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Impact of schizophrenia-associated risk genes on brain functional networks and executive deficits: a study of individuals with schizophrenia and genetic high risk

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Original Article

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Abstract

Background. Schizophrenia (SCZ) and genetic high-risk (GHR) individuals exhibit deficits in brain functional networks and cognitive function, potentially impacted by SCZ risk genes. This study aims to delineate these impairments in SCZ and GHR individuals, and further explore how risk genes affect brain networks and executive function.

Methods. A total sample size of 292 participants (100 SCZ, 68 GHR, and 124 healthy controls [HCs]) in the study. The Wisconsin Card Sorting Test (WCST) and resting-state functional magnetic resonance imaging (rs-fMRI) are utilized to evaluate executive function and brain network topology. SCZ-related polygenic risk scores (SCZ-PRS) were used to evaluate genetic risk levels. WCST and PRS were not applied to all participants.

Results. Significant reductions in nodal efficiency and degree centrality (D_{nodal}) were observed within the right median cingulate and paracingulate gyri (MCPG_R) in both SCZ and GHR groups, compared to HCs. There were significant correlations between SCZ-PRS, D_{nodal} in MCPG_R, and WCST scores. Moreover, D_{nodal} in MCPG_R completely mediated the relationship between SCZ-PRS and executive function. The enrichment analysis of these risk genes indicates their involvement in biological processes of signal transduction and synaptic transmission.

Conclusions. This study highlights the pivotal role of impaired cingulate function in mediating the effects of genetic risks on executive deficits, offering new insights into the genetic-neurocognitive nexus in schizophrenia and potential targets for clinical interventions.

Introduction

Schizophrenia (SCZ) is a markedly heritable neurodevelopmental disorder characterized by brain functional and structural abnormalities alongside cognitive impairments (Jauhar, Johnstone, & McKenna, 2022). Existing heritability estimates range from 64% in familial investigations to approximately 80% in twin studies (Hilker et al., 2018; Lichtenstein et al., 2009; Sullivan, Kendler, & Neale, 2003). Relatives of patients with SCZ face a significantly higher risk than individuals without a family history, possibly up to 11-fold (Le, Kaur, Meiser, & Mj, 2020) and manifest subtle changes in imaging traits and cognitive performance (da Motta, Pato, Barreto Carvalho, & Castilho, 2021; Dodell-Feder, Delisi, & Hooker, 2014). The study of individuals with SCZ and those at genetic high risk (GHR) is pivotal for elucidating the genetic underpinnings of neurodevelopmental and cognitive impairment.

Since the late 19th century, pioneers have suggested that SCZ might stem from brain connectivity aberrations (Collin, Turk, & van den Heuvel, 2016), a concept that evolved into the dysconnection hypothesis later proposed by Friston and Frith (Friston & Frith, 1995). Advancements in neuroimaging have supported these theories, revealing anomalies in both white matter fibers and functional connectivity (FC) in patients with SCZ (Camchong, MacDonald, Bell, Mueller, & Lim, 2011; Carreira Figueiredo, Borgan, Pasternak, Turkheimer, & Howes, 2022; W. Zhu, Wang, Yu, Zhang, & Zhang, 2023). The application of graph theory and network analysis to neuroimaging data further identified atypical changes in brain networks of patients with SCZ, such as altered clustering coefficients and efficiency levels (Y. Liu et al., 2008), deepening our understanding of the widespread connectivity disorder in SCZ. A crucial question for future research, highlighted by a meta-analysis, is whether disparities in functional networks

represent susceptibility traits inherent in subjects genetically predisposed to SCZ (Kambeitz et al., 2016).

GHR individuals hold great value, as they can identify genetic liability across various phenotypes and reflect susceptibility. Approximately 62.5% of functional dysconnectivity is linked to genetic predisposition (Guo et al., 2020; Yin et al., 2021). Shared abnormalities were observed in both SCZ and GHR individuals, such as decreased FC, lower clustering coefficients, and higher global efficiency of networks (Lin et al., 2021; Lo et al., 2015). Noteworthily, despite the observed aberrant changes in brain function of GHR, they do not progress to SCZ but rather exhibit cognitive impairments (da Motta et al., 2021).

Cognitive function relies on the complex neural coordination within brain networks (Shine et al., 2019, 2016; van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009), and its impairments are associated with brain functional networks in patients with SCZ (Bassett et al., 2009; He et al., 2012; Menon, Palaniyappan, & Supekar, 2023). Executive function as a vitally cognitive domain is impaired in both SCZ and GHR individuals (da Motta et al., 2021; Thuaire, Rondepierre, Vallet, Jalenques, & Izaute, 2022). Moreover, machine-learning analyses have further divulged that the more the functional brain patterns of GHR individuals approximated those of patients with SCZ, the lower their cognitive assessment scores were (Jing et al., 2019; W. Liu et al., 2020). These studies indicate that SCZ genetic loadings may be crucial in influencing the dysconnection of SCZ brain networks and cognitive impairments.

SCZ, characterized by polygenic variations, can be initially identified via genome-wide association studies (GWASs) aimed at discerning millions of SCZ-associated single nucleotide polymorphisms (SNPs) dispersed throughout the genome (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Subsequently, polygenic risk scores (PRSs) are utilized to calculate the additive genetic susceptibility of each individual, complemented by functional gene enrichment analysis (A. R. Martin, Daly, Robinson, Hyman, & Neale, 2019). Our preceding study identified a correlation between SCZ-PRS and deficits in local efficiency based on structural hemispheric asymmetry in SCZ and GHR cohorts (Zhu et al., 2021). One study involving two cohorts found that SCZ-PRS is associated with a wide functional connectome in healthy controls (HCs) and a reduced connectome correlated with intelligence quotient (IQ) in SCZ (Cao, Zhou, & Cannon, 2021). Additionally, the fractional amplitude of low-frequency fluctuations (fALFF) was found to mediate the association between SCZ-susceptible SNPs and working memory in a mixed SCZ and HC cohort (Luo et al., 2018). However, current research into the relationship among SCZ-PRS, brain functional networks, and executive deficits is scarce. Whether and how SCZ-PRS influences cognitive impairments in SCZ and GHR individuals through the mediation of neural development in functional networks remains unclear.

To explore the relationships among SCZ-associated risk genes, function networks, and neurocognition in SCZ and GHR, this study proposes two hypotheses: first, that SCZ and GHR share altered functional networks, where these abnormal networks are associated with SCZ-related risk genes and contribute to executive deficits. Second, compared to GHR and HC, SCZ exhibits unique disease-specific alterations, characterized by broader network dysconnectivities. Based on these hypotheses, the study outlines four aims: identify common functional network alterations and executive impairments in SCZ and GHR, explore whether these shared changes are associated with risk genes, elucidate how risk genes have impacts and their biological role, and finally, identify disease-specific changes.

Methods

Participants

This study comprised a cohort of 292 participants (aged 18–55 years), comprising 100 SCZ patients, 68 GHR individuals, and 124 HCs.

The SCZ patients were recruited from two clinical centers: the First Affiliated Hospital of China Medical University and the Shenyang Mental Health Centre. The GHR participants were all first-degree relatives of patients presenting with SCZ in these two clinical centers. HCs were recruited from the local community via targeted advertisements. All participants underwent psychiatric evaluation using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) Axis I Disorders (SCID-I). Assessments were conducted by two trained psychiatrist co-authors (S.T. and Z.Y.). SCZ participants met DSM-IV-TR diagnostic criteria. GHR individuals showed no personal history of Axis I disorders, and HCs exhibited neither personal nor familial history of Axis I disorders. Moreover, GHR underwent the Structured Interview for Prodromal Syndromes (SIPS) to confirm the absence of prodromal psychotic symptoms.

All participants were subjected to strict exclusion criteria, which encompassed the following: (1) substance abuse or dependence, including alcohol; (2) presence of any major medical condition; (3) neurological disorders; (4) history of head trauma resulting in loss of consciousness for ≥5 min; (5) contraindications for MRI; and (6) suboptimal quality of acquired MRI data.

Ethical approval for the study was obtained from the Medical Science Research Ethics Committee of the First Affiliated Hospital of China Medical University ([2012]25-1), and written informed consent was obtained from all participants.

Clinical and cognitive data

To assess symptom severity, three scales were applied: the Brief Psychiatric Rating Scale (BPRS) (Bech, Larsen, & Andersen, 1988), the 17-item version of the Hamilton Rating Scale for Depression (HAMD-17) (Hamilton, 1960), and the Hamilton Rating Scale for Anxiety (HAMA) (Hamilton, 1959).

To evaluate executive cognition, the Wisconsin Card Sorting Test (WCST) was completed by 56 patients with SCZ, 57 individuals at GHR, and 120 HCs, including the scores of correct responses (CR), categories completed (CC), total errors (TE), perseverative errors (PE), and nonperseverative errors (NPE).

MRI data

Image acquisition

MRI scans were conducted at the Image Institute of the First Affiliated Hospital of China Medical University utilizing a GE Signa HD 3.0-T scanner (General Electric, Milwaukee, USA). Resting-state functional MRI (rs-fMRI) data were collected with a gradient-echo planar imaging sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°, slice thickness = 3 mm, number of slices = 35, no gap, FOV = 240 × 240 mm^2, matrix = 64 × 64), including 200 volumes over 400 s. To reduce noise and motion, participants used earplugs and foam pads and were instructed to keep their eyes closed without falling asleep during the scan.

Data preprocessing

Rs-fMRI data preprocessing, conducted using SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/) and DPABI6.1 (Advanced edition;

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Yan, Wang, Zuo, & Zang, 2016) on MATLAB 2022a, involved steps such as converting DICOM to NIFTI, removing the first 10 time points, slice timing, realignment for excessive head motion (>3 mm or 3° were excluded), spatial normalization to MNI space (3 mm voxels), Gaussian smoothing (6 mm FWHM), linear detrending, removing nuisance covariates (Friston 24, white matter, cerebrospinal fluid, global signals), and low-frequency filtering (0.01–0.08 Hz).

Construction of brain functional network

To construct a brain functional network, the Automated Anatomical Labeling (AAL) template divided the brain into 90 regions of interest (ROIs), serving as network nodes. Edges were established by FC between ROIs. Blood oxygen level-dependent signal averages from voxels in each ROI provided time series data. A 90 × 90 matrix emerged from calculating Pearson correlation coefficients among ROI pairs, later transformed into Fisher's Z-scores. A weighted approach then assigned varying weights to edges based on FC strength (Wen et al., 2018; Yang et al., 2021).

Brain functional network analysis

To ensure the small-world attributes of the network and align with prior studies, a wide range of network sparsity thresholds was set: 0.09–0.30 (step size 0.01) (Su, Hsu, Lin, & Lin, 2015; Zhang et al., 2011). Supplementary Table 1 provides a explanation of the network metrics, as established in previous studies (Wang, Zuo, & He, 2010; Wu, Li, Zhou, Zhang, & Long, 2020). This study assessed global efficiency (E_{glob}), local efficiency (E_{loc}), and the shortest path length (L_p), alongside nodal metrics including nodal degree centrality (D_{nodal}), nodal global efficiency (E_{nodal}), and nodal local efficiency (E_{nodal_loc}). Areas under the curve (AUCs) were calculated for these metrics across all sparsity thresholds to provide a summary scalar. The analysis was facilitated by GRETNA, a dedicated network analysis toolbox operating on the MATLAB platform (Wang et al., 2015).

Genetic data

Genotyping and imputation

Genome-wide genotype data were available for 78 participants (30 SCZ and 48 GHR). Blood samples were obtained between 10:00 and 15:00, utilizing ethylenediaminetetraacetic acid anticoagulant tubes, and subsequently stored at a temperature of −80 °C until subjected to assay. Genomic DNA extraction from the whole blood samples was conducted by standard methods. The Illumina Global Screening Array-24 v1.0 BeadChip (Illumina, San Diego, CA) was employed for genome-wide variant screening, rendering data of 642,824 predetermined gene variants, alongside 53,411 custom variants. Comprehensive criteria for data exclusion and genotype imputation can be found in the Supplementary Materials (Section 1, page 1).

Calculation of PRSs

PRSs were computed by multiplying the count of risk alleles by the effect size attributed to each allele, followed by the summation of the products across all SNPs for each individual (Martin et al., 2019). In line with our previous study (Zhu et al., 2021), we used the 2018 GWAS results as the discovery sample (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. & Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018). In this study, genetic factors associated with SCZ were analyzed in 33,426 individuals with SCZ and 32,541 controls from this dataset. Using our imputed genotyping data as the target sample, we performed p-value clumping in PRSice (www.PRSice.info) to retain strongly correlated SNPs, applying parameters of $r^2 = 0.1$ and a distance of 250 kb. PRSs were then calculated for each participant across eleven p-value thresholds (PTs): 0.0001, 0.001, 0.01, 0.015, 0.02, 0.025, 0.03, 0.035, 0.04, 0.045, and 0.05.

Functional enrichment analyses

Based on the dbSNP database, all SNPs within the SCZ-PRS under a certain p-value threshold most associated with network metrics were extracted and mapped to genes using position-based mapping, aligning SNPs to corresponding gene annotations by their rs names. Specifically, we utilized the latest dbSNP information available in the file All_20180423.vcf.gz, which can be downloaded from ftp://ftp.ncbi.nih.gov/snp/organisms/human_9606_b151_GRCh37p13/VCF/. This file is based on the GRCh37p13 genome build. Further details are provided on the NCBI dbVar resource page at https://www.ncbi.nlm.nih.gov/dbvar/content/org_summary/. The resultant gene lists were then uploaded into DAVID V6.8 (https://DAVID.ncifcrf.gov/) to conduct Gene Ontology analyses (Huang, Sherman, & Lempicki, 2009a; 2009b). Bonferroni correction was applied, ensuring a significance level of 0.05.

Statistical analysis

Differences in demographic, clinical, and cognitive variables

Differences across the three groups were assessed using chi-squared tests to compare sex and handedness variations and one-way analysis of variance (ANOVA) to investigate differences in age and total scores on clinical scales (BPRS, HAMD-17, and HAMA). To discern distinctions in WCST scores, a one-way analysis of covariance (ANCOVA) was used, with sex and age as covariates. In cases where post hoc comparisons were required, a pairwise analysis was performed. The least significant difference (LSD) correction was used for homogenous variance, and the Tamhane correction was used for other cases (significance at adjusted $p < 0.05$).

Differences in network metrics

ANCOVAs with sex and age as covariates were employed to assess differences in global network metrics (E_{glob}, E_{loc}, L_p) and the AUC for each nodal metric (D_{nodal}, E_{nodal}, E_{nodal_loc}) across the 90 nodes (significance at $p_{FDR} < 0.05$).

Relationship between PRS, network metrics, and cognitive tests

In the SCZ and GHR groups, the partial correlation analysis (sex and age as covariates) was applied to investigate the relationship between SCZ-PRS, shared alterations in topological properties, and similar changes in WCST scores observed in both SCZ and GHR individuals (significance at $p_{FDR} < 0.05$). Additionally, mediation analysis was executed to probe the potential impact of the common network metric alterations as mediators on the association between SCZ-PRS (causal variable) and cognitive function (outcome variable), with sex, age, and group as covariates. To conduct this analysis, the PROCESS macro within SPSS (Version 3.2, developed by Dr. Andrew F. Hayes) was utilized, and significance testing was performed using 5000 bias-corrected bootstrap samples. By summarizing the methods used by mediators, standard deviation (SD) and 95% confidence interval (CI) were utilized.

Significance was set at $p < 0.05$ (two-tailed) for all tests. Analyses not specifically delineated were performed using SPSS 26.0.

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Results

Demographic, clinical, and cognitive characteristics

In the total sample with neuroimaging data ($N = 292$), no significant differences in terms of age and sex were observed among the SCZ, GHR, and HC groups. All participants were right-handed. Compared to the GHR and HC groups, the SCZ group exhibited significantly higher scores across the BPRS, HAMD-17, and HAMA total scores (see Table 1).

In the subsample with both neuroimaging and WCST assessments (N = 233), group differences emerged in executive function measures. The WCST scores of CR and CC were the highest in the HC group, followed by the GHR and SCZ groups. The scores of TE, PE, and NPE were the highest in the SCZ group, followed by the GHR and HC groups (see Table 1, Figure 1a).

Within the genetic subsample with PRS data ($N = 78$), age remained balanced across groups, while the SCZ group had a higher female proportion than GHR. This demographic variation was accounted for in subsequent association and mediation analyses through covariance adjustment.

Brain functional network characteristics

In comparison to GHR and HC groups, the SCZ group displayed increased L_p ($p = 0.006$, $p_{FDR} = 0.042$) and reduced E_{glob} ($p = 0.012$, $p_{FDR} = 0.042$), see Figure 1b,c and Supplementary Table 2.

Regarding E_{nodal}, significant distinctions emerged in the right median cingulate and paracingulate gyri (MCPG_R), where post hoc analysis revealed a reduction in both SCZ and GHR groups compared to the HC group ($p < 0.001$, $p_{FDR} < 0.001$). Moreover, in MCPG_R, both SCZ and GHR groups exhibited a decreased D_{nodal} ($p = 0.001$, $p_{FDR} = 0.045$). D_{nodal} in the right middle temporal gyrus (MTG_R) exhibited variance, with the SCZ group surpassing the GHR and HC groups ($p < 0.001$, $p_{FDR} < 0.001$), see Figure 1d–e. E_{nodal_loc} levels were decreased in specific brain regions within the SCZ group, including the left calcarine fissure and surrounding cortex (CAL_L), right calcarine fissure and surrounding cortex (CAL_R), left lingual gyrus (LING_L), and right lingual gyrus (LING_R) ($p < 0.001$, $p_{FDR} < 0.001$), see Figure 1f,g and Supplementary Table 2.

Table 1. Demographic, clinical, and cognitive characteristics of the SCZ, GHR, and HC

Characteristic	Mean ± SD or no. (%)			$F/\chi 2$	p value	Post hoc analysis
n = 292 with Network data	SCZ (n = 100)	GHR (n = 68)	HC (n = 124)			
Age, years	29.37 ± 9.54	28.82 ± 8.28	31.15 ± 9.79	1.687	0.187	–
Female	62 (62%)	34 (50%)	76 (61%)	2.915	0.233	–
Handedness, right	100(100%)	68(100%)	124(100%)	–	–	–
Medication, yes	74 (74%)	N/A	N/A	–	–	–
First episode, yes	62 (62%)	N/A	N/A	–	–	–
Outpatients, yes	87 (87%)	N/A	N/A	–	–	–
Duration, months	33.04 ± 47.03	N/A	N/A	–	–	–
BPRS, total score	32.36 ± 12.07	18.87 ± 1.84	18.47 ± 1.19	114.148	<0.001*	SCZ > HC SCZ > GHR
HAMD–17, total score	7.59 ± 6.49	2.28 ± 3.54	1.22 ± 2.23	60.117	<0.001*	SCZ > HC SCZ > GHR
HAMA, total score	7.41 ± 7.39	1.59 ± 3.21	1.21 ± 2.29	49.113	<0.001*	SCZ > HC SCZ > GHR
n = 233 with Network and WCST	SCZ (n = 56)	GHR (n = 57)	HC (n = 120)			
Age, years	28.71 ± 9.19	29.46 ± 8.47	31.05 ± 9.91	1.353	0.261	–
Female	34 (60.7%)	30 (52.6%)	74 (62%)	1.374	0.503	–
Medication, yes	45 (80%)	N/A	N/A	–	–	–
First episode, yes	37 (66%)	N/A	N/A	–	–	–
Outpatients, yes	48 (86%)	N/A	N/A	–	–	–
Correct responses (CR)	20.89 ± 9.05	26.65 ± 11.28	31.08 ± 11.79	16.434	<0.001*	SCZ < GHR < HC
Categories completed (CC)	2.04 ± 1.84	3.16 ± 2.18	4.07 ± 2.17	18.363	<0.001*	SCZ < GHR < HC
Total errors (TE)	27.00 ± 9.24	21.35 ± 11.28	16.92 ± 11.79	16.003	<0.001*	SCZ > GHR > HC
Perseverative errors (PE)	9.45 ± 6.26	7.12 ± 5.56	5.82 ± 6.53	6.472	0.002	SCZ > GHR > HC
Nonperseverative errors (NPE)	17.55 ± 7.20	14.05 ± 8.07	11.06 ± 7.11	15.139	<0.001*	SCZ > GHR > HC
n = 78 with Network and PRS	SCZ (n = 30)	GHR (n = 48)	HC (n = 0)			
Age, years	28.00 ± 9.36	29.77 ± 8.26	–	−0.875	0.384	–
Female	23 (76.7%)	25 (52.1%)	–	4.714	0.030*	SCZ > GHR

Abbreviations: BPRS, Brief Psychiatric Rating Scale; HAMD-17, the 17-item version of the Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; WCST, Wisconsin Card Sorting Test; PRS, polygenic risk scores.
*$p < 0.05$.

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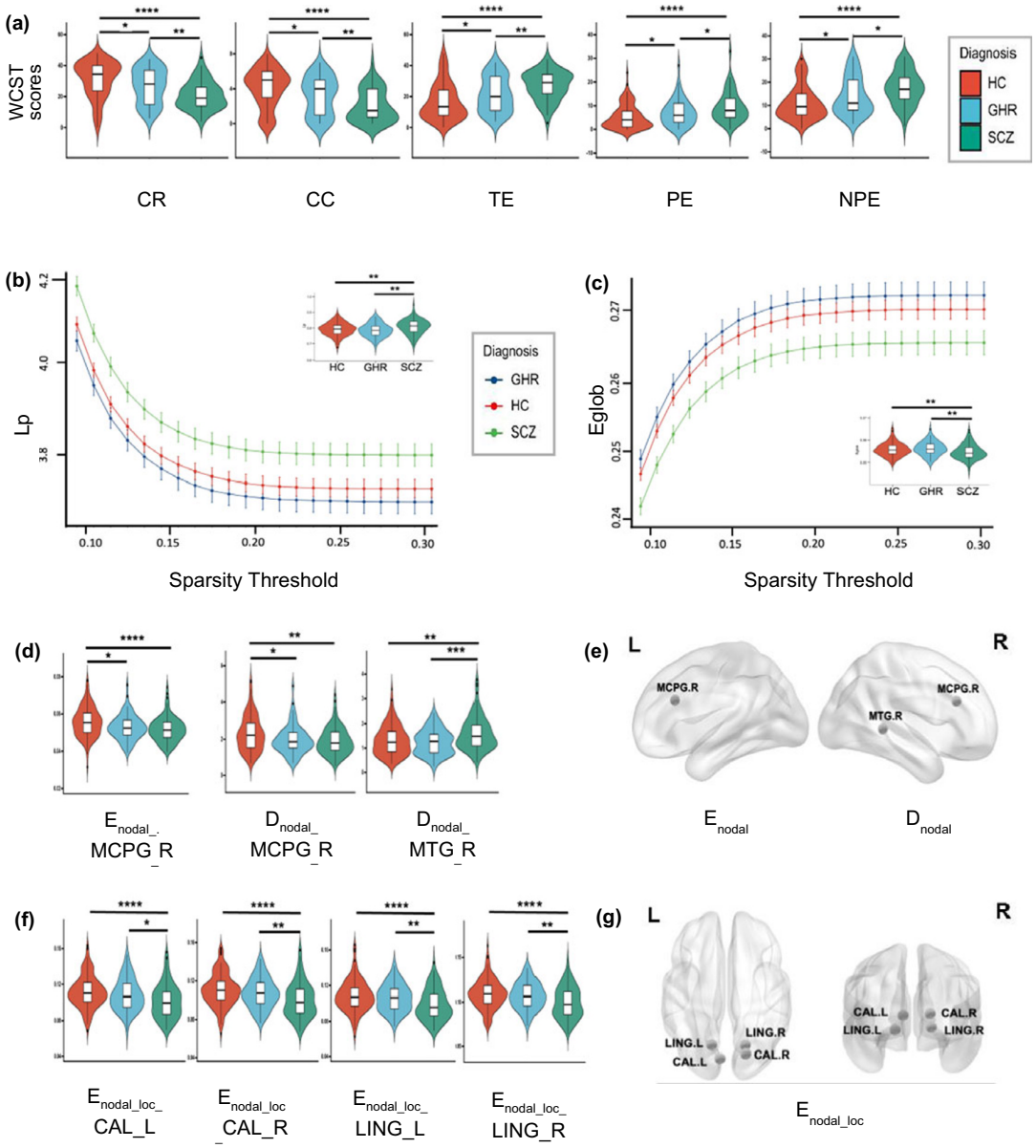

Figure 1. WCST and brain functional network characteristics.
(a) was the violin diagram showing the comparison of WCST scores among groups. (b) LP was increased in the SCZ group. (c) Eglob was decreased in the SCZ group. (d) and (f) were the violin diagram showing the comparison of nodal metrics among groups. (e) and (g) were the regions showing a significant difference in nodal metrics.
Abbreviations: WCST, Wisconsin Card Sorting Test; CR, correct responses; CC, categories completed; TE, total errors; PE, perseverative errors; NPE, nonperseverative errors; L_p, the shortest length path; E_{glob}, global efficiency; E_{nodal}, nodal efficiency; D_{nodal}, nodal degree centrality; E_{nodal_loc}, nodal local efficiency; R, right; L, left; MCPG, median cingulate and paracingulate gyri; MTG, middle temporal gyri; CAL, calcarine fissure and surrounding cortex; LING, lingual gyri.
A significant level of $p_{FDR} < 0.05$.

Correlation between PRS and network metrics

There were 78 individuals (30 SCZ and 48 GHR) with available genetic data (demographic characteristics of participants see Supplementary Table 3). Significant correlations were identified between SCZ-PRS and two nodal metrics – E_{nodal} and D_{nodal} within MCPG_R. These metrics displayed concurrent alterations in both the SCZ and GHR groups. After FDR correction, the association with D_{nodal} in MCPG_R remained significant across six thresholds: PT_0.015 ($r = -0.274$, $p = 0.016$, $p_{FDR} = 0.035$), PT_0.025 ($r = -0.267$, $p = 0.020$, $p_{FDR} = 0.037$), PT_0.035 ($r = -0.298$, $p = 0.009$, $p_{FDR} = 0.049$), PT_0.040 ($r = -0.288$, $p = 0.012$, $p_{FDR} = 0.033$), PT_0.045 ($r = -0.293$, $p = 0.010$, $p_{FDR} = 0.037$), and PT_0.050 ($r = -0.266$, $p = 0.020$, $p_{FDR} = 0.031$). However, there was no significant correlation observed in E_{nodal} after FDR correction (Figure 2 and Supplementary Table 4). There was no association between the PRS and SCZ disease-specific alterations (Supplementary Table 5).

Correlation between network metrics and WCST

There were 113 individuals (56 SCZ and 57 GHR) competed WCST (demographic characteristics of participants see Supplementary Table 6). Significant correlations were established between the five subtest scores and the two nodal metrics - E_{nodal} and D_{nodal} within

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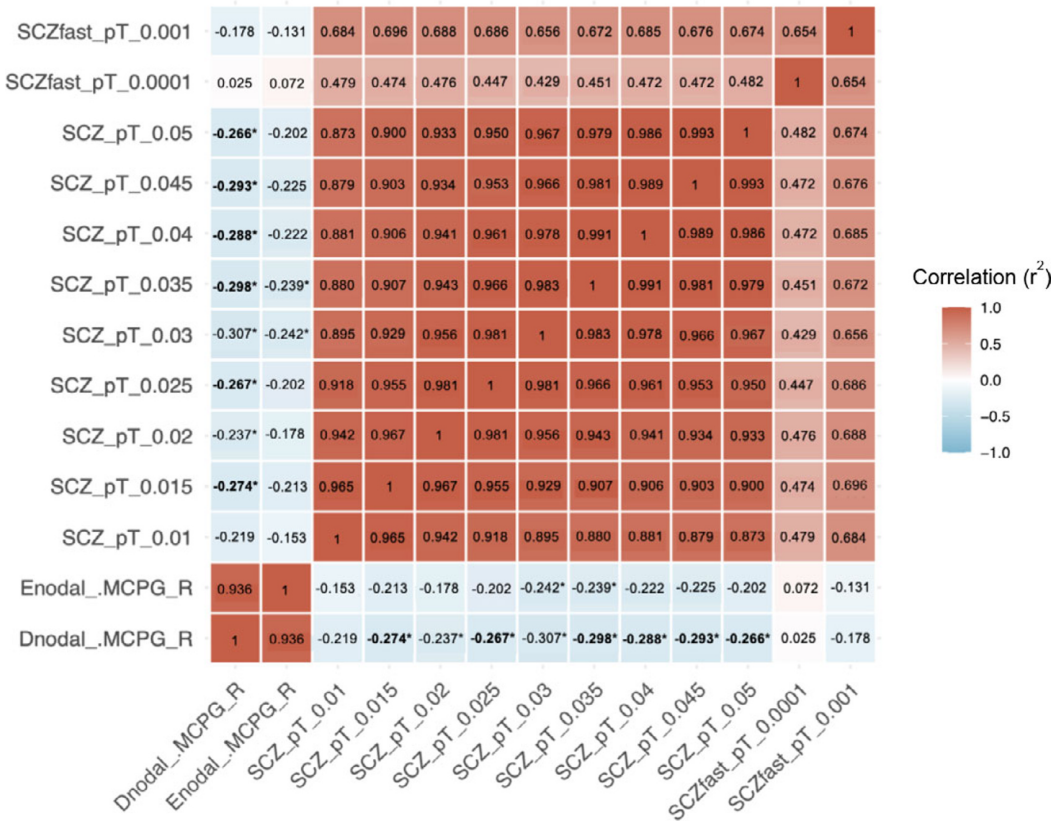

Figure 2. Association of SCZ-PRS with nodal metrics in the SCZ and GHR group.
Abbreviations: PT, p-value threshold; Enodal, nodal efficiency; Dnodal, nodal degree centrality; MCPG, median cingulate and paracingulate gyri; R, right.
*a significant level of $p < 0.05$, bold type was $p_{FDR} < 0.05$.

MCPG_R (see Supplementary Table 7). After FDR correction, the D_{nodal} of MCPG_R was positively correlated with CR ($r = 0.234$, $p = 0.013$, $p_{FDR} = 0.033$), CC ($r = 0.220$, $p = 0.020$, $p_{FDR} = 0.033$), and negatively correlated with TE ($r = -0.220$, $p = 0.020$, $p_{FDR} = 0.025$) (see Figure 3a–c and Supplementary Table 7). There was no association between the PRS and cognitive alterations (Supplementary Tables 8 and 9). There was no association between the WCST and SCZ disease-specific alterations (Supplementary Table 5).

Mediated moderation analysis

After mediation analysis, three mediation models were established (demographic characteristics of participants see Supplementary Table 8). D_{nodal} in MCPG_R fully mediated the association between the SCZ_PT_0.035 and CR (Path AB, Indirect effect = −14886.854; 95%CI: −29495.314 to −844.529, Figure 3d), between the PRS and CC (Path AB, indirect effect = −3150.880; 95%CI: −5891.580 to − 473.907, Figure 3e), and between the PRS and TE (Path AB, indirect effect = 14886.854; 95%CI: 481.107 to 29223.972, Figure 3f).

Functional enrichment analyses

To elucidate the biological underpinnings of SCZ-associated genes within SCZ-PRS, we conducted functional enrichment analyses for SCZ-PRS genes at a *p-value* threshold of 0.035 (PT_0.035), which has the smallest *p-value* and the most significant association with D_{nodal} in MCPG_R. A total of 30 Gene Ontology terms, mainly in biological processes, were identified for these SCZ-PRS genes. These enriched terms chiefly revolved around the regulation of signal transduction (particularly small GTPase-mediated signal transduction), Ca^{2+} transmembrane transport, and the modulation of synaptic transmission (Figure 4 and Supplementary Table 10).

Discussion

This study uniquely integrates genetics, brain functional networks (endophenotype), and executive function (clinical symptoms) in individuals with SCZ and those at GHR, providing valuable insights into the disease progression trajectory of polygenic hereditary disorders. The results showed how SCZ-associated risk genes influence altered functional networks and the association between executive deficits and genetically regulated alterations in functional networks. Specifically, we found that the common functional network alterations related to genetic susceptibility in both SCZ and GHR groups manifested as decreased E_{nodal} and D_{nodal} in the MCPG_R. Additionally, the diminished D_{nodal} levels were associated with SCZ-PRS and executive deficits. Importantly, our study revealed that the effect of SCZ-PRS on the executive functions is completely mediated through altered D_{nodal} in MCPG_R. And the biological function of SCZ-PRS involves intracellular signal transduction, Ca^{2+} transmembrane transport, and modulation of synaptic transmission.

Brain network alterations in SCZ and GHR

We found common alterations in brain functional network metrics within the SCZ and GHR groups. Compared to the HC group, both

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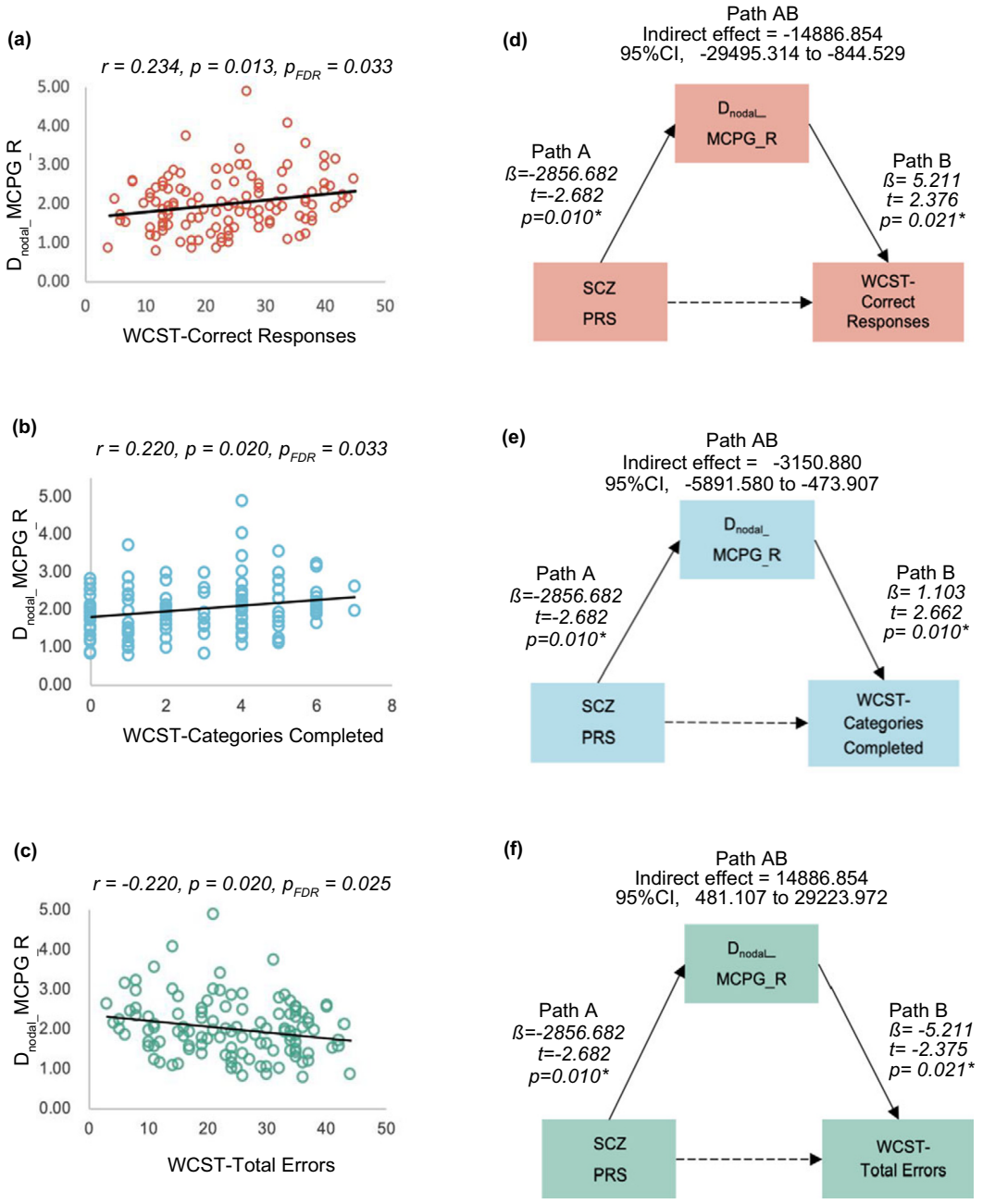

Figure 3. Scatter plot and mediation model in SCZ and GHR groups.
(a) was scatter plots showing D_{nodal} in the right MCPG was positively correlated to the scores of WCST correct responses. (b) showed D_{nodal} was positively correlated to WCST categories completed. (d) showed D_{nodal} was negatively correlated WCST total errors. (d) was mediation model showing D_{nodal} in the right MCPG significantly mediated the association between SCZ-PRS and correct responses. (e) showed D_{nodal} significantly mediated the association between SCZ-PRS and categories completed. (f) showed D_{nodal} significantly mediated the association between SCZ-PRS and total errors. The dotted line represents a non-significant correlation.
Abbreviations: D_{nodal}, nodal degree centrality; MCPG, median cingulate and paracingulate gyri; R, right; WCST, Wisconsin Card Sorting Test.
A significant level of $p_{FDR} < 0.05$.

SCZ and GHR groups exhibited decreased E_{nodal} and D_{nodal} in MCPG_R, with no significant differences between them. The decreased D_{nodal} represented the reduced direct connections of the cingulate gyrus with other nodes, while the decreased E_{nodal} indicated a declined capacity for information exchange in the cingulate gyrus. Futhermore, our findings revealed these alterations potentially represent genetic susceptibility to SCZ. The results partly align with Lo et al., who also found altered E_{nodal} of the cingulate gyrus in both SCZ and GHR groups, specifically in the anterior and posterior cingulate cortex, and the MCPG_R (Lo et al., 2015).

Moreover, multiple studies have consistently reported compromised cingulate gyrus function in SCZ, manifesting as reduced E_{nodal_loc}, diminished D_{nodal} and clustering coefficient, and lower activation during task-based fMRI (Lynall et al., 2010; Oertel et al., 2019; Yan et al., 2015). The collective evidence highlights a reduced involvement of the cingulate gyrus in overall brain activity in patients with SCZ and individuals at GHR, indicating its role as a

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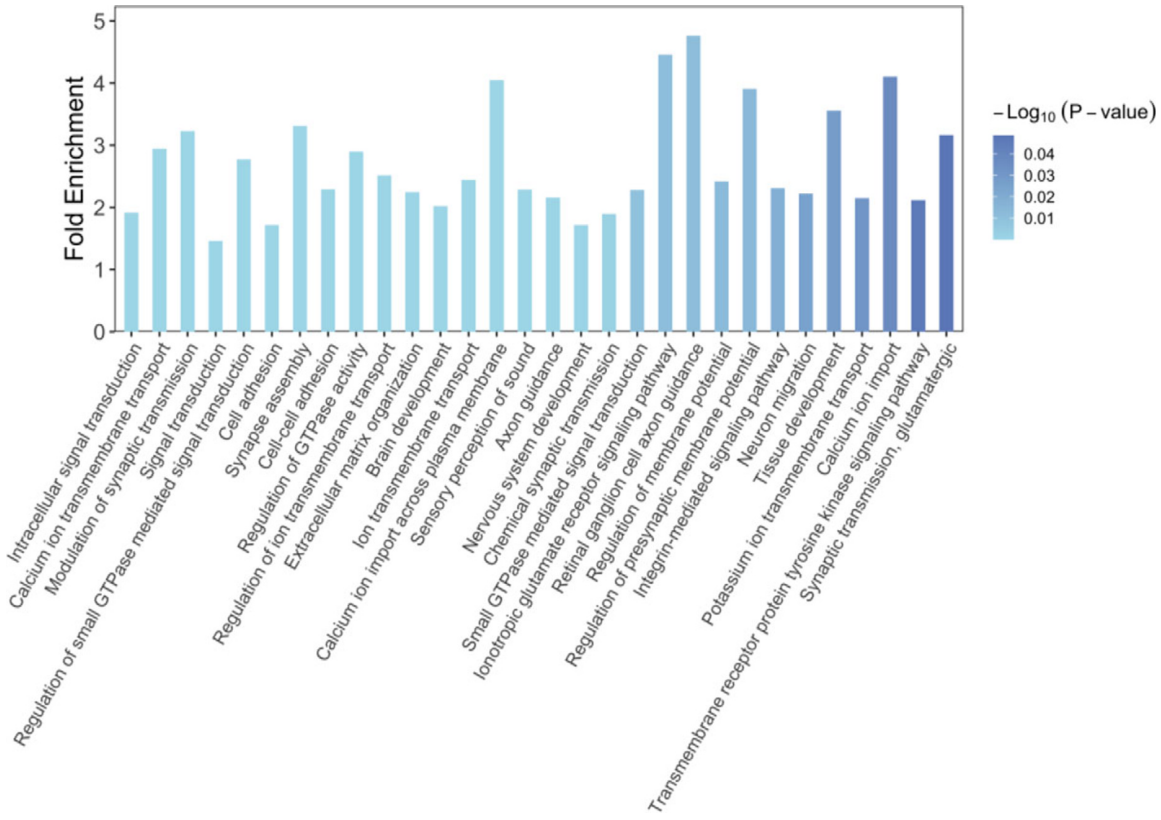

Figure 4. Significant gene ontology enrichment analysis for risk genes of SCZ-PRSs.

genetic susceptibility marker that could contribute to preventing disease development.

Unique brain network alterations in SCZ

We also found the SCZ group exhibited unique disease-specific alterations, compared to GHR and HC. Firstly, increased D_{nodal} in the MTG_R of the SCZ group suggests heightened interactions between the temporal gyrus and other brain regions and potentially a compensatory response, a known phenomenon in SCZ (Lynall et al., 2010). Additionally, the SCZ group showed reduced E_{nodal_loc} in the bilateral calcarine and lingual gyri, indicating less efficient information transfer. The role of E_{nodal_loc} in SCZ, however, requires further exploration. Moreover, we observed lower E_{glob} and higher L_p in SCZ, indicating the network global information processing was diminished, aligning with previous SCZ research (Ganella et al., 2017; Ho et al., 2020; Zhu et al., 2016). The SCZ group exhibits broader abnormalities in functional networks compared to the GHR group, manifesting as a gene-susceptibility reduction in specific brain region FC and a disease-specific decline in whole brain network efficiency.

Associations between PRS, network metrics, and executive deficits

We observed a negative correlation between decreased D_{nodal} in MCPG_R and SCZ-PRS scores in the SCZ and GHR groups. This implies that higher PRSs are associated with reduced connections between the cingulate gyrus and other brain regions. Concurrently, analyses utilizing UK Biobank data revealed significant associations of SCZ-PRS with fractional anisotropy, mean diffusivity, and neurite density index of cingulate gyrus, suggesting that genetic effects on multiple MRI phenotypes are located in the cingulate (Stauffer et al., 2021). Further supporting this, recent Mendelian randomization analysis posits that genetic variations in the cingulate gyrus may be causal for SCZ (Stauffer et al., 2023). In addition, this is complementary to our early finding in brain structural networks that PRSs are associated with E_{loc} deficits in SCZ and GHR populations (Zhu et al., 2021). In summary, our PRS findings suggest that aberrant brain functional networks may reflect the overall additive genetic vulnerability of SCZ.

This study demonstrated that, in both SCZ and GHR groups, D_{nodal} in MCPG_R was positively correlated with both CR and CC scores, while negatively correlated with TE scores. This suggests that altered brain functional networks may impact cognitive performance, aligning with previous research. Specifically, task-based fMRI investigations have revealed that prolonged task completion times in patients with SCZ are linked to reductions in the clustering coefficient and E_{loc} (He et al., 2012). Additionally, Bassett et al. identified a correlation between impaired working memory and decreased E_{glob} in SCZ (Bassett et al., 2009). Furthermore, machine-learning analyses revealed that the closer the functional brain patterns of GHR approximated those of SCZ, the poorer their executive function performance (Liu et al., 2020). Our findings provide additional evidence, indicating a decline in genetic susceptibility-related connectivity between the cingulate gyrus and other brain regions, correlating with reduced executive function in SCZ and GHR.

Altered functional networks mediating the association between SCZ-PRS and executive deficits

Our findings indicated that D_{nodal} in MCPG_R fully mediated the association between SCZ-PRS and executive function in both SCZ

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and GHR groups, suggesting that gene-regulated functional network disruption may serve as an early biomarker for executive function impairments. Our findings were similar to a study using independent component analysis, which found that fALFF mediated the relationship between SCZ-susceptible SNPs and working memory in mixed SCZ and HC cohorts, considering diagnosis as a covariate (Luo et al., 2018). Another study found an association between SCZ-PRS and the functional connectome in HCs, with parallel findings of reduced connectomes and associated IQ deficits in an independent SCZ cohort (Cao et al., 2021). However, the two teams failed to encompass continuous pathophysiology in one patient cohort and ignored cognitive impairment in GHR. Our study revealed that brain dysfunction mediated the association between genetic factors and cognitive deficits in both individuals with SCZ and those at GHR.

Furthermore, our functional enrichment analysis revealed that risk genes are implicated in processes like signal transduction, Ca^{2+} transmembrane transport, and synaptic transmission. Signal transduction, particularly small GTPase-mediated signaling, acts as a messenger for information carriage and contributes to axon guidance (Nikolic, 2002). Ca^{2+} transmembrane transport plays a pivotal role in regulating neurotransmitter release and synaptic strength through Ca^{2+} levels (Neher & Sakaba, 2008). Synaptic transmission regulation directly impacts information transfer between neurons (Martin, Grimwood, & Morris, 2000). Overall, these risk genes significantly affect synaptic plasticity and transmission, impacting neurodevelopment and information exchange. This leads to disrupted connectivity between the cingulate gyrus and other brain regions, manifesting as noticeable declines in cognitive functions.

Limitations

This study has some limitations. First, although we observed no significant differences in cognitive performance or network metrics between medicated and unmedicated SCZ patients – likely due to the small size of the unmedicated subgroup – we cannot fully exclude antipsychotic effects on their relationships; larger, drug-naive cohorts are needed. Similarly, no differences emerged between first-episode and multiepisode – perhaps because most SCZ participants were first-episode with limited medication exposure – and no differences between in- and outpatients, suggesting these factors had minimal impact on our results. Second, its cross-sectional design limits the ability to observe longitudinal brain alterations and cognitive changes in GHR individuals, particularly whether GHR progresses to SCZ. Third, the modest SCZ sample size limits our ability to explore disease-specific brain regions fully. Similarly, WCST and PRS analyses were restricted to subgroups, although post hoc power analyses confirmed sufficient statistical power. Moreover, future studies could examine gene–environment interactions to clarify how environmental factors shape SCZ risk-gene effects on brain networks and cognition.

Conclusion

The decreased connections of the right median cingulate-paracingulate gyri with other regions were observed in both SCZ and GHR groups, potentially indicating genetic susceptibility. Additionally, these reduced connections were linked to SCZ-related risk genes and WCST scores. Crucially, the reduced involvement of the cingulate gyrus in overall brain activity mediated the effect of SCZ-related risk genes on executive deficits in SCZ and GHR groups, and these risk genes were involved in signal transduction, Ca^{2+} transmembrane transport, and synaptic transmission. Significantly, the SCZ group displayed broader functional network abnormalities, characterized by reduced gene susceptibility in specific regions and a disease-specific decline in whole network efficiency. Our findings provide new insights into the genetic link to neurodevelopmental mechanisms and cognitive impairment, highlight the role of the cingulate gyrus, and contribute to a deeper understanding of the genetic and neuropathological basis of SCZ.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291725101177.

Data availability statement. The data supporting the study's findings can be obtained from the corresponding author (Yanqing Tang) upon reasonable request.

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Competing interests. The authors declare none.

References

Bassett, D. S., Bullmore, E. T., Meyer-Lindenberg, A., Apud, J. A., Weinberger, D. R., & Coppola, R. (2009). Cognitive fitness of cost-efficient brain functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, **106**(28), 11747–11752. https://doi.org/10.1073/pnas.0903641106.

Bech, P., Larsen, J. K., & Andersen, J. (1988). The BPRS: Psychometric developments. *Psychopharmacology Bulletin*, **24**(1), 118–121.

Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. & Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2018). Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell*, **173**(7), 1705, e16–1715. https://doi.org/10.1016/j.cell.2018.05.046.

Camchong, J., MacDonald, A. W., Bell, C., Mueller, B. A., & Lim, K. O. (2011). Altered functional and anatomical connectivity in schizophrenia. *Schizophrenia Bulletin*, **37**(3), 640–650. https://doi.org/10.1093/schbul/sbp131.

Cao, H., Zhou, H., & Cannon, T. D. (2021). Functional connectome-wide associations of schizophrenia polygenic risk. *Molecular Psychiatry*, **26**(6), 2553–2561. https://doi.org/10.1038/s41380-020-0699-3.

Carreira Figueiredo, I., Borgan, F., Pasternak, O., Turkheimer, F. E., & Howes, O. D. (2022). White-matter free-water diffusion MRI in schizophrenia: A systematic review and meta-analysis. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, **47**(7), 1413–1420. https://doi.org/10.1038/s41386-022-01272-x.

Collin, G., Turk, E., & van den Heuvel, M. P. (2016). Connectomics in schizophrenia: From early pioneers to recent brain network findings. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*, **1**(3), 199–208. https://doi.org/10.1016/j.bpsc.2016.01.002.

da Motta, C., Pato, M. T., Barreto Carvalho, C., & Castilho, P. (2021). The neurocognitive and functional profile of schizophrenia in a genetically homogenous European sample. *Psychiatry Research*, **304**, 114140. https://doi.org/10.1016/j.psychres.2021.114140.

Dodell-Feder, D., Delisi, L. E., & Hooker, C. I. (2014). The relationship between default mode network connectivity and social functioning in individuals at

familial high-risk for schizophrenia. *Schizophrenia Research*, **156**(1), 87–95. https://doi.org/10.1016/j.schres.2014.03.031.

Friston, K. J., & Frith, C. D. (1995). Schizophrenia: A disconnection syndrome? *Clinical Neuroscience (New York, N.Y.)*, **3**(2), 89–97.

Ganella, E. P., Bartholomeusz, C. F., Seguin, C., Whittle, S., Bousman, C., Phassouliotis, C., … Zalesky, A. (2017). Functional brain networks in treatment-resistant schizophrenia. *Schizophrenia Research*, **184**, 73–81. https://doi.org/10.1016/j.schres.2016.12.008.

Guo, S., He, N., Liu, Z., Linli, Z., Tao, H., & Palaniyappan, L. (2020). Brain-wide functional Dysconnectivity in schizophrenia: Parsing diathesis, resilience, and the effects of clinical expression. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, **65**(1), 21–29. https://doi.org/10.1177/0706743719890174.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*, **23**(1), 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology*, **32**(1), 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x.

He, H., Sui, J., Yu, Q., Turner, J. A., Ho, B.-C., Sponheim, S. R., … Calhoun, V. D. (2012). Altered small-world brain networks in schizophrenia patients during working memory performance. *PLoS One*, **7**(6), e38195. https://doi.org/10.1371/journal.pone.0038195.

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., … Glenthøj, B. (2018). Heritability of schizophrenia and schizophrenia Spectrum based on the Nationwide Danish twin register. *Biological Psychiatry*, **83**(6), 492–498. https://doi.org/10.1016/j.biopsych.2017.08.017.

Ho, N. F., Tng, J. X. J., Wang, M., Chen, G., Subbaraju, V., Shukor, S., … Medalia, A. (2020). Plasticity of DNA methylation, functional brain connectivity and efficiency in cognitive remediation for schizophrenia. *Journal of Psychiatric Research*, **126**, 122–133. https://doi.org/10.1016/j.jpsychires.2020.03.013.

Huang, D. W., Sherman, B. T., & Lempicki, R. A. (2009a). Bioinformatics enrichment tools: Paths toward the comprehensive functional analysis of large gene lists. *Nucleic Acids Research*, **37**(1), 1–13. https://doi.org/10.1093/nar/gkn923.

Huang, D. W., Sherman, B. T., & Lempicki, R. A. (2009b). Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nature Protocols*, **4**(1), 44–57. https://doi.org/10.1038/nprot.2008.211.

Jauhar, S., Johnstone, M., & McKenna, P. J. (2022). Schizophrenia. *Lancet*, **399**(10323), 473–486. https://doi.org/10.1016/S0140-6736(21)01730-X.

Jing, R., Li, P., Ding, Z., Lin, X., Zhao, R., Shi, L., … Fan, Y. (2019). Machine learning identifies unaffected first-degree relatives with functional network patterns and cognitive impairment similar to those of schizophrenia patients. *Human Brain Mapping*, **40**(13), 3930–3939. https://doi.org/10.1002/hbm.24678.

Kambeitz, J., Kambeitz-Ilankovic, L., Cabral, C., Dwyer, D. B., Calhoun, V. D., van den Heuvel, M. P., … Malchow, B. (2016). Aberrant functional whole-brain network architecture in patients with schizophrenia: A meta-analysis. *Schizophrenia Bulletin*, **42**(Suppl 1), S13–S21. https://doi.org/10.1093/schbul/sbv174.

Le, L., Kaur, R., Meiser, B., & Mj, G. (2020). Risk of schizophrenia in relatives of individuals affected by schizophrenia: A meta-analysis. *Psychiatry Research*, **286**, 112852. https://doi.org/10.1016/j.psychres.2020.112852.

Lichtenstein, P., Yip, B. H., Björk, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F., & Hultman, C. M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *Lancet*, **373**(9659), 234–239. https://doi.org/10.1016/S0140-6736(09)60072-6.

Lin, X., Li, W., Dong, G., Wang, Q., Sun, H., Shi, J., … Lu, L. (2021). Characteristics of multimodal brain Connectomics in patients with schizophrenia and the unaffected first-degree relatives. *Frontiers in Cell and Developmental Biology*, **9**, 631864. https://doi.org/10.3389/fcell.2021.631864.

Liu, W., Zhang, X., Qiao, Y., Cai, Y., Yin, H., Zheng, M., … Wang, H. (2020). Functional connectivity combined with a machine learning algorithm can classify high-risk first-degree relatives of patients with schizophrenia and identify correlates of cognitive impairments. *Frontiers in Neuroscience*, **14**, 577568. https://doi.org/10.3389/fnins.2020.577568.

Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., Song, M., … Jiang, T. (2008). Disrupted small-world networks in schizophrenia. *Brain*, **131**(4), 945–961. https://doi.org/10.1093/brain/awn018.

Lo, C.-Y. Z., Su, T.-W., Huang, C.-C., Hung, C.-C., Chen, W.-L., Lan, T.-H., … Bullmore, E. T. (2015). Randomization and resilience of brain functional networks as systems-level endophenotypes of schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, **112**(29), 9123–9128. https://doi.org/10.1073/pnas.1502052112.

Luo, N., Sui, J., Chen, J., Zhang, F., Tian, L., Lin, D., … Jiang, T. (2018). A schizophrenia-related genetic-brain-cognition pathway revealed in a large Chinese population. *eBioMedicine*, **37**, 471–482. https://doi.org/10.1016/j.ebiom.2018.10.009.

Lynall, M.-E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., & Bullmore, E. (2010). Functional connectivity and brain networks in schizophrenia. *Journal of Neuroscience*, **30**(28), 9477–9487. https://doi.org/10.1523/JNEUROSCI.0333-10.2010.

Martin, A. R., Daly, M. J., Robinson, E. B., Hyman, S. E., & Neale, B. M. (2019). Predicting polygenic risk of psychiatric disorders. *Biological Psychiatry*, **86**(2), 97–109. https://doi.org/10.1016/j.biopsych.2018.12.015.

Martin, S. J., Grimwood, P. D., & Morris, R. G. (2000). Synaptic plasticity and memory: An evaluation of the hypothesis. *Annual Review of Neuroscience*, **23**, 649–711. https://doi.org/10.1146/annurev.neuro.23.1.649.

Menon, V., Palaniyappan, L., & Supekar, K. (2023). Integrative brain network and salience models of psychopathology and cognitive dysfunction in schizophrenia. *Biological Psychiatry*, **94**(2), 108–120. https://doi.org/10.1016/j.biopsych.2022.09.029.

Neher, E., & Sakaba, T. (2008). Multiple roles of calcium ions in the regulation of neurotransmitter release. *Neuron*, **59**(6), 861–872. https://doi.org/10.1016/j.neuron.2008.08.019.

Nikolic, M. (2002). The role of rho GTPases and associated kinases in regulating neurite outgrowth. *The International Journal of Biochemistry & Cell Biology*, **34**(7), 731–745. https://doi.org/10.1016/s1357-2725(01)00167-4.

Oertel, V., Kraft, D., Alves, G., Knöchel, C., Ghinea, D., Storchak, H., … Stäblein, M. (2019). Associative memory impairments are associated with functional alterations within the memory network in schizophrenia patients and their unaffected first-degree relatives: An fMRI study. *Frontiers in Psychiatry*, **10**, 33. https://doi.org/10.3389/fpsyt.2019.00033.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, **511**(7510), 421–427. https://doi.org/10.1038/nature13595

Shine, J. M., Bissett, P. G., Bell, P. T., Koyejo, O., Balsters, J. H., Gorgolewski, K. J., … Poldrack, R. A. (2016). The dynamics of functional brain networks: Integrated network states during cognitive task performance. *Neuron*, **92**(2), 544–554. https://doi.org/10.1016/j.neuron.2016.09.018.

Shine, J. M., Breakspear, M., Bell, P. T., Ehgoetz Martens, K. A., Shine, R., Koyejo, O., … Poldrack, R. A. (2019). Human cognition involves the dynamic integration of neural activity and neuromodulatory systems. *Nature Neuroscience*, **22**(2), 289–296. https://doi.org/10.1038/s41593-018-0312-0.

Stauffer, E.-M., Bethlehem, R. A. I., Dorfschmidt, L., Won, H., Warrier, V., & Bullmore, E. T. (2023). The genetic relationships between brain structure and schizophrenia. *Nature Communications*, **14**(1), 7820. https://doi.org/10.1038/s41467-023-43567-7.

Stauffer, E.-M., Bethlehem, R. A. I., Warrier, V., Murray, G. K., Romero-Garcia, R., Seidlitz, J., & Bullmore, E. T. (2021). Grey and white matter microstructure is associated with polygenic risk for schizophrenia. *Molecular Psychiatry*, **26**(12), 7709–7718. https://doi.org/10.1038/s41380-021-01260-5.

Su, T.-W., Hsu, T.-W., Lin, Y.-C., & Lin, C.-P. (2015). Schizophrenia symptoms and brain network efficiency: A resting-state fMRI study. *Psychiatry Research*, **234**(2), 208–218. https://doi.org/10.1016/j.pscychresns.2015.09.013.

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, **60**(12), 1187–1192. https://doi.org/10.1001/archpsyc.60.12.1187.

Thuaire, F., Rondepierre, F., Vallet, G. T., Jalenques, I., & Izaute, M. (2022). Executive deficits in schizophrenia: Mediation by processing speed and its relationships with aging. *Psychological Medicine*, **52**(6), 1126–1134. https://doi.org/10.1017/S0033291720002871.

van den Heuvel, M. P., Stam, C. J., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Efficiency of functional brain networks and intellectual performance. *Journal of Neuroscience*, **29**(23), 7619–7624. https://doi.org/10.1523/JNEUROSCI.1443-09.2009.

Wang, J., Wang, X., Xia, M., Liao, X., Evans, A., & He, Y. (2015). GRETNA: A graph theoretical network analysis toolbox for imaging connectomics.

https://doi.org/10.1017/S0033291725101177 Published online by Cambridge University Press

Frontiers in Human Neuroscience, **9**, 386. https://doi.org/10.3389/fnhum.2015.00386.

Wang, J., Zuo, X., & He, Y. (2010). Graph-based network analysis of resting-state functional MRI. *Frontiers in Systems Neuroscience*, **4**, 16. https://doi.org/10.3389/fnsys.2010.00016.

Wen, H., Liu, Y., Rekik, I., Wang, S., Chen, Z., Zhang, J., … He, H. (2018). Combining disrupted and discriminative topological properties of functional connectivity networks as neuroimaging biomarkers for accurate diagnosis of early Tourette syndrome children. *Molecular Neurobiology*, **55**(4), 3251–3269. https://doi.org/10.1007/s12035-017-0519-1.

Wu, B., Li, X., Zhou, J., Zhang, M., & Long, Q. (2020). Altered whole-brain functional networks in drug-naïve, first-episode adolescents with major depression disorder. *Journal of Magnetic Resonance Imaging*, **52**(6), 1790–1798. https://doi.org/10.1002/jmri.27270.

Yan, C.-G., Wang, X.-D., Zuo, X.-N., & Zang, Y.-F. (2016). DPABI: Data Processing & Analysis for (resting-state) brain imaging. *Neuroinformatics*, **14**(3), 339–351. https://doi.org/10.1007/s12021-016-9299-4.

Yan, H., Tian, L., Wang, Q., Zhao, Q., Yue, W., Yan, J., … Zhang, D. (2015). Compromised small-world efficiency of structural brain networks in schizophrenic patients and their unaffected parents. *Neuroscience Bulletin*, **31**(3), 275–287. https://doi.org/10.1007/s12264-014-1518-0.

Yang, H., Chen, X., Chen, Z.-B., Li, L., Li, X.-Y., Castellanos, F. X., … Yan, C.-G. (2021). Disrupted intrinsic functional brain topology in patients with major depressive disorder. *Molecular Psychiatry*, **26**(12), 7363–7371. https://doi.org/10.1038/s41380-021-01247-2.

Yin, P., Zhao, C., Li, Y., Liu, X., Chen, L., & Hong, N. (2021). Changes in brain structure, function, and network properties in patients with first-episode schizophrenia treated with antipsychotics. *Frontiers in Psychiatry*, **12**, 735623. https://doi.org/10.3389/fpsyt.2021.735623.

Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., He, Y., & Gong, Q. (2011). Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biological Psychiatry*, **70**(4), 334–342. https://doi.org/10.1016/j.biopsych.2011.05.018.

Zhu, J., Wang, C., Liu, F., Qin, W., Li, J., & Zhuo, C. (2016). Alterations of functional and structural networks in schizophrenia patients with auditory verbal hallucinations. *Frontiers in Human Neuroscience*, **10**, 114. https://doi.org/10.3389/fnhum.2016.00114.

Zhu, W., Wang, Z., Yu, M., Zhang, X., & Zhang, Z. (2023). Using support vector machine to explore the difference of function connection between deficit and non-deficit schizophrenia based on gray matter volume. *Frontiers in Neuroscience*, **17**, 1132607. https://doi.org/10.3389/fnins.2023.1132607.

Zhu, Y., Wang, S., Gong, X., Edmiston, E. K., Zhong, S., Li, C., … Tang, Y. (2021). Associations between hemispheric asymmetry and schizophrenia-related risk genes in people with schizophrenia and people at a genetic high risk of schizophrenia. *British Journal of Psychiatry*, **219**(1), 392–400. https://doi.org/10.1192/bjp.2021.47.

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