacity for FI in the sensory areas and a compensatory increase in the cognition and information integration areas of SZPs. Both NCp and NLe measure nodal capacity for FS.[1] SZPs showed decreased AUC for these metrics in almost the same brain areas. Thus, the findings in the two metrics confirmed each other, suggesting that SZPs had decreased nodal capacity for FS in the sensory areas. Furthermore, the findings in Bc and NLp further verified these conclusions.

In summarising the nodal network perspective findings, SZPs exhibited reduced nodal capacity for FI and FS in the sensory areas, accompanied by a compensatory increase in nodal capacity for FI in the cognition and information integration areas.

Associations between TP-FCS and symptoms or cognitions

Despite the enhanced synchronisation in SZPs than HCs, the negative correlation between the AUC for synchronisation and the severity of positive symptoms in SZPs suggests that this heightened synchronisation may serve as a resistance or compensatory mechanism against the exacerbation of positive symptoms among SZPs. An association was also determined between

Table 1 Correlations between topological properties and symptoms or cognitions in patients after controlling for age, gender and educational level

Symptom and cognitive domains	Scales	AUC for topological properties	r	P value	R^2	df
Positive symptoms of schizophrenia	P scale	Synchronisation	–0.13	0.005	0.02	488
Negative symptoms of schizophrenia	N scale	Global network efficiency	–0.09	0.050	0.01	488
		Betweenness centrality in the right gyrus rectus	–0.17	< 0.001	0.03	488
Speed of processing	BACS: symbol coding	Betweenness centrality in the right parahippocampal gyrus	0.23	< 0.001	0.05	233
		Betweenness centrality in the right gyrus rectus	0.26	< 0.001	0.07	233
	Category fluency: animal naming	Clustering coefficients	0.15	0.020	0.02	232
		Network local efficiency	0.15	0.021	0.02	232
		Gamma	0.14	0.038	0.02	232
	Trail making test: part A	Hierarchy	0.14	0.033	0.02	231
		Assortativity	–0.16	0.014	0.03	231
		The Z-score of assortativity	–0.16	0.015	0.03	231
		Network local efficiency	–0.16	0.016	0.03	231
		Nodal local efficiency in the right paracentral gyrus	–0.24	< 0.001	0.06	231
		Clustering coefficients	–0.15	0.018	0.02	231
		Lambda	–0.15	0.023	0.02	231
Visual learning	BVMT-R	Betweenness centrality in the left superior occipital gyrus	0.24	< 0.001	0.06	232
		Clustering coefficients	0.16	0.015	0.03	232
The ability to inhibit cognitive interference	Color-word interference	Nodal local efficiency in the cerebellum vermis IV/V	0.25	< 0.001	0.06	220

AUC, area under the curve; BACS, Brief Assessment of Cognition in Schizophrenia; BVMT-R, Brief Visuospatial Memory Test-Revised; N scale, negative scale; P scale, positive scale.

increased negative symptoms and decreased Eg, together with reduced Bc in the right gyrus rectus. This finding suggests that negative symptoms in patients may result from a reduction in the efficiency of global information communication and a decrease in the effect of the right gyrus rectus on the flow of information between other nodes.[5 6 9]

We found that global network metrics (including Cp, Eloc, assortativity, hierarchy, Gamma and Lambda) and nodal network metrics (including Bc and NLe) were associated with cognitive functions (including the speed of processing, visual learning and the ability to inhibit cognitive interference) in SZPs. Moreover, SZPs exhibited decreased Cp, Eloc and assortativity, as well as increased hierarchy. Consequently, the observed A-TP-SCs indicate that decreased global FS and resilience in functional networks are pathological impairments in schizophrenia.[6–8]

Limitations

A notable strength of this study lies in its distinction as the first large-scale exploration of TP-FCs and A-TP-SCs in SZPs. The observed correlation coefficients ranged from 0.08 to 0.26, with most coefficients below 0.2. Consequently, the minimum sample size of 200 SZPs might not adequately identify A-TP-SC in SZPs.[12] Another strength is evident in the high consistency of results concerning TP-FCs, measuring the same attribute of the functional connectomes. In addition, there are consistently observed associations between diminished cognitive functions and decreased FS and resilience in SZPs. These robustly support the conclusions of this study.

However, we did not explore factors (eg, age, gender, economic status, geographical source and antipsychotic use) affecting SZP topology because of the subgroup sample size requirement of more than 200 SZPs. SZPs and HCs in this study were age-matched and gender-matched, but SZPs exhibited a

lower educational level, consistent with real-world reports. The predominant age distribution of patients corresponds to the predominant age range of SZPs in China (18–34 years).[23] To verify whether including patients in the rapid developmental phase of adolescence, specifically those aged 12–16, impacted the study results, we excluded patients and HCs of this age group (43 SZPs and 31 HCs). The results remained consistent with those of all subjects. Thus, including patients and HCs aged 12–16 did not impact the study results. However, since the number of patients and HCs aged 12–16 in this study was relatively small, we cannot determine whether age or development might influence the TP-FCs, or whether there are any differences in TP-FCs between adolescents and adults. A previous study found that nodal characteristics such as betweenness centrality decreased, while degree centrality and nodal efficiency increased with age in healthy Chinese participants.[24] Therefore, age and development may influence the TP-FCs. While no significant gender difference was observed between SZPs and HCs, the patient group had a higher proportion of women. This discrepancy is attributed to dataset E recruiting more women than men, contrasting with approximate headcount and schizophrenia prevalences in both genders in China.[23] A recent meta-analysis revealed a gender influence on Eloc in SZPs,[4] emphasising the need for further research on gender impact on TP-FCs in SZPs.[25] Sourced from four cities (three datasets from Xinxiang and one each from Nanjing, Changsha and Foshan), the data encompass the northern, central and southern regions of China. Notably, the dataset lacks representation from the economically disadvantaged western regions of China. Previous studies on TP-FCs in SZPs did not consider economic factors; nonetheless, the impact of the economy on TP-FCs in China needs to be explored because of its recognised effects on other functional brain metrics.[26] Moreover, the geographical source potentially includes many factors such as economy, culture and environment that may influence the TP-FC results.[27] However, with the current sample, we were unable to explore this issue. Analysing the data separately from each site would drastically reduce the sample size, thereby significantly compromising statistical power. Thus, with the current sample, the consistency of results across different data sources would not adequately address whether the geographical source of the data may influence the TP-FC results. Future multicentre studies with large samples at each site are needed to explore the influence of the geographical source of the data on the TP-FCs. A recent meta-analysis underscored topology disparities in structural connectome studies between untreated SZPs and those with antipsychotic use.[4] However, the effect of antipsychotic use on TP-FCs was not evaluated in the meta-analysis because of data limitations. The current study includes both drug-naive and antipsychotic-exposed SZPs, emphasising the need for further research into the influence of antipsychotic use on TP-FCs.

Implications

In summary, this large-scale study investigated TP-FCs and A-TP-SCs in SZPs. Analysis of global network metrics revealed that SZPs maintained small-worldness and global FI capacity, despite compromised global FS and resilience against insults. Exploring nodal network metrics, we observed a reduction in nodal FI and FS capacity in the sensory areas of SZPs. Conversely, a compensatory increase in nodal FI capacity was found in areas associated with cognition and information integration. A-TP-SCs were identified, confirming that the diminished FS and resilience are pathological impairments in schizophrenia. The results of A-TP-SCs or TP-FCs, which measure the same attribute of the functional connectomes, are highly internally unified, supporting the findings of this study.

Furthermore, several potential clinical implications and guidance for the treatment and intervention of SZPs can be drawn from these findings. First, targeted interventions for specific brain regions showing abnormal TP-FCs are recommended. Neuromodulation techniques, such as transcranial magnetic stimulation or transcranial direct current stimulation, might be used to modulate brain network connectivity and potentially improve TP-FCs.[28 29] Second, personalised treatment plans should be developed. Assessments of TP-FCs might be incorporated into the diagnostic and monitoring process to help create individualised treatment plans.[30] Furthermore, symptom-specific approaches should be considered to address the symptoms and cognitive deficits associated with diminished functional segregation and resilience. Third, changes in TP-FCs may be used to monitor treatment effects. For instance, improvements in TP-FCs following pharmacological treatment or cognitive therapy could be quantified, providing objective measures of treatment efficacy. Lastly, further research into the mechanisms underlying diminished functional segregation and resilience in schizophrenia will facilitate the development of more targeted and effective treatments. Supporting the development of innovative therapies aimed at enhancing brain functional segregation and resilience could potentially lead to new treatment avenues. By integrating these insights into clinical practice, healthcare providers can improve the effectiveness of treatments for schizophrenia, leading to better management of symptoms and enhanced cognitive functioning for SZPs.

Author affiliations
[1]Department of Psychiatry, National Clinical Research Center for Mental Disorders, and National Center for Mental Disorders, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[2]Department of Psychiatry, the Affiliated Brain Hospital of Nanjing Medical University, Nanjing Brain Hospital, Nanjing, Jiangsu, China
[3]Department of Psychiatry, The Second Affiliated Hospital of Xinxiang Medical University, Xinxiang, Henan, China
[4]Department of Clinical Psychology, Psychology School of Xinxiang Medical University, Xinxiang, Henan, China

[5]Department of Psychosomatic Medicine, The Second Affiliated Hospital of Xinxiang Medical University, Xinxiang, Henan, China
[6]Department of Psychiatry, The Third People's Hospital of Foshan, Foshan, Guangdong, China
[7]Department of Radiology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[8]Department of Radiology, Tianjin Medical University General Hospital, Tianjin, China
[9]Department of Psychiatry, Qiqihar Medical University, Qiqihar, Heilongjiang, China

Contributors HY and YHan participated in methodology, data curation, formal analysis and manuscript writing. XX, HZ, YHe, GX and HL were engaged in data curation. FL contributed to methodology. PL contributed to conceptualisation. JZ contributed to conceptualisation and methodology. WG was involved in methodology, data curation, manuscript review and funding acquisition. All authors had complete access to the study data and shared final responsibility for the decision to submit for publication. WG acts as the guarantor of this study.

Funding This study was funded by the National Natural Science Foundation of China (82171508) and the Natural Science Foundation of Hunan (2023JJ30758).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University (registration number: 20161215, 20151230 and 2021-33), the Ethics Committee of the Second Xiangya Hospital of Central South University (registration number: 2012045), the Ethics Committee of the Affiliated Nanjing Brain Hospital of Nanjing Medical University (registration number: 2017-KY017) and the Medical Ethics Committee of the Third People's Hospital of Foshan (registration number: FSSY-LS201915). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID iD
Wenbin Guo http://orcid.org/0000-0002-1626-2465

REFERENCES

1 Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 2010;52:1059–69.
2 Wang J-H, Zuo X-N, Gohel S, *et al*. Graph theoretical analysis of functional brain networks: test-retest evaluation on short-and long-term resting-state functional MRI data. *PLoS One* 2011;6:e21976.
3 Kambeitz J, Kambeitz-Ilankovic L, Cabral C, *et al*. Aberrant functional whole-brain network architecture in patients with schizophrenia: a meta-analysis. *Schizophr Bull* 2016;42 Suppl 1:S13–21.
4 Gao Z, Xiao Y, Zhu F, *et al*. The whole-brain connectome landscape in patients with schizophrenia: a systematic review and meta-analysis of graph theoretical characteristics. *Neurosci Biobehav Rev* 2023;148:105144.
5 Yu Q, Sui J, Rachakonda S, *et al*. Altered topological properties of functional network connectivity in schizophrenia during resting state: a small-world brain network study. *PLoS ONE* 2011;6:e25423.
6 Yu M, Dai Z, Tang X, *et al*. Convergence and divergence of brain network dysfunction in deficit and non-deficit schizophrenia. *Schizophr Bull* 2017;43:1315–28.
7 Erdeniz B, Serin E, İbadi Y, *et al*. Decreased functional connectivity in schizophrenia: the relationship between social functioning, social cognition and graph theoretical network measures. *Psychiatry Res Neuroimaging* 2017;270:22–31.
8 Bordier C, Nicolini C, Forcellini G, *et al*. Disrupted modular organization of primary sensory brain areas in schizophrenia. *Neuroimage Clin* 2018;18:682–93.
9 Su T-W, Hsu T-W, Lin Y-C, *et al*. Schizophrenia symptoms and brain network efficiency: a resting-state fMRI study. *Psychiatry Research: Neuroimaging* 2015;234:208–18.
10 Ma Q, Tang Y, Wang F, *et al*. Transdiagnostic dysfunctions in brain modules across patients with schizophrenia, bipolar disorder, and major depressive disorder: a connectome-based study. *Schizophr Bull* 2020;46:699–712.
11 Marek S, Tervo-Clemmens B, Calabro FJ, *et al*. Reproducible brain-wide association studies require thousands of individuals. *Nature New Biol* 2022;603:654–60.
12 DeYoung CG, Sassenberg T, Abend R, *et al*. Reproducible between-person brain-behavior associations do not always require thousands of individuals. *PsyArXiv* [Preprint] 2022.
13 Peeters SCT, Gronenschild EHBM, van Amelsvoort T, *et al*. Reduced specialized processing in psychotic disorder: a graph theoretical analysis of cerebral functional connectivity. *Brain Behav* 2016;6:e00508.
14 Wang Y-W, Chen X, Yan C-G. Comprehensive evaluation of harmonization on functional brain imaging for multisite data-fusion. *Neuroimage* 2023;274:120089.
15 Fortin J-P, Parker D, Tunç B, *et al*. Harmonization of multi-site diffusion tensor imaging data. *Neuroimage* 2017;161:149–70.
16 Dai Y-R, Wu Y-K, Chen X, *et al*. Eight-week antidepressant treatment changes intrinsic functional brain topology in first-episode drug-naïve patients with major depressive disorder. *J Affect Disord* 2023;329:225–34.
17 Wang S, Zhan Y, Zhang Y, *et al*. Abnormal functional connectivity strength in patients with adolescent-onset schizophrenia: a resting-state fMRI study. *Eur Child Adolesc Psychiatry* 2017;26:839–45.
18 Guo W, Liu F, Liu J, *et al*. Abnormal causal connectivity by structural deficits in first-episode, drug-naive schizophrenia at rest. *Schizophr Bull* 2015;41:57–65.
19 Shan X, Liao R, Ou Y, *et al*. Increased regional homogeneity modulated by metacognitive training predicts therapeutic efficacy in patients with schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2021;271:783–98.
20 Shan X, Zhang H, Dong Z, *et al*. Increased subcortical region volume induced by electroconvulsive therapy in patients with schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2021;271:1285–95.
21 Gao S, Lu S, Shi X, *et al*. Distinguishing between treatment-resistant and non-treatment-resistant schizophrenia using regional homogeneity. *Front Psychiatry* 2018;9:282.
22 Jing H, Zhang C, Yan H, *et al*. Deviant spontaneous neural activity as a potential early-response predictor for therapeutic interventions in patients with schizophrenia. *Front Neurosci* 2023;17:1243168.
23 Huang Y, Wang Y, Wang H, *et al*. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *Lancet Psychiatry* 2019;6:211–24.
24 Shah C, Liu J, Lv P, *et al*. Age related changes in topological properties of brain functional network and structural connectivity. *Front Neurosci* 2018;12:318.
25 Li X, Zhou W, Yi Z. A glimpse of gender differences in schizophrenia. *Gen Psychiatr* 2022;35:e100823.
26 Finn AS, Minas JE, Leonard JA, *et al*. Functional brain organization of working memory in adolescents varies in relation to family income and academic achievement. *Dev Sci* 2017;20:e12450.
27 Zhang Y, Fan L, Caspers S, *et al*. Cross-cultural consistency and diversity in intrinsic functional organization of Broca's Region. *Neuroimage* 2017;150:177–90.
28 Xie Y, He Y, Guan M, *et al*. Low-frequency rTMS treatment alters the topographical organization of functional brain networks in schizophrenia patients with auditory verbal hallucination. *Psychiatry Res* 2022;309:114393.
29 Ruttorf M, Kristensen S, Schad LR, *et al*. Transcranial direct current stimulation alters functional network structure in humans: a graph theoretical analysis. *IEEE Trans Med Imaging* 2019;38:2829–37.
30 Lin P, Sun J, Lou X, *et al*. Consensus on potential biomarkers developed for use in clinical tests for schizophrenia. *Gen Psychiatr* 2022;35:e100685.

Haohao Yan is a second-year PhD student in the Department of Psychiatry at the Second Xiangya Hospital of Central South University in China. He obtained his master's degree in Psychiatry and Mental Health from the Second Xiangya Hospital of Central South University, China in 2022. He obtained his bachelor of Medicine degree in Clinical Medicine from Nanchang University, China in 2019. His current main research interests include employing a multimodal imaging approach to comprehend the structural and functional dysfunctions in the brains of patients with mental disorders. Furthermore, he explores models for diagnosing and predicting treatment responses based on neuroimaging data. His main research interests include identifying biomarkers for mental disorders.

Yiding Han is a third-year master's student in the Department of Psychiatry at the Second Xiangya Hospital of Central South University in China. She obtained her bachelor of Psychiatry degree from Xinxiang Medical University, China in 2021. Her current research focuses on the cognitive impairments of mental disorders. Her main research interests include identifying brain networks underlying cognitive impairments.