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Causal effect of three autoimmune diseases on brain functional networks and cerebrospinal fluid metabolites to underlie the pathogenesis of autoimmune psychosis: a two-sample mendelian randomization analysis

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Abstract

Background Autoimmune diseases such as Systemic Lupus Erythematosus (SLE), Sjögren's Syndrome (SS), and Hashimoto's Thyroiditis (HT) frequently exhibit neuropsychiatric manifestations, including cognitive impairment, depression, anxiety, and so on, yet the exact pathogenesis underlying this association remain incompletely understood. Dysfunction of brain resting-state functional networks and cerebrospinal fluid (CSF) metabolite disturbances have been widely reported in psychiatric disorders. However, the application of resting-state functional magnetic resonance imaging (rsfMRI) and CSF metabolomics in the diagnosis and monitoring of autoimmune psychosis is still limited.

Methods A two-sample Mendelian randomization (MR) analysis was performed to investigate the causal relationships between three autoimmune diseases (SLE, SS, and HT, $n = 14,267$ to 402,090 individuals) and 191 rsfMRI phenotypes ($n = 47,276$ individuals), as well as 338 CSF metabolites. The genome-wide association study (GWAS) of three autoimmune diseases was used as the exposure, whereas rsfMRI phenotypes and 338 CSF metabolites were treated as the outcome. Inverse variance weighted (IVW) with P value < 0.05 was regarded as the primary approach for calculating causal estimates. Additionally, the false discovery rate (FDR)-adjusted P value (P_{FDR}) < 0.05 was utilized

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to account for multiple testing. MR Egger method, weighted median method, simple mode method and weighted mode method were used for sensitive analysis.

Results Our analyses identified 5 causal relationships between SLE and the 191 rsfMRI phenotypes, 48 between SS and the 191 rsfMRI phenotypes, and 4 between HT and the 191 rsfMRI phenotypes. Additionally, we found 8 causal relationships between HT and CSF metabolites. Furthermore, all three diseases were significantly associated with the temporal lobe and triple networks (default mode network (DMN), salience network (SN), and central executive network (CEN)), which are the core brain regions and functional networks for cognition. Following FDR correction, 6 causal relationships between SS and the 191 rsfMRI phenotypes were further validated.

Conclusions Our study pinpoints important brain functional networks and CSF metabolites potentially implicated in the pathogenesis of psychiatric disorders associated with autoimmune diseases and highlights critical brain regions for the development of novel therapeutics.

Highlights

- Resting-state functional magnetic resonance imaging (rsfMRI) and CSF metabolomics offer promising methods for elucidating the neurobiology of autoimmune psychosis, yet their application in diagnosing autoimmune psychosis remains limited.
- This is the first study to identify the causal relationship between autoimmune diseases, brain dysfunction, and CSF metabolism using a two-sample Mendelian randomization analysis.
- Our results reveal important brain functional networks and CSF metabolites potentially implicated in the pathogenesis of autoimmune psychosis and highlight critical brain regions for the development of novel therapeutics.

Keywords Mendelian randomization, Autoimmune disease, rsfMRI, CSF metabolite

Introduction

Autoimmune diseases constitute a wide array of conditions characterized by disrupted immunoregulation, which triggers the production of specific autoantibodies, ultimately causing inflammation and multifaceted organ involvement [1]. Recent research suggests that autoimmune conditions such as Systemic Lupus Erythematosus (SLE), Sjögren's Syndrome (SS), and Hashimoto's Thyroiditis (HT) may increase the risk of developing psychiatric disorders [2–5]. Notably, the expert consensus document titled "*Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin*" highlights that systemic autoimmune diseases like SLE and HT, which are marked by elevated levels of antinuclear antibodies (ANA) and thyroid antibodies, respectively, are recognized as significant risk factors for the development of psychiatric illnesses [6]. While the exact pathogenesis underlying this association remains unclear, emerging evidence suggests a complex interplay between neuroinflammation, immune dysregulation, and autoantibodies. SLE, characterized by the presence of autoantibodies and immune complexes, is a prime example of this link. Previous epidemiologic studies have demonstrated strong associations between SLE and a variety of psychiatric disorders such as anxiety and depression [7]. The pathophysiology of psychiatric disorders in SLE likely involves multiple factors, including genetic predisposition, vascular lesions, Blood-Brain Barrier (BBB) dysfunction, and autoimmune-mediated neuronal damage. SS, another autoimmune disorder, is associated with dryness of mucous membranes and glands. Neurological manifestations in SS, such as cognitive deficits and peripheral neuropathy, highlight the potential for central nervous system (CNS) involvement. Magnetic resonance imaging (MRI) findings in SS patients often include white matter hyperintensities (WMHs) and cortical atrophy, suggesting neuroinflammation and structural changes. HT, an autoimmune thyroid disorder, has also been linked to psychiatric symptoms, although the evidence is less robust. Thyroid dysfunction and immune dysregulation may contribute to mood disturbances and cognitive impairments [8].

Diagnosing autoimmune psychosis remains challenging due to the nonspecific nature of psychiatric symptoms and the absence of definitive biomarkers. However, recent consensus guidelines propose a diagnostic approach based on clinical criteria, including the presence of red flags, serum, and cerebrospinal fluid (CSF) autoantibody testing, neuroimaging, and other CSF examinations [4]. Conventional MRI and CSF antibody detection have been crucial tools in the diagnosis of autoimmune psychosis, but their limitations are becoming increasingly apparent. Conventional MRI often fails to detect the subtle structural changes associated with autoimmune psychosis in over 50% of the cases, particularly in the white matter, which can be crucial for identifying the presence of this disease [9, 10]. CSF antibody detection, as an effective tool for identifying specific types of psychosis, such as anti-NMDA receptor encephalitis,

also has its limitations. The sensitivity and specificity of CSF antibody testing can vary depending on the specific antibody being detected, and some autoimmune psychosis subtypes may be challenging to diagnose using this method alone. Therefore, the exploration of alternative diagnostic approaches is crucial for improving the accuracy and efficiency of autoimmune psychosis diagnosis. Resting-state functional magnetic resonance imaging (rsfMRI) and CSF metabolomics offer promising alternative methods for understanding the neurobiology of autoimmune psychosis and may provide valuable complementary information to conventional MRI and CSF antibody testing. rsfMRI, a non-invasive technique, reveals the intrinsic functional connectivity of the brain at rest. A variety of brain intrinsic resting-state networks have been discovered using fMRI, including salience, default mode, central executive, somatomotor, attention and so on [11]. Accumulating evidence indicates dysfunction of brain resting-state functional networks in psychiatric disorders. Studies have shown altered connectivity patterns in patients with neuropsychiatric SLE, including reduced connectivity within the default mode network and increased connectivity in the frontoparietal network [12]. These changes are associated with cognitive deficits and mood disorders, suggesting a potential role for rsfMRI in diagnosing and monitoring these conditions [13]. CSF metabolomics, on the other hand, provides insights into the metabolic disturbances within the CNS. A study investigating the CSF metabolites in patients with acute encephalitis identified alterations in the tryptophan-kynurenine and nitric oxide pathways, which are potential biomarkers for neuroinflammation [14]. These findings highlight the utility of CSF metabolomics in uncovering the pathophysiological mechanisms of neuroinflammatory diseases. By combining these advanced imaging and metabolomics techniques, we may gain a more comprehensive understanding of the neurobiology of autoimmune psychosis and develop novel diagnostic and therapeutic strategies. However, the potential of rsfMRI and CSF metabolomics in diagnosing and monitoring autoimmune psychosis has not yet been fully realized due to limited research and small sample sizes. Larger, well-characterized patient cohorts are needed to address these limitations and to understand the complex and heterogeneous nature of pathology.

MR is a robust causal inference method that employs genetic variants as instrumental variables (IVs) to explore the causal relationship between exposure and outcome. By harnessing the inherent randomness of genetic variants, which are randomly assigned during gamete formation, MR overcomes the limitations of traditional observational studies, such as confounding and reverse causation [15]. This method effectively mimics the randomization process of clinical trials, offering a robust framework for causal inference. Recent studies have successfully employed MR to investigate the causal association between brain dysfunction and psychiatric disorders [16]. However, the exploration of the causal relationship between autoimmune diseases, particularly SLE - a condition commonly associated with psychiatric comorbidities - and brain dysfunction, along with its potential impact on CSF metabolism, remains uncharted territory. This gap in research underscores the necessity for further investigation using MR to uncover the potential causal mechanisms underlying the association between autoimmune diseases and brain function, thereby paving the way for the identification of novel disease targets and the development of targeted interventions for autoimmune-related psychiatric disorders. In this study, we employed a two-sample MR approach to investigate the causal relationship between autoimmune diseases, specifically SLE, SS, and HT, and their potential influence on brain dysfunction and CSF metabolism. The exposure variables were three autoimmune diseases, while the outcomes included 191 brain rsfMRI phenotypes and 338 CSF metabolites. This study represents the first attempt to assess the causal relationship between autoimmune diseases, brain dysfunction, and CSF metabolism using MR.

Methods

Data source

GWASs of autoimmune diseases

To systematically investigate the causal relationship between autoimmune diseases and brain functional networks as well as cerebrospinal fluid metabolites, we conducted an MR analysis using publicly available GWAS on autoimmune diseases. To avoid the disparities arising from genetic diversity among different racial lineages and other environmental factors, we exclusively incorporated GWAS datasets derived from European-descent samples. We performed MR analysis utilizing GWAS datasets for three autoimmune diseases: SLE, SS, and HT. Since the GWASs of rsfMRI phenotypes were from the UK Biobank study, to minimize the potential impact of sample overlap between GWASs of autoimmune diseases and fMRI phenotypes on MR inferences, we utilized the GWASs of autoimmune diseases that did not include samples from UK Biobank study. Summary statistics for SLE were obtained from a publicly available IEU GWAS database (https://gwas.mrcieu.ac.uk), including 5,201 cases and 9,066 controls of European ancestry [17]. Summary statistics for SS were extracted from the FinnGen Release 8 database (https://www.finngen.fi/en), including 2,735 cases and 399,355 controls of European ancestry [18]. Summary statistics for HT were obtained from the GWAS Catalog database (https://www.ebi.ac.uk/gwas/), including 15,654 cases and 379,986 controls of European ancestry [19].

GWASs of brain rsfMRI

The rsfMRI data in this research were sourced from four cohort studies: UK Biobank, Adolescent Brain Cognitive Development (ABCD), Philadelphia Neurodevelopmental Cohort (PNC), and Human Connectome Project (HCP). A total of 47,276 individuals were included in these studies. The data consisted of rsfMRI images, which were processed following a unified pipeline to generate 76 amplitude traits reflecting regional neuronal activity and 1,695 pairwise functional connectivity traits quantifying interregional coactivity, alongside 6 global functional connectivity measures. Considering that genetic factors exert a lesser influence on brain functional networks compared to structural aspects, the researchers conducted a genome-wide association study (GWAS) on 1,777 neuroimaging phenotypes to discover genetic variants influencing intrinsic brain activity. A Bonferroni-adjusted significance threshold of 2.8×10^{-11} (5×10^{-8}/1,777) was applied to select significantly associated phenotypes. Consequently, 191 traits were identified as significantly impacted by genetic variations, comprising 75 amplitude traits (nodes), 111 pairwise functional connectivities (edges), and 5 global functional connectivities. These phenotypes covered various networks, including salience, default mode, central executive, somatomotor, attention, limbic, and visual networks [20].

GWASs of CSF metabolites

Our research utilized GWAS Catalog datasets focusing on CSF metabolites. The data for the 338 CSF metabolites were obtained from the Wisconsin Alzheimer's Disease Research Center (WADRC) and Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort studies. The analysis included both patients and healthy controls, with a total of 689 participants initially involved. The metabolites were identified and quantified using non-targeted metabolomics with UPLC-MS/MS technology, followed by data processing and stringent quality control procedures, ultimately retaining metabolites with ≥ 50% availability across the cohort [21].

Selection criteria for IVs

The validity of the MR analysis was predicated on three fundamental assumptions: (1) the IVs exhibited a strong correlation with the exposure; (2) the IVs influenced the outcome solely through the exposure; and (3) the IVs were not associated with any confounding variables. Consequently, to satisfy these assumptions, we filtered the instruments before MR analyses. Firstly, we selectively included SNPs that displayed a strong correlation with the exposure ($P < 5 \times 10^{-8}$). Secondly, to ensure the independence of the SNPs, linkage disequilibrium (LD) clumping was performed. This process utilized the clump function within the R package TwoSampleMR available at https://github.com/MRCIEU/TwoSampleMR, employing the parameters of $r^2 = 0.001$ and a window size of 10,000 kilobase pairs (kb). Thirdly, outcome-related SNPs with a p-value exceeding 5×10^{-5} were excluded. Additionally, we removed SNPs that were associated with confounding factors such as alcohol drinking, smoking, education, and socioeconomic status [16]. For querying the confounding factors, we utilized data sourced from the NHGRI-EBI Catalog at https://www.ebi.ac.uk/gwas/. The SNPs with *F*-statistics < 10 were excluded to maintain data quality. *F*-statistics were calculated using the formula $F = \text{Beta}^2/\text{SE}^2$ [22, 23].The application of Steiger test was utilized to mitigate the risk of reverse causality and enhance the robustness of instrumental variable selection [24].

MR analyses

In this study, we employed two-sample MR analyses to explore the causal relationships between three autoimmune diseases and rsfMRI, as well as CSF metabolites. Before performing MR analyses, the data on exposure and outcome were harmonized, and palindromic SNPs with minor allele frequency close to 0.5 were removed. The MR analyses were performed using three autoimmune diseases as exposure, brain rsfMRI, and CSF metabolites as outcome. Five high-efficiency methods were applied including the inverse variance weighted (IVW) method, MR Egger method, weighted median method, simple mode method, and weighted mode method, IVW was regarded as the primary approach. Additionally, the false discovery rate (FDR)-adjusted *P* value (P_{FDR}) < 0.05 was utilized to account for multiple testing.

A series of sensitivity analyses were conducted to test the robustness of MR estimation.

Cochrane's Q test and leave-one-out sensitivity analysis were performed to assess the heterogeneity ($P < 0.05$) among SNPs. MR-Egger intercept and MR-PRESSO global test were used to detect the presence of pleiotropy ($P < 0.05$) and to eliminate the effects of pleiotropy by removing outliers [25].

The following three conditions were used to determine whether there was a causal effect of the exposure and outcome: (1) A significant difference in the IVW method ($P < 0.05$), (2) Consistency in the estimation directions of all methods, and (3) Non-significance in both the MR-Egger intercept test and the MR-PRESSO global test ($P > 0.05$). All of the analyses were primarily conducted in R Studio using the TwoSampleMR package and MRPRESSO package.

Results

Overview of the study

To explore the potential causalities between autoimmune diseases and brain resting-state functional networks as well as CSF metabolites, we performed the two-sample

MR analyses by utilizing GWAS summary statistics of rsfMRI phenotypes (the largest GWASs of rsfMRI phenotypes so far), CSF metabolites, SLE trait, SS trait, and HT trait. An overview of the study design is shown in Fig. 1.

To meet the fundamental assumptions of MR, we rigorously controlled the quality of IVs, and only single-nucleotide polymorphisms (SNPs) that showed significant associations ($P < 5 \times 10^{-8}$) with exposure were selected as IVs, initially 40 SNPs related to SLE, 7 SNPs related to SS, 2 SNPs related to HT were reserved. In addition, the IVs with *F*-statistic values ≤ 10 and associated with confounding factors (alcohol drinking, smoking, education, and socioeconomic status) were excluded. Furthermore, reverse causality-related SNPs by the Steiger test and outliers calculated by MRPRESSO were removed after harmonization. Finally, 34 significant SNPs for SLE, 6 SNPs for SS, and 2 SNPs for HT traits were performed subsequent MR analysis between autoimmune diseases and brain functional networks, while 28 significant SNPs for SLE, 4 SNPs for SS and 2 SNPs for HT traits were chosen for MR analysis between autoimmune diseases and CSF metabolites.

MR of autoimmune diseases on brain functional networks

The risk of autoimmune diseases may affect the neural activity of relevant brain regions and the connectivity of functional networks. To explore the causal effects of three autoimmune diseases on brain functional networks, we performed MR analyses between autoimmune diseases and rsfMRI phenotypes. In this study, we identified 57 potential causal associations between autoimmune diseases and brain functional networks (rsfMRI phenotypes). The risk of autoimmune diseases mainly affects spontaneous neural activity or connectivity in different brain regions, including the triple networks, the subcortical-cerebellum network, the default mode network, and so on. (Figures 2, 3, 4, 5 and 6, Supplementary Tables S1–S4).

Effects of SLE on brain functional networks

We identified 5 causal relationships between the risk of SLE and rsfMRI phenotypes. As shown in Fig. 2 and Supplementary Table S1, a higher risk of SLE increased the activity of the cerebellum or temporal (IVW OR = 1.008, 95% CI: 1.000-1.016, $P = 0.048$), increased the connectivity between the precuneus or cuneus or cingulate gyrus and cerebellum (IVW OR = 1.010, 95% CI: 1.001–1.019, $P = 0.037$), and increased the functional connectivity of the global measure (IVW OR = 1.014, 95% CI: 1.004–1.025, $P = 0.009$), which are affiliated with subcortical-cerebellum network, the triple networks (default mode, central executive, and salience), as well as default mode or central executive and subcortical-cerebellum network. A higher risk of SLE decreased the functional connectivity between the superior frontal gyrus and inferior frontal gyrus (IVW OR = 0.988, 95% CI: 0.979–0.997, $P = 0.013$), and decreased the connectivity between the temporal lobe or frontal lobe or supplementary motor area and frontal lobe (IVW OR = 0.990, 95% CI: 0.981-1.000, $P = 0.040$), and mainly affect default mode or central executive network and salience or default mode network. The MR-Egger test and MR-PRESSO global test did not reveal significant horizontal pleiotropy, Cochrane's Q test and leave-one-out sensitivity (Supplementary Figs. S1–S5) did not reveal significant heterogeneity. However, after correction for multiple testing (FDR), no significant correlation was detected.

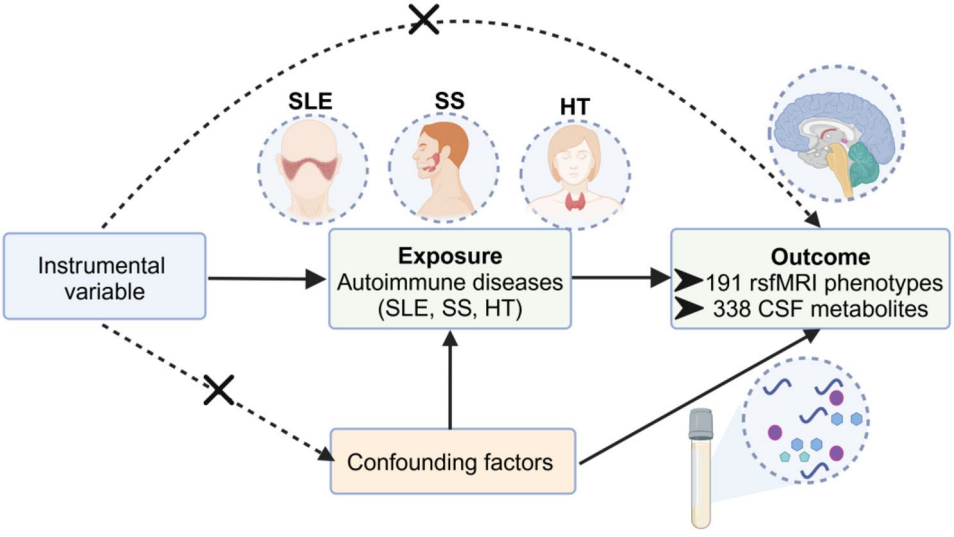

Fig. 1 The overview of the study design. The illustration was created using BioRender (https://biorender.com/). SLE, Systemic Lupus Erythematosus; SS, Sjögren's Syndrome; HT, Hashimoto's Thyroiditis; rsfMRI, resting-state functional magnetic resonance imaging; CSF, cerebrospinal fluid

(A)

Outcome (location)	fMRI network	Nsnp	Methods	p value	OR(95%CI)
pheno73 (node) Cerebellum|Temporal	Subcortical-cerebellum	33	IVW	0.048	1.008(1.000-1.016)
pheno460 (edge) (Precuneus|Cuneus| Cingulate) &(Cerebellum)	(Default_mode| Central_executive) &(Subcortical-cerebellum)	34	IVW	0.037	1.010(1.001-1.019)
pheno1134 (edge) (Frontal_Sup) &(Frontal_Inf)	(Default_mode| Central_executive) &(Default_mode| Central_executive)	34	IVW	0.013	0.988(0.979-0.997)
pheno1189 (edge) (Temporal|Frontal| Supp_Motor_Area) &(Frontal)	(Default_mode| Salience) &(Salience| Default_mode)	34	IVW	0.040	0.990(0.981-1.000)
pheno1701 (edge) (Global_measure)	Triple_netwoks (Default_mode, Central_executive, Salience)	34	IVW	0.009	1.014(1.004-1.025)

(B)

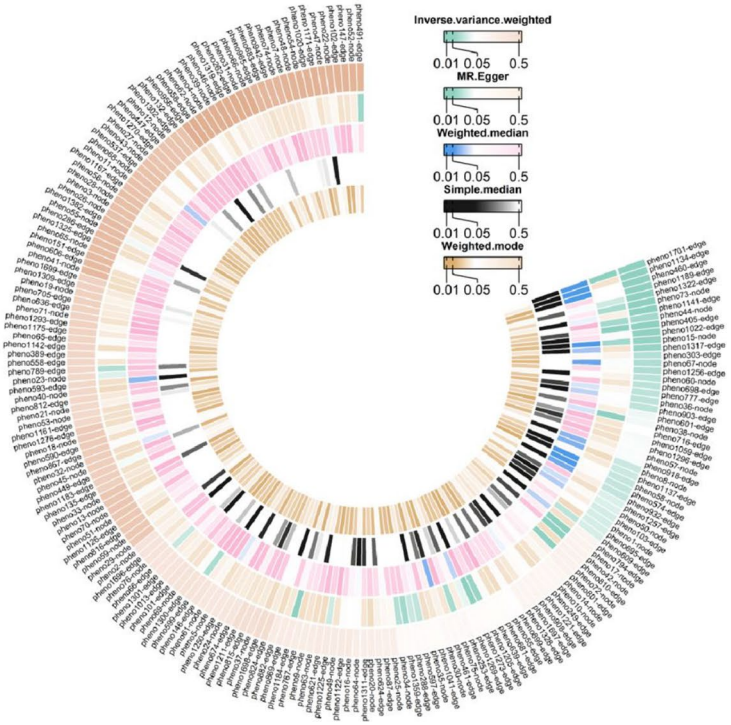

Fig. 2 (**A**) The results of the significant causalities estimated between SLE risk and rsfMRI phenotypes using the MR-IVW method ($P < 0.05$) and (**B**) All results of causalities between SLE risk and rsfMRI phenotypes using five MR methods, the data points are arranged in a clockwise direction based on the increasing order of p-values obtained from the IVW method. fMRI, resting-state functional magnetic resonance imaging; Nsnp: number of SNPs; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted

Effects of SS on brain functional networks

We uncovered a causal relationship between SS and 48 rsfMRI phenotypes, including 30 amplitude traits (nodes) that reflect regional spontaneous neural activity, and 18 pairwise functional connectivities (edges) (Figs. 3–4, Supplementary Tables S2–S3). Our findings indicated that SS risk was positively associated with neural activity in the temporal lobe (IVW OR = 1.039, 95% CI: 1.018–1.059, $P = 0.000$)/ (IVW OR = 1.035, 95% CI: 1.014–1.057, $P = 0.001$), parietal lobe (IVW OR = 1.034, 95% CI: 1.014–1.055, $P = 0.001$), precentral gyrus or frontal lobe or supplementary motor area (IVW OR = 1.032, 95% CI: 1.011–1.053, $P = 0.003$), superior temporal gyrus (IVW OR = 1.031, 95% CI: 1.010–1.052, $P = 0.003$) at resting state, which was the five phenotypes with the strongest effect size. Furthermore, we discovered that SS risk was positively associated with functional connectivities between the superior frontal gyrus and parietal

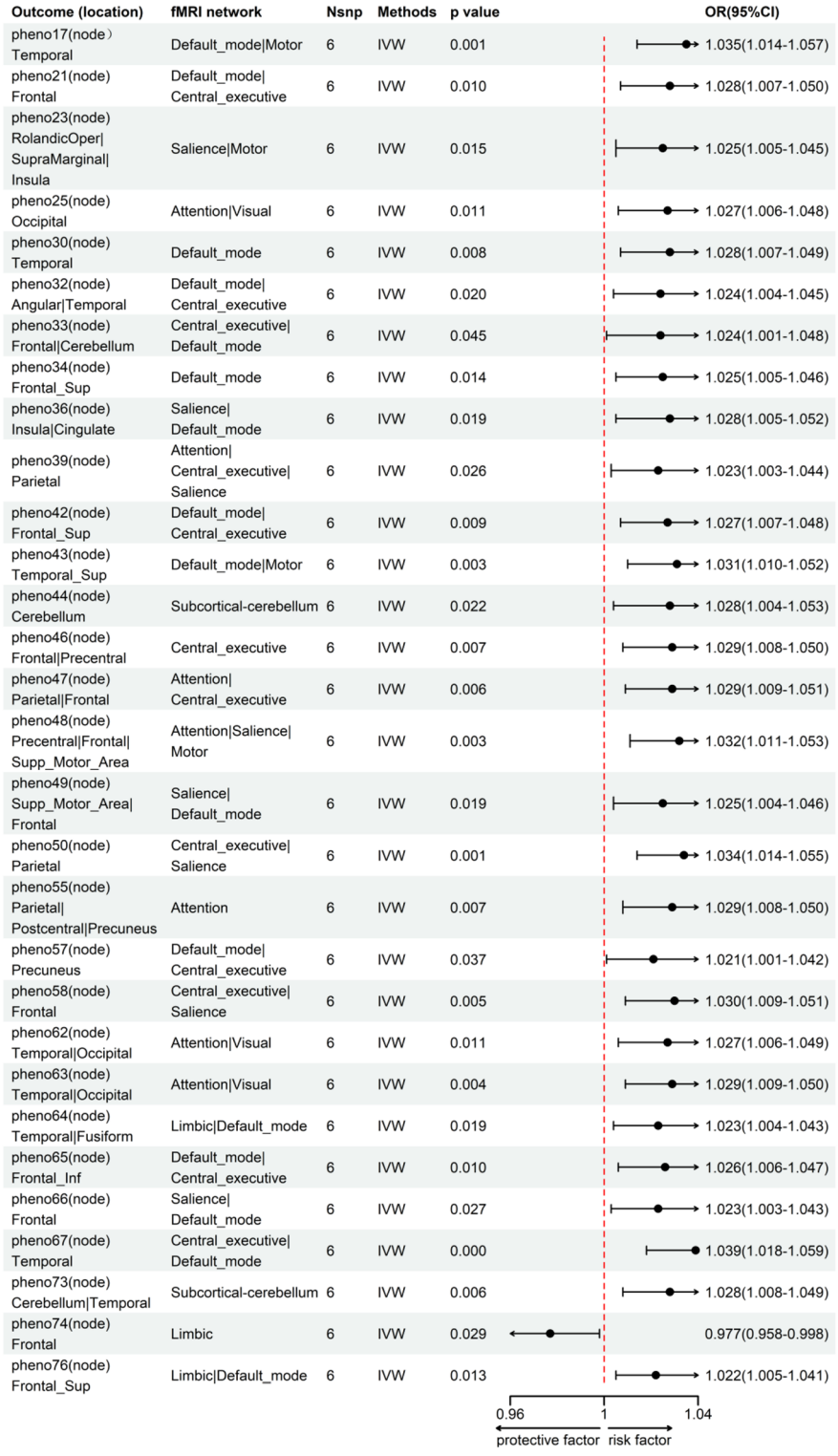

Fig. 3 The results of the significant causalities estimated between SS risk and rsfMRI phenotypes (node) using the MR-IVW method ($P < 0.05$). fMRI, resting-state functional magnetic resonance imaging; Nsnp: number of SNPs; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted

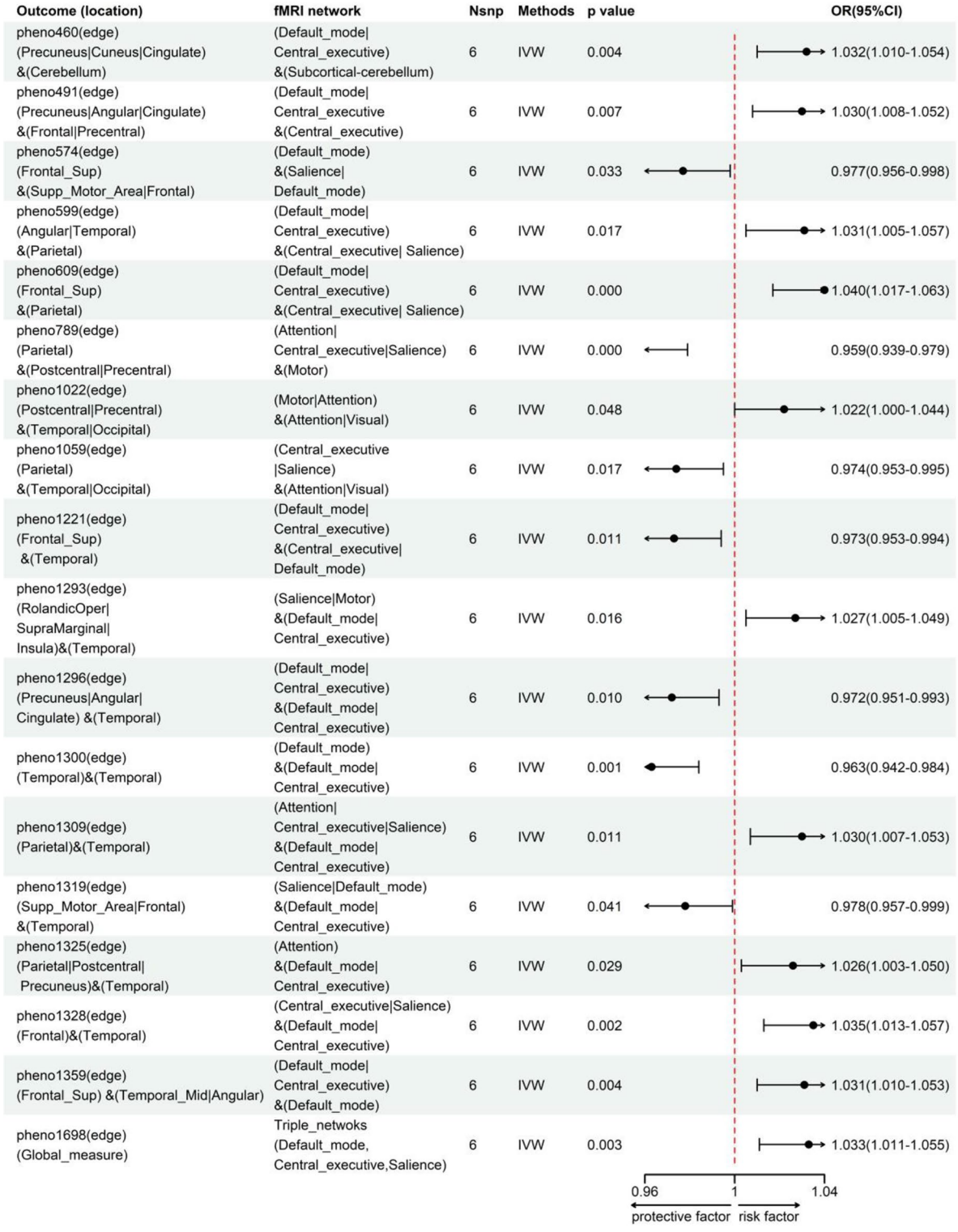

Fig. 4 The results of the significant causalities estimated between SS risk and rsfMRI phenotypes (edge) using the MR-IVW method ($P < 0.05$). fMRI, resting-state functional magnetic resonance imaging; Nsnp: number of SNPs; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted

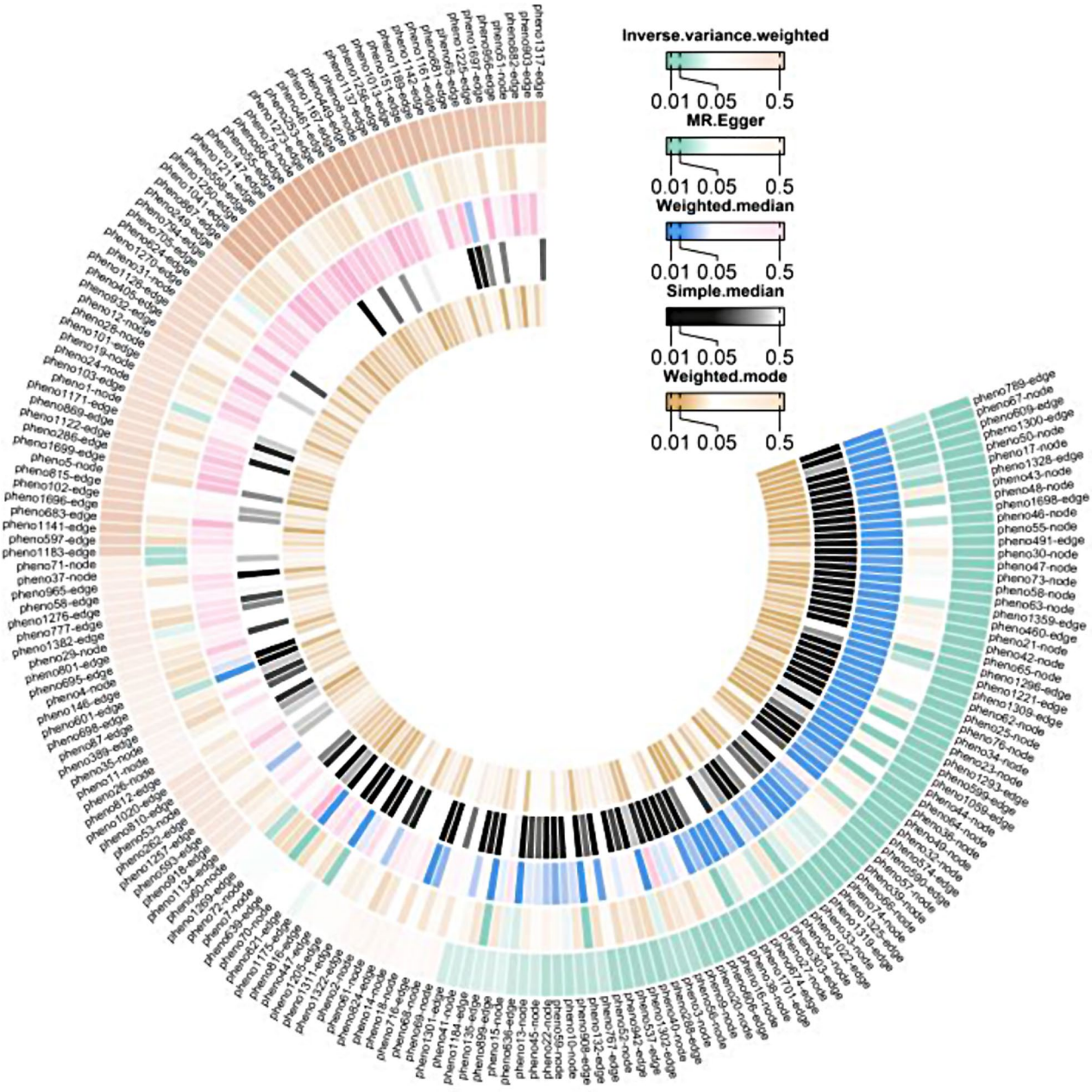

Fig. 5 All results of causalities between SS risk and rsfMRI phenotypes using five MR methods, the data points are arranged in a clockwise direction based on the increasing order of p-values obtained from the IVW method

lobe network (IVW OR = 1.040, 95% CI: 1.017–1.063, $P = 0.000$), frontal lobe and temporal lobe network (IVW OR = 1.035, 95% CI: 1.013–1.057, $P = 0.002$), global measure network (IVW OR = 1.033, 95% CI: 1.011–1.055, $P = 0.003$), precuneus or cuneus or cingulate cortex and cerebellum (IVW OR = 1.032, 95% CI: 1.010–1.054, $P = 0.004$), superior frontal gyrus and middle temporal gyrus or angular gyrus (IVW OR = 1.031, 95% CI: 1.010–1.053, $P = 0.004$), which were the five phenotypes with the strongest effect size. The MR-Egger test and MR-PRESSO global test did not reveal significant horizontal pleiotropy, Cochrane' Q test and leave-one-out sensitivity (Supplementary Figs. S6–S53) did not reveal significant heterogeneity. After FDR correction, 6 causal relationships between SS and the 191 rsfMRI phenotypes remained significant. Specifically, SS risk was positively associated with neural activity in the temporal lobe (P_{FDR} = 0.020/0.035), and parietal lobe (P_{FDR} = 0.032) at resting state. Additionally, a higher risk of SS decreased the connectivity between the parietal lobe and postcentral gyrus (P_{FDR} = 0.014), as well as the functional connectivity of the temporal lobe and temporal lobe (P_{FDR} = 0.025), increased

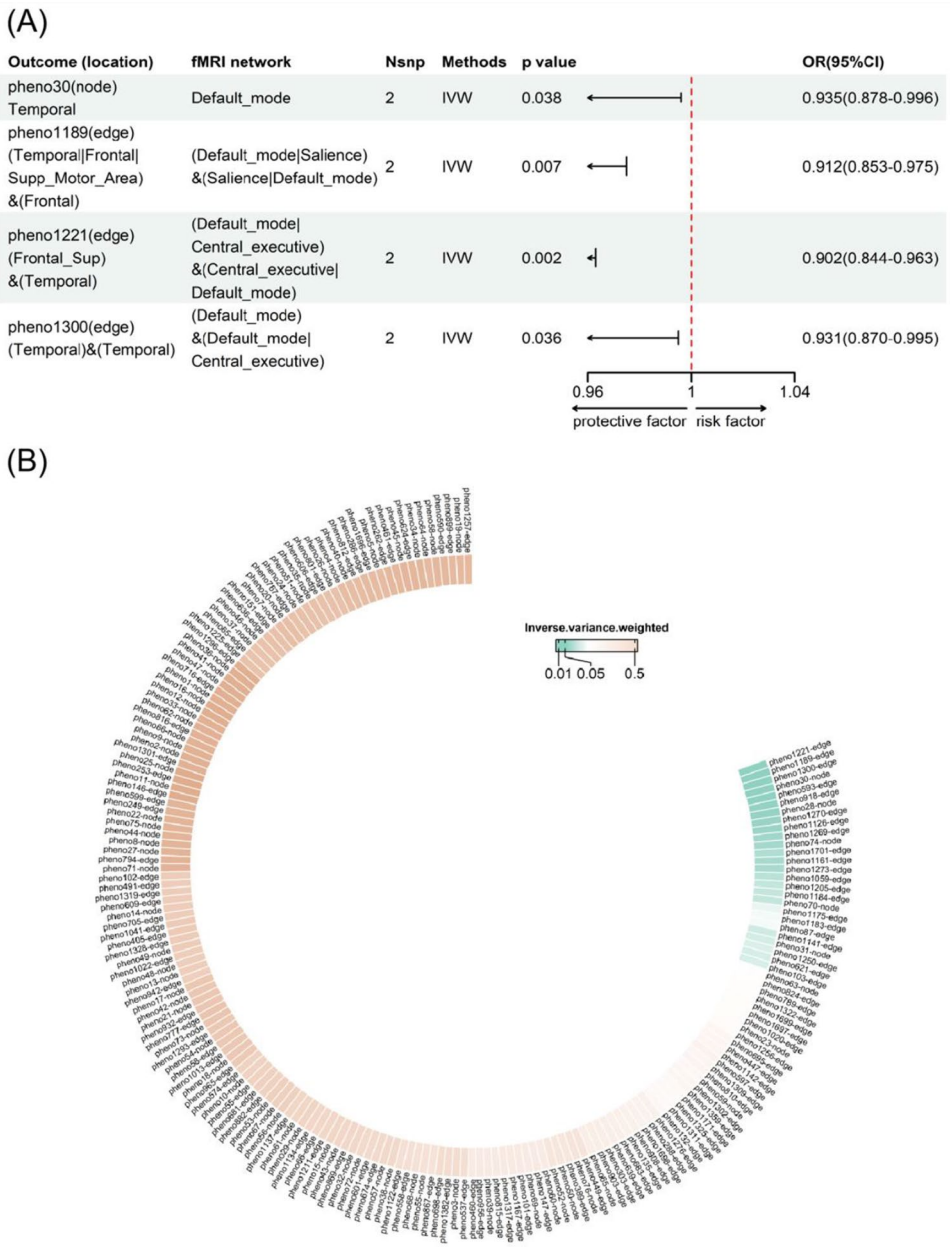

Fig. 6 (**A**) The results of the significant causalities estimated between HT risk and rsfMRI phenotypes using the MR-IVW method ($P < 0.05$) and (**B**) All results of causalities between HT risk and rsfMRI phenotypes using the MR-IVW method, the data points are arranged in a clockwise direction based on the increasing order of p-values obtained from the IVW method. fMRI, resting-state functional magnetic resonance imaging; Nsnp: number of SNPs; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted

functional connectivity of the superior frontal gyrus and parietal lobe (P_{FDR} = 0.025) (Supplementary Fig. S54).

Effects of HT on brain functional networks

We identified 4 causal relationships between the risk of HT and rsfMRI phenotypes. As shown in Fig. 6 and Supplementary Table S4, a higher risk of HT decreased the spontaneous neural activity of the temporal lobe (IVW OR = 0.935, 95% CI: 0.878–0.996, $P = 0.038$), decreased the functional connectivity of the temporal lobe or frontal lobe or supplementary motor area and frontal lobe (IVW OR = 0.912, 95% CI: 0.853–0.975, $P = 0.007$), decreased the connectivity between the superior frontal gyrus and temporal lobe (IVW OR = 0.902, 95% CI: 0.844–0.963, $P = 0.002$), decreased functional connectivity of the temporal lobe and temporal lobe (IVW OR = 0.931, 95% CI: 0.870–0.995, $P = 0.036$), which mainly affect default mode network, default mode or salience and salience or default mode network, default mode or central executive and central executive or default mode network, default mode

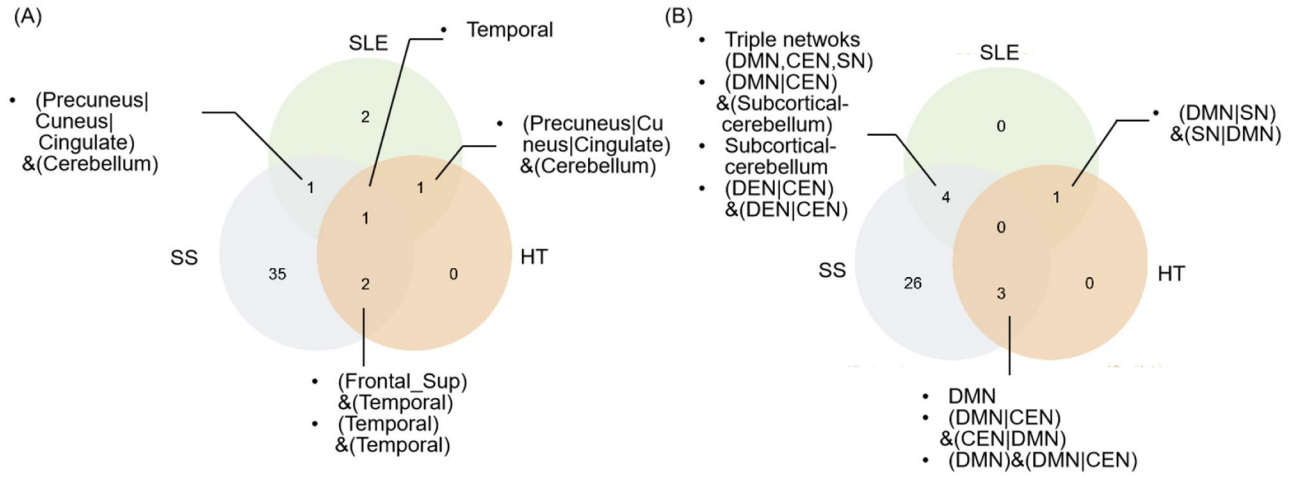

Fig. 7 Identification of robust causal rsfMRI phenotypes associated with SLE, SS, and HT using the Venn Diagram. (**A**) rsfMRI phenotypes (nodes); (**B**) rsfMRI phenotypes (edges). SLE, Systemic Lupus Erythematosus; SS, Sjögren's Syndrome; HT, Hashimoto's Thyroiditis; DMN, default mode network; SN, salience network; CEN, central executive network

Outcome	Exposure	Nsnp	Methods	p value	OR(95%CI)
3-methyl-2-oxovalerate levels	Hashimoto's thyroiditis	2	IVW	0.042	0.925(0.858-0.997)
4-acetamidobutanoate levels	Hashimoto's thyroiditis	2	IVW	0.006	0.889(0.816-0.967)
Acisoga levels	Hashimoto's thyroiditis	2	IVW	0.006	0.723(0.575-0.910)
Fructose levels	Hashimoto's thyroiditis	2	IVW	0.049	1.075(1.000-1.156)
Homocarnosine levels	Hashimoto's thyroiditis	2	IVW	0.031	0.654(0.445-0.961)
Hydroxy-cmpf levels	Hashimoto's thyroiditis	2	IVW	0.040	1.517(1.019-2.261)
Indoleacetate levels	Hashimoto's thyroiditis	2	IVW	0.010	0.717(0.556-0.924)
Tryptophan betaine levels	Hashimoto's thyroiditis	2	IVW	0.031	0.685(0.486-0.967)

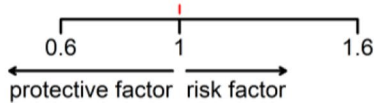

Fig. 8 The results of the significant causalities estimated between HT risk and CSF metabolites using the MR-IVW method ($P < 0.05$). Nsnp: number of SNPs; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted

and default mode or central executive network. The MR-Egger test and MR-PRESSO global test did not reveal significant horizontal pleiotropy, and Cochrane's Q test did not reveal significant heterogeneity. Insufficient number of SNPs for leave-one-out sensitivity analysis. However, after FDR correction no significant correlation was detected.

Specifically, we found that SLE, SS, and HT are significantly associated with a common brain region: the temporal lobe (Fig. 7). Additionally, we observed that SLE and SS were both related to the "triple networks". Although HT was not directly associated with the "triple networks", its functional network encompassed the default mode network (DMN), salience network (SN), and central executive network (CEN), suggesting potential dysregulation in these three functional networks.

MR of autoimmune diseases on CSF metabolites

We identified 8 causal relationships between the risk of HT and CSF metabolites. As shown in Fig. 8, Supplementary Fig. S55, and Supplementary Table S5, a higher risk of HT increased the Hydroxy-cmpf levels (IVW OR = 1.517, 95% CI: 1.019–2.261, $P = 0.040$), Fructose levels (IVW OR = 1.075, 95% CI: 1.000 -1.156, $P = 0.049$),

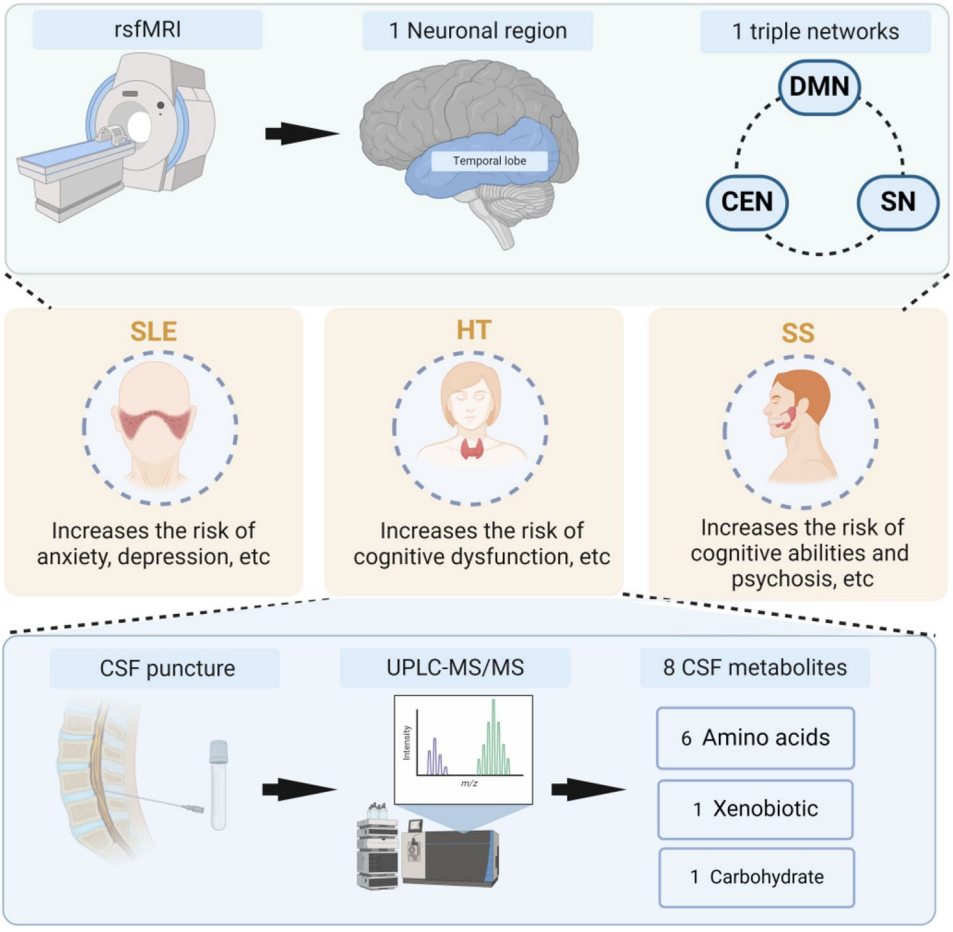

Fig. 9 Main results in the present study. The illustration was created using BioRender (https://biorender.com/). rsfMRI, resting-state functional magnetic resonance imaging; DMN, default mode network; SN, salience network; CEN, central executive network; SLE, Systemic Lupus Erythematosus; SS, Sjögren's Syndrome; HT, Hashimoto's Thyroiditis; CSF, cerebrospinal fluid, UHPLC-MS/MS, Ultra performance liquid chromatography/tandem mass spectrometry

decreased the 3-methyl-2-oxovalerate levels (IVW OR = 0.925, 95% CI: 0.858–0.997, $P = 0.042$), 4-acetamidobutanoate levels (IVW OR = 0.889, 95% CI: 0.816–0.967, $P = 0.006$), Acisoga levels (IVW OR = 0.723, 95% CI: 0.575–0.910, $P = 0.006$), Indoleacetate levels (IVW OR = 0.717, 95% CI: 0.556–0.924, $P = 0.010$), Tryptophan betaine levels (IVW OR = 0.685, 95% CI: 0.486–0.967, $P = 0.031$), and Homocarnosine levels (IVW OR = 0.654, 95% CI: 0.445–0.961, $P = 0.031$). The MR-Egger test and MR-PRESSO global test did not reveal significant horizontal pleiotropy, and Cochrane's Q test did not reveal significant heterogeneity. Insufficient number of SNPs for leave-one-out sensitivity analysis. However, after FDR correction no significant correlation was detected.

Discussion

In this study, we employed a two-sample MR analysis to investigate the potential causal relationships between three autoimmune diseases: SLE, SS, and HT, and 191 rsfMRI phenotypes, as well as 338 CSF metabolites. The research identified SLE risk was associated with 5 rsfMRI phenotypes, SS was associated with 48 rsfMRI phenotypes, and HT was significantly associated with 4 rsfMRI phenotypes. Additionally, all of three diseases were significantly associated with the temporal lobe and triple networks (DMN, SN, and CEN). In addition, HT was identified to have a causal relationship with 8 CSF metabolites, including 6 amino acids, 1 xenobiotic, and 1 carbohydrate. The primary results of this study were summarized in Fig. 9. These results may provide novel insights into the pathophysiology of autoimmune disease-related psychiatric disorders and hint at potential new non-invasive therapeutic strategies for these conditions.

The prevalence of psychiatric disorders in SLE is 14 -75%, manifested by a wide variety of psychiatric clinical symptoms including insomnia, anxiety disorders, depression, schizophrenia, mood disturbances, etc., especially anxiety and depression [26]. Our study found that the SLE risk was positively associated with increased global functional connectivity, indicating impaired global functional connectivity of the triple networks in SLE patients.

The triple networks consist of the SN, CEN, and DMN, which are the three core networks for cognition [27]. Accumulating evidence indicates the dysregulation of triple networks plays a pivotal role in the pathogenesis of psychiatric disorders [28, 29]. The dynamic interplay between these three networks is crucial for facilitating complex, goal-directed behaviors. Disturbances in these interactions can lead to aberrant mappings of external stimuli and internal mental processes, potentially contributing to maladaptive behaviors and cognitive deficits [30]. The SN primarily comprises the anterior insula and the dorsal anterior cingulate cortex, and disruptions within this network may underlie the reduced attention to social stimuli observed in patients with autism spectrum disorder (ASD). The DMN encompasses the medial prefrontal cortex (PFC), posterior cingulate cortex, precuneus, and temporoparietal junction, with dysfunction in this network potentially suggesting to be an early marker for cognitive dysfunction in SLE [13]. In patients with SLE, increased connectivity in posterior DMN regions have been observed compared to healthy controls. Specifically, a study by Papadaki et al. reported hyperconnectivity in the posterior DMN, particularly in the precuneus and superior parietal lobe in both SLE patients with and without neuropsychiatric symptoms [30]. Furthermore, perfusion disturbances have been detected in the DMN of SLE patients. Barraclough et al. noted that SLE patients with greater disease activity demonstrated increased hemodynamic lag in the posterior cingulate cortex, a key node of the DMN. These findings highlight the interplay between cerebral perfusion and functional connectivity within the DMN in SLE, which may contribute to cognitive dysfunction observed in SLE patients. The CEN includes the dorsolateral PFC and parietal cortex, and impairments in this network may account for the deficits in cognitive flexibility [16]. Abnormalities in CEN connectivity have been observed in lupus patients, both with and without neuropsychiatric manifestations, through resting-state functional MRI studies. These findings suggest potential impairments in cognitive control and executive functions in SLE, which may be associated with the disease process itself or related comorbidities [30]. In addition to the above-mentioned networks, our MR analysis also observed the higher risk of SLE increased the functional connectivities of the cerebellum or temporal involved in subcortical-cerebellum network, which is an important component of the brain functional networks and it modulates cognitive functions [31]. The observed abnormalities in these network further suggest that SLE risk may lead to widespread network connectivity impairments, encompassing the DMN, CEN, SN, and subcortical-cerebellum networks, ultimately contributing to cognitive disorders in SLE patients.

It is well established that SS patients have a higher prevalence of depressive disorder and anxiety disorder, sleeping disorder, bipolar disorder, schizophrenia, and cognitive impairment [32]. Cognitive dysfunction is particularly prevalent, some studies indicated that 80% of SS patients exhibit varying degrees of cognitive impairment [33]. However, the physiological traits underlying psychiatric disorders in SS are little known. We focused on underlying neural traits and function networks in SS using a rsfMRI method. In this study, our MR results showed a fairly complex landscape of SS rsfMRI traits, which indicates widespread involvement of brain regions and functional networks. We uncovered a causal relationship between SS and 48 rsfMRI phenotypes, including 30 amplitude traits (nodes) that reflect regional spontaneous neural activity, and 18 pairwise functional connectivities (edges) that quantify the interregional coactivity. For amplitude traits, the 5 functional brain regions with the strongest effect size were the temporal lobe, parietal lobe, precentral gyrus or frontal lobe or supplementary motor area, and superior temporal gyrus. Specially, SS risk increased the abnormal brain activities of the above five regions involving central executive or default mode network, default mode or motor network, central executive and salience network, attention or salience or motor network, and default mode or motor network, which essentially cover triple networks. Temporal lobe abnormalities are implicated in language comprehension, memory deficits, and emotional disturbances in cognitive disorders like Alzheimer's disease [34]. Frontal lobe dysfunctions contribute to executive dysfunction, attention deficits, and social impairments seen in frontal-temporal dementia and Parkinson's disease with cognitive decline [35]. Parietal lobe disturbances can lead to somatosensory deficits, apraxia, and spatial perception impairments, evident in parietal lobe dementia and subcortical vascular dementia [36]. The technetium-99 m−ethyl cysteinate dimer (99mTc-ECD) brain single-photon emission computed tomography (SPECT) detected significantly more hypoperfused areas in SS patients, mainly in frontal, parietal, and temporal cortices, which are significantly associated with neuropsychological assessment abnormalities, primarily executive and visuospatial disorders [37]. For functional connectivity traits, SS risk also increased functional connectivities of global measure in triple networks. This significance persisted even after FDR correction. Taken together, our MR-based evidence indicated that SS has an impact on the neuronal activity of the temporal lobe, parietal lobe, precentral gyrus or frontal lobe or supplementary motor area, etc., and functional connectivity of triple networks.

In this study, we also explored the causal relationships between HT and 191 rsfMRI phenotypes. The results indicated that HT risk was negatively associated

with decreased neural activity of the temporal lobe, and decreased functional connectivity of the temporal lobe or frontal lobe or supplementary motor area and frontal lobe, which mainly affect triple networks. Integrating the findings above, it can be concluded that SLE, SS, and HT were significantly associated with a common brain region: the temporal lobe. The temporal lobe primarily includes the primary auditory cortex, Wernicke's area, Broca's area, and the hippocampus, which play key roles in auditory processing, language comprehension, memory formation and retrieval, and emotion regulation. Dysfunction of the temporal lobe has been implicated in various mental disorders, including anxiety, depression, and so on [38]. Researches suggest that the amygdala, involved in fear processing and emotional learning, may contribute to anxiety symptoms when hyperactive [39]. The hippocampal atrophy and neuronal loss, observed in depression, may lead to cognitive impairments, exacerbating depressive symptoms [40]. Moreover, abnormal functional connectivity between the temporal lobe and other brain regions may also contribute to the development of these conditions [41]. Additionally, we observed that SLE, SS, and HT were both related to the core networks for cognition– triple networks as mentioned above.

In addition, we also explored the causal relationship between three autoimmune diseases and CSF metabolites. Our findings did not reveal a causal relationship between SLE, SS, and CSF metabolites. However, we did identify HT was associated with 8 metabolites. Some of these metabolites have well-established roles and mechanisms in mental disorders. The latest cohort data from 2000 individuals indicated that high levels of glucose were associated with future risk of depression, anxiety, and stress-related disorders [42]. Current studies suggested that tryptophan betaine, derived from tryptophan, has beneficial effects on neuroprotection and combating cellular oxidative stress. For neurodegenerative diseases like Alzheimer's and Parkinson's, betaine may be a therapeutic approach. Based on this, we believe that tryptophan betaine complexes may serve as blood biomarkers for autoimmune psychosis [43].

Our advantage lies in the utilization of a large-scale GWAS summary dataset of rsfMRI, valuable cerebrospinal fluid metabolomics data for MR analysis. The rsfMRI data offers a more sensitive approach to studying brain diseases compared to conventional MRI by focusing on functional connectivity and subtle changes in brain activity. This allows for the detection of altered patterns of communication between brain regions, even before the onset of clinical symptoms or structural abnormalities. For example, rsfMRI studies in SLE patients have revealed altered functional connectivity within and between critical brain networks, associated with cognitive dysfunction and neuropsychiatric symptoms, even in patients with stable disease [44]. This study employed rsfMRI data to explore functional connectivity abnormalities in autoimmune psychosis, aiming to understand their neural substrates and facilitate early identification and non-invasive treatments such as repetitive transcranial magnetic stimulation (rTMS) or non-invasive brain stimulation (NIBS).

The present study has the following limitations: Firstly, given that the relationships between these three types of autoimmune diseases and the occurrence of mental disorders are already established, this research will not elaborate further on the MR analysis of the causal relationship between autoimmune diseases and psychosis. Secondly, since the GWAS datasets we used are mainly from European populations, more work is needed to validate our findings in other populations. Finally, despite the rigorous steps taken to identify and account for instrumental variable anomalies, the potential for horizontal pleiotropy effects may still be present. Despite these limitations, to the best of our knowledge, this is presumably the first study to utilize MR analysis to investigate the causal relationships between autoimmune diseases and rsfMRI traits, and CSF metabolites, aiming to uncover the pathogenesis of autoimmune psychosis.

Conclusions

In summary, we identified 5 causal relationships between SLE and 191 rsfMRI phenotypes, 48 between SS and 191 rsfMRI phenotypes, and 4 between HT and 191 rsfMRI phenotypes, along with 8 causal relationships between HT and CSF metabolites. Our study pinpoints important brain functional networks and CSF metabolites potentially implicated in the pathogenesis of autoimmune psychosis and highlights critical brain regions for the development of novel therapeutics.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06113-1.

Supplementary Material 1

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Author contributions

Weiman Shi: Writing original draft, Conceptualization, Formal analysis, Methodology, Software. Min Chen: Writing original draft, Conceptualization, Formal analysis, Methodology. Rongai Wang: Investigation, Validation, Visualization. Chengping Wen: Conceptualization, Supervision, Writing review & editing. Lin Huang: Conceptualization, Supervision, Writing review & editing. Qiao Wang: Conceptualization, Supervision, Writing review & editing.

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Declarations

Ethics approval
This MR research utilized only published or publicly available GWAS data. Each participant received ethical approval and informed consent for the respective study, as detailed in the original publication and consortium.

Competing interest
None declared.

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