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Irritable Bowel Syndrome Is Associated With Brain Health by Neuroimaging, Behavioral, Biochemical, and Genetic Analyses

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ABSTRACT

BACKGROUND: Irritable bowel syndrome (IBS) interacts with psychopathology in a complex way; however, little is known about the underlying brain, biochemical, and genetic mechanisms.

METHODS: To clarify the phenotypic and genetic associations between IBS and brain health, we performed a comprehensive retrospective cohort study on a large population. Our study included 171,104 participants from the UK Biobank who underwent a thorough assessment of IBS, with the majority also providing neuroimaging, behavioral, biochemical, and genetic information. Multistage linked analyses were conducted, including phenome-wide association analysis, polygenic risk score calculation, and 2-sample Mendelian randomization analysis.

RESULTS: The phenome-wide association analysis showed that IBS was linked to brain health problems, including anxiety and depression, and poor cognitive performance. Significantly lower brain volumes associated with more severe IBS were found in key areas related to emotional regulation and higher-order cognition, including the medial orbitofrontal cortex/ventromedial prefrontal cortex, anterior insula, anterior and mid-cingulate cortices, dorsolateral prefrontal cortex, and hippocampus. Higher triglycerides, lower high-intensity lipoprotein, and lower platelets were also related ($p < 1 \times 10^{-10}$) to more severe IBS. Finally, Mendelian randomization analyses demonstrated potential causal relationships between IBS and brain health and indicated possible mediating effects of dyslipidemia and inflammation.

CONCLUSIONS: For the first time, this study provides a comprehensive understanding of the relationship between IBS and brain health phenotypes, integrating perspectives from neuroimaging, behavioral performance, biochemical factors, and genetics, which is of great significance for clinical applications to potentially address brain health impairments in patients with IBS.

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Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain, bloating, and bowel dysfunction that affects approximately 1 in 10 people worldwide (1,2). A growing body of evidence suggests that IBS is associated with brain health. Individuals with IBS have an increased risk of developing mental health conditions, including anxiety disorders, depressive disorders, and somatic symptom disorders (3–5). Primarily because of a lack of diverse data, almost all previous studies of the association between IBS and brain health have focused on one (or a few) specific phenotype. The overall picture of the phenotypic links between IBS and brain health in the general population remains unclear.

There has been increasing recognition of the potential role of dysfunction of the brain-gut axis (6–8) in the pathogenesis of IBS and its impact on brain health. Brain regions in frontolimbic and sensorimotor networks showed abnormal functional connectivity in IBS individuals with depressive symptoms (9). Treatments targeting the disordered brain-gut axis in IBS had potentially positive effects, which suggests that maintaining brain health may benefit patients with IBS (10). These previous studies suggest a potential role for brain structure and function in the pathogenesis of IBS. However, few neuroimaging studies have examined the association between the brain and IBS, and the sample sizes have been relatively small (usually dozens of participants) (9,11,12). Moreover, contemporary research primarily emphasizes brain regions at a broader level rather than implementing voxel-level analysis, which offers higher resolution, enabling the precise identification of specific brain regions linked to IBS. These may limit the ability to capture robust and stable IBS-related brain alterations that may also be correlated with brain health.

Emerging evidence suggests an association between IBS and metabolic dysregulation as well as immune system activation, which implies that biochemical factors in the peripheral nervous system may play a role in IBS pathophysiology because the brain-gut axis involves a complex network of

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interactions (13–15). Despite the increasing evidence, previous studies have predominantly concentrated on microbiome metabolism, and there has been limited exploration of individual metabolism using blood indicators (16,17). Meanwhile, to gain a deeper understanding of the inherent biological link between IBS and brain health, a recent study conducted from a genetic perspective has identified shared genes between IBS and mood disorders (18). However, the genetic predisposition between IBS and brain health and biochemical factors remains unknown. Taking all of the above together, the neurobiological substrates that link IBS and brain health are complex and multifaceted, encompassing phenotypes, endophenotypes (neuroimaging), biochemical factors, and genetic information. There is a pressing need for an integrated framework that encompasses diverse data modalities, enabling a comprehensive understanding of the neurobiological underpinnings, which will enhance our understanding of the links between IBS and brain health.

In this study, to determine the association between IBS and brain health and correlated biological substrates, we analyzed data from 171,104 participants from the UK Biobank (UKB) with various measurements such as brain imaging, behavioral assessments, biochemical markers, and genetic information. Our primary aim was to investigate the association between IBS and brain health, examining their phenotypic and genetic connections. We set 3 main objectives for this study. The first aim was to explore the relationship between IBS symptoms and brain health measures. The second aim was to estimate the relationships between IBS symptoms and brain structure and biochemical markers, which may provide great insight into brain-gut interactions in IBS. Finally, we aimed to clarify the potential genetic association between IBS symptoms, brain health, and biochemical indicators using Mendelian randomization (MR) analysis. We hypothesized that IBS would be phenotypically and genetically associated with a broad range of brain health–related phenotypes and biochemical indicators, such as depression, anxiety, brain structure, dyslipidemia, and inflammation markers.

METHODS AND MATERIALS

Study Population

We utilized data from the UKB cohort, which included 500,000 participants between ages 38 and 72 years at recruitment. The UKB cohort was approved by the North West Multi-centre Research Ethics Committee (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics), which provided oversight for this study. Written informed consent was obtained from all participants. The data utilized in the analyses presented herein include demographic characteristics, assessments of IBS, behavioral assessments, diet assessments, neuroimaging scans, and biochemical markers (Table S1 in Supplement 2). IBS symptoms were measured by the Digestive Health Questionnaire (2017–2018), which defined the IBS symptom severity score (IBS-SSS) as the total score of 5 items (Table S2 in Supplement 2). Three items had a prompt question with a "No" or "Yes" answer, for example, "Do you currently (in the last 3 months) suffer from abdominal pain?". Answering "No" would produce a 0 score, and answering "Yes" would result in the participant being given a 0 to 100 scale to report their severity, such as "How severe is your abdominal pain? (0 meaning no pain and 100 meaning severe pain)". The other 2 items were related to bowel habit satisfaction and life interference and used a 0 to 100 score to measure severity. The IBS-SSS was calculated for 171,104 participants, and a high score indicated severe symptoms. In the current study, we focused on IBS symptoms rather than IBS diagnosis (n = 44,993) (Supplement) because the timing of collection of the IBS-SSS coincided with the data collection time for most brain health phenotypes, ensuring a reasonable association between them to avoid time interval bias as much as possible. Nevertheless, we also included IBS diagnostic data for validation in our case-control analysis.

Statistical Analysis

Association of IBS With Behavioral, Neuroimaging, and Biochemical Markers. First, we performed a phenome-wide association analysis on the IBS-SSS and the polygenic risk score (PRS) of IBS-SSS. The R package PHESANT (19), an automated rule-based tool, was used for processing. Phenotypes were categorized into 4 data formats, including continuous, ordered categorical, unordered categorical, and binary. The analysis encompassed phenotypes from various UKB categories following a previous study (20), including population characteristics, health-related outcomes, assessment centers, and online follow-up. For specificity and clarity, we selected a finer classification, which resulted in 20 categories following the UKB showcase framework (Supplement). Then, we focused the analysis on the associations between IBS symptom and brain health measures (mental health and cognitive function). To further explore the potential influential factors between IBS and brain health, we analyzed the associations of IBS symptoms with diet intake, brain structure (gray matter volume at the voxel level), and biochemical markers, which may play an important role in brain-gut interactions with IBS. Finally, we used clinical IBS diagnosis to replicate identified associations. The following variables were used as covariates: age, sex, body mass index, Townsend deprivation index, educational qualifications, smoking status, and drinking status. In addition, total intracranial volume and scanning site were added as covariates in the neuroimaging analysis, and genetic principal components were added as covariates in the PRS analysis. False discovery rate correction was performed in the brain structure association analysis, and Bonferroni correction was used in other analyses. A corrected p value $< .05$ was set as the level for significance.

Functional Annotation, Neurotransmitter, and Transcriptomic Analyses Related to IBS-Associated Brain Map. We performed a voxel-level association analysis between IBS and brain structure to generate an IBS-associated brain map for subsequent analyses. First, we used Neurosynth (21) to decode functions of brain regions exhibiting associations with IBS. Secondly, we used JuSpace (22) to identify neurotransmitter maps correlated with the IBS-associated brain map (Table S3 in Supplement 2). Finally, we used a partial least squares (PLS) regression to explore the weighted linear combinations of expression patterns for 15,408 genes from the Allen Human Brain Atlas database (23,24) and ranked genes according to their associations with the IBS-associated brain map. Then we used Metascape (25) to

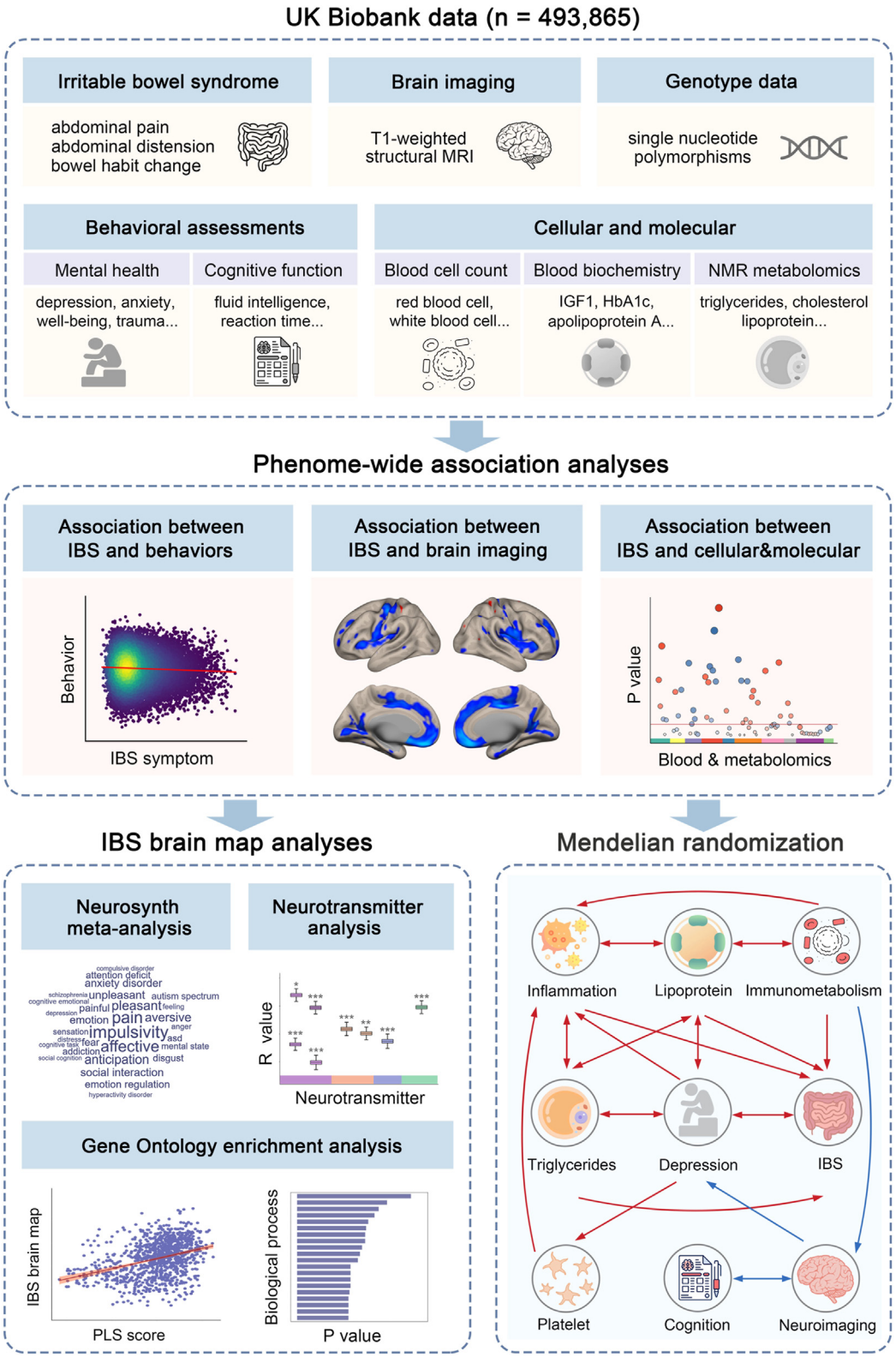

Figure 1. Study design. (Top panel) UK Biobank data utilized in the study, including irritable bowel syndrome (IBS), brain imaging, genotype data, behavioral assessments, and cellular and molecular data. (Middle panel) Association of IBS with behavioral assessments, brain imaging, cellular, and molecular data. (Bottom left panel) IBS-associated brain map analyses, including Neurosynth meta-analysis, neurotransmitter analysis, and gene ontology enrichment analysis. (Bottom right panel) Directional association of IBS with behavioral assessments, brain imaging, and cellular and molecular data. HbA1c, glycated hemoglobin A1c; IGF1, insulin-like growth factor 1; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance; PLS, partial least squares.

identify the gene ontology (GO) terms that were enriched at the top and bottom of the ranked gene list. A permutation test (n = 10,000) was performed to test the significance (false discovery rate correction, $p < .05$), using BrainSMASH (26) to generate surrogate maps. Other details are provided in the Supplement.

Genetic Associations Between IBS and Categories of Interest by MR Analysis. To further investigate the relationships between IBS and different indicator systems, we investigated potential phenotypic and genetic associations between IBS and typical brain health markers representative of each indicator system. First, phenotypic associations involved 10 categories, including IBS-SSS, IBS-SSS PRS, depression, cognitive function, neuroimaging, immunometabolism, lipoprotein particle concentrations, triglycerides, inflammation, and platelets. For categories that had multiple phenotypes, we selected the phenotypes that were significantly associated with IBS in each category (Table S4 in Supplement 2), then adjusted directions according to their associations with IBS, and finally, normalized and averaged the values to represent a categorical score.

Second, genetic associations were investigated using 2-sample MR analyses, including inverse-variance weighting (IVW), weighted median, and MR-Egger implemented in the R package TwoSampleMR (https://mrcieu.github.io/TwoSampleMR/). MR analyses were performed using the same categories as phenotypic associations, excluding IBS-SSS PRS. The genetic instruments were selected at $p < 1 \times 10^{-6}$, and then we removed correlated single nucleotide polymorphisms ($r^2 > 0.1$). We performed the heterogeneity test using the IVW (obtain the Q value) and MR-Egger (obtain the Q' value) models. Then Q_R value ($Q_R = Q' / Q$) was calculated to select models, where Q_R close to 1 represents IVW and MR-Egger fitting the model equally well, while Q_R much less than 1 represents the MR-Egger method being better. The pleiotropy test was performed using MR-Egger.

RESULTS

Demographic Information

We included 493,865 participants ages 47 to 84 years (54% female) at the time of completing the Digestive Health Questionnaire. A total of 171,104 participants ages 47 to 81 years (57% female) had an IBS-SSS, with a mean ± SD of 82.9 ± 89.9 (Figure S1 in Supplement 1); women had higher scores than men (Figure S2 in Supplement 1). In addition, 44,993 participants (34,365 participants with IBS-SSS) met the diagnostic criteria and served as IBS cases, and there were 301,070 control cases. IBS cases showed significantly higher IBS-SSS than controls ($t_{107,235} = 231$, $p < 1 \times 10^{-300}$) (Figure S3 in Supplement 1). A total of 492,004 participants had an assessment of depressive symptoms (Table S5 in Supplement 2), and 145,808 participants completed a detailed mental health questionnaire (Table S6 in Supplement 2). Data on cognitive function were collected through a touchscreen questionnaire (Table S7 in Supplement 2). We also included T1-weighted structural magnetic resonance imaging data of 39,578 participants in the analysis. The demographic characteristics of participants with IBS-SSS are shown in Table S8 in Supplement 2. Figure 1 shows the research approaches of the study.

Phenome-Wide Association Analyses Between IBS and Brain Health

Through the phenome-wide analysis, IBS symptoms showed associations with a wide range of phenotypes across 20 categories (Figure 2A; Table S9 in Supplement 2). Notably, the brain health–related phenotypes of psychosocial factors and mental health showed the highest t values (Figure 2B). In addition, the PRS of IBS symptoms also showed associations with psychosocial factors (Figures S4, S5 in Supplement 1; Table S10 in Supplement 2). Specifically, the severity of IBS symptoms was significantly correlated with each domain of mental health (Figure 2C; Table S11 in Supplement 2), such as depressive symptoms ($r = 0.229$, $p < 1 \times 10^{-300}$), anxiety symptoms ($r = 0.235$, $p < 1 \times 10^{-300}$), and well-being ($r = -0.244$, $p < 1 \times 10^{-300}$). These results indicated that having more severe IBS symptoms was correlated with poorer brain health status, which was further replicated in the IBS cases versus controls analysis (Table S12 in Supplement 2).

Meanwhile, lower cognitive function, another important reflector of brain health status, also showed significant associations with the severity of IBS symptoms (Figure 2C; Table S11 in Supplement 2), such as fluid intelligence ($r = -0.060$, $p = 1.28 \times 10^{-50}$), reaction time ($r = 0.017$, $p = 8.69 \times 10^{-13}$), and pair matching ($r = 0.025$, $p = 9.61 \times 10^{-25}$). These associations of IBS with mental health and cognitive function did not differ by sex (Table S11 in Supplement 2). Moreover, almost every mental health assessment was significantly correlated with the IBS-SSS PRS (Tables S13, S14 in Supplement 2). In addition, we identified the intake of 17 categories of food and drink that were significantly associated with IBS symptoms (Table S15 in Supplement 2). Intake of fresh fruit had the highest negative correlation with IBS ($r = -0.032$, $p = 7.67 \times 10^{-38}$), while salt-added foods had the highest positive correlation ($r = 0.033$, $p = 1.63 \times 10^{-42}$). The analysis also showed less fresh fruit intake among IBS cases (Table S16 in Supplement 2).

Association of IBS With Brain Structure and Biochemical Markers

Next, we estimated cortical and subcortical brain volumes related to IBS utilizing voxel-based morphometry analysis. Most of the significant regional brain volumes showed negative correlations with IBS symptoms (Figure 3; Figure S6 in Supplement 1; Table S17 in Supplement 2). The volumes of brain regions such as the medial orbitofrontal cortex/ventromedial prefrontal cortex extending into the anterior cingulate cortex, dorsolateral prefrontal cortex, anterior and mid-cingulate cortices, anterior insula, hippocampus, parahippocampal cortex, thalamus, precentral gyrus, and supplementary motor area were negatively associated with IBS symptoms. Positive associations were found for a few subcortical regions, including the globus pallidus, caudate, and putamen. In a case-control analysis, significantly lower volume was found for the mid-orbitofrontal cortex/ventromedial prefrontal cortex, parahippocampal gyrus, mid-cingulate cortex, and the triangular part of the inferior frontal gyrus (Figure S7 in Supplement 1).

We also observed that a total of 38 blood markers and 83 metabolic markers were significantly correlated with IBS

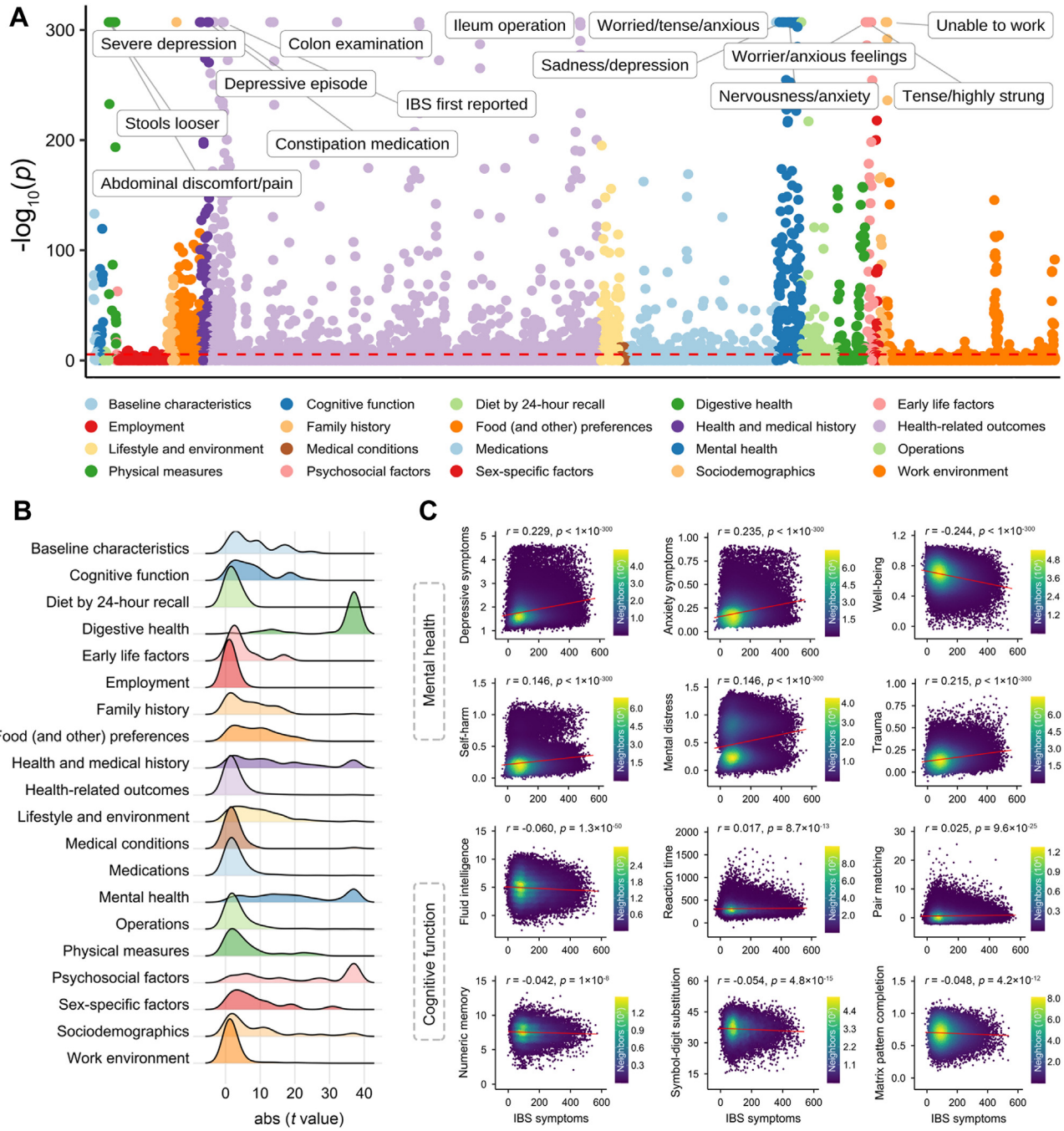

Figure 2. Phenome-wide association of irritable bowel syndrome (IBS). **(A)** Manhattan plot showing the *p* values for associations of IBS with phenotypes in 20 categories. The height of each data point denotes the negative logarithm of the univariate correlation *p* value between IBS and 1 phenotype. The color of the data point denotes different categories. The red dashed horizontal line denotes the Bonferroni threshold for multiple comparisons ($\alpha = 0.05$). The variables were adjusted for covariates of age, sex, and assessment center. **(B)** Plot showing the distribution of the absolute (abs) *t* value of the phenotypes in each category. **(C)** Density scatter plot and linear regression line showing the significant associations of IBS with behavioral assessments, including mental health (depressive symptoms, anxiety symptoms, well-being, self-harm, mental distress, and trauma) and cognitive function (fluid intelligence, reaction time, pair matching, numeric memory, symbol-digit substitution, and matrix pattern completion) after Bonferroni correction ($\alpha = 0.05$). The variables were adjusted for covariates of age, sex, body mass index, Townsend deprivation index, educational qualifications, smoking status, and drinking status.

(Bonferroni correction, $p < .05$) (Figure 3C). Triglycerides ($r = 0.038$, $p = 1.58 \times 10^{-53}$), high-density lipoprotein (HDL) cholesterol ($r = -0.037$, $p = 4.27 \times 10^{-46}$), red blood cell count ($r = -0.026$, $p = 1.76 \times 10^{-25}$), and neutrophil count ($r = 0.025$, $p = 1.57 \times 10^{-24}$) were among the most significant of the blood markers. For metabolite markers, cholesterol in very

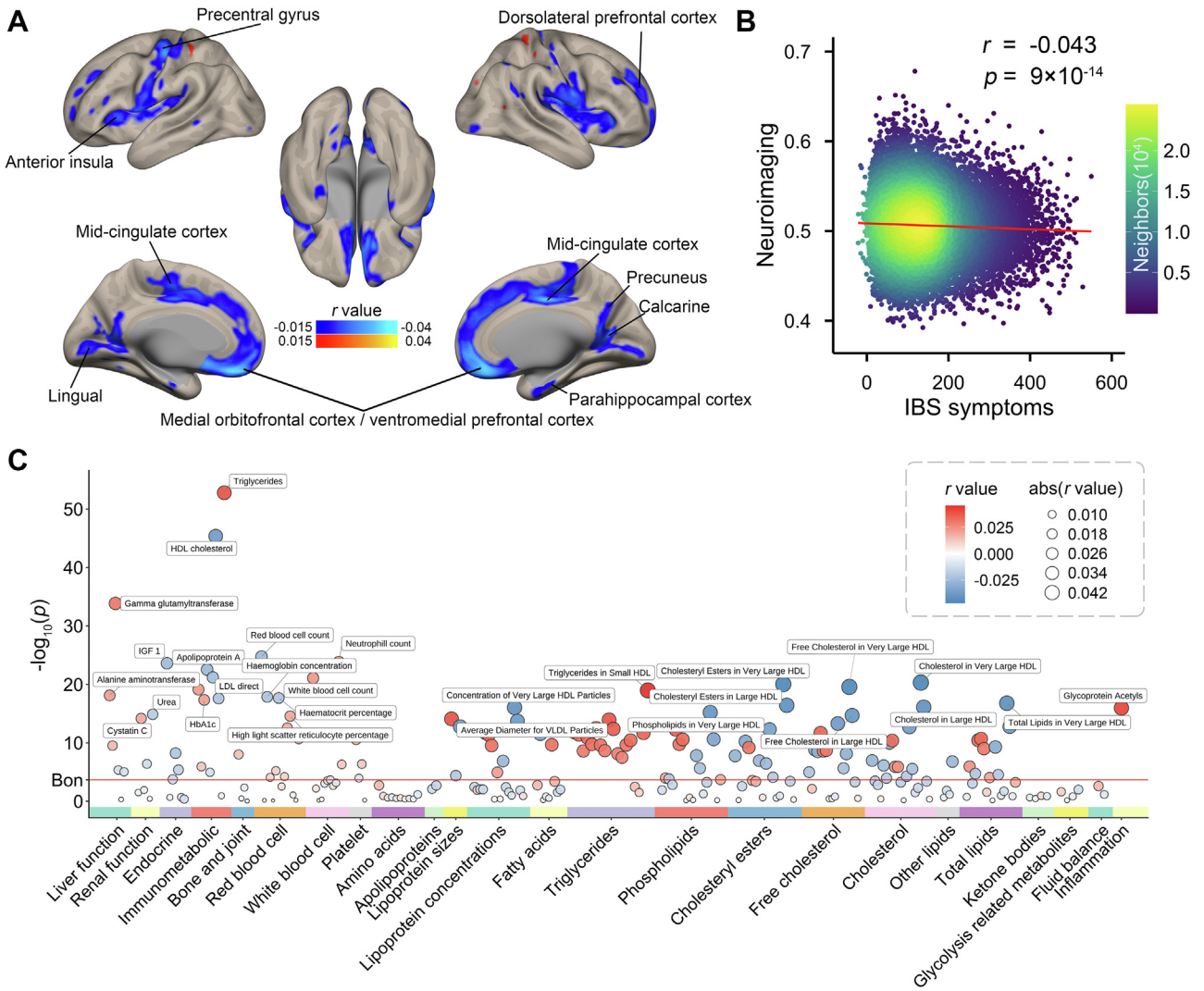

Figure 3. Association of irritable bowel syndrome (IBS) with brain structure and biochemical markers. **(A)** Significant associations between IBS and cortical volumes adjusted for age, sex, body mass index, Townsend deprivation index, educational qualifications, smoking status, drinking status, total intracranial volume, and imaging scanning sites after false discovery rate correction ($\alpha = 0.05$). **(B)** Significant association between IBS and the average brain volume of all negatively associated voxels, adjusted for age, sex, body mass index, Townsend deprivation index, educational qualifications, smoking status, drinking status, total intracranial volume, and imaging scanning sites. **(C)** Associations of IBS with biochemical markers, adjusted for age, sex, body mass index, Townsend deprivation index, educational qualifications, smoking status, and drinking status. The height of each data point denotes the negative logarithm of the univariate correlation p value between IBS and 1 marker. The color and size of the data point denote r value. The red horizontal line denotes the Bonferroni threshold for multiple comparisons ($\alpha = 0.05$). HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; IGF1, insulin-like growth factor 1; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

large HDL ($r = -0.047$, $p = 4.83 \times 10^{-21}$) and cholesteryl esters in very large HDL ($r = -0.046$, $p = 8.93 \times 10^{-21}$) were among the most significant. These biomarkers also consistently showed significant differences between IBS cases and controls. For example, the triglyceride level in IBS cases was higher than that in controls ($t = 13.94$, $p = 4.49 \times 10^{-44}$). Overall, most markers in the category immunometabolism showed high correlations with IBS, and each metabolite in the category triglycerides showed a positive correlation with IBS (r values = 0.011–0.045). More results are provided in Tables S18 and S19 in Supplement 2. In addition, we examined the correlations between brain volumes in regions associated with IBS and biochemical markers. Most of the brain regions were associated with at least one biochemical marker (Table S20 in Supplement 2). For example, the volume of the medial orbital gyrus was associated with the categories white blood cell, red blood cell, and immunometabolism.

Functional Annotation, Neurotransmitter Architecture, and Transcriptomic Profile Related to the IBS-Associated Brain Map

Brain volumes in the IBS-associated regions (Figure 3A) presented positive associations with cognitive performance such

as language skills and memory processing and negative associations with emotions such as impulsivity and affective disorders (Figure 4A; Table S21 in Supplement 2). Among neurotransmitters (22), serotonin transporter had the highest association (r = −0.226, p = .001) with the brain regions associated with IBS (Figure 4B; Table S22 in Supplement 2). Then, we performed spatial association analyses between the IBS-associated brain volumetric map and gene expression profiles (23,24) using PLS regression (Table S23 in Supplement 2). The gene expression map of the first PLS (PLS1) component showed significant spatial association with the IBS-associated brain map (r = 0.353, p = .005) (Figure 4D). Finally, we ranked the genes according to the corrected weight in the PLS regression to perform gene ontology enrichment analysis. Based on the normalized PLS1 weights, there were 1574 genes in the PLS1+ gene set ($z > 4$) and 968 genes in the PLS1− gene set ($z < -4$). Figure 4E, F shows the top 20 cellular components, such as postsynapse and presynapse,

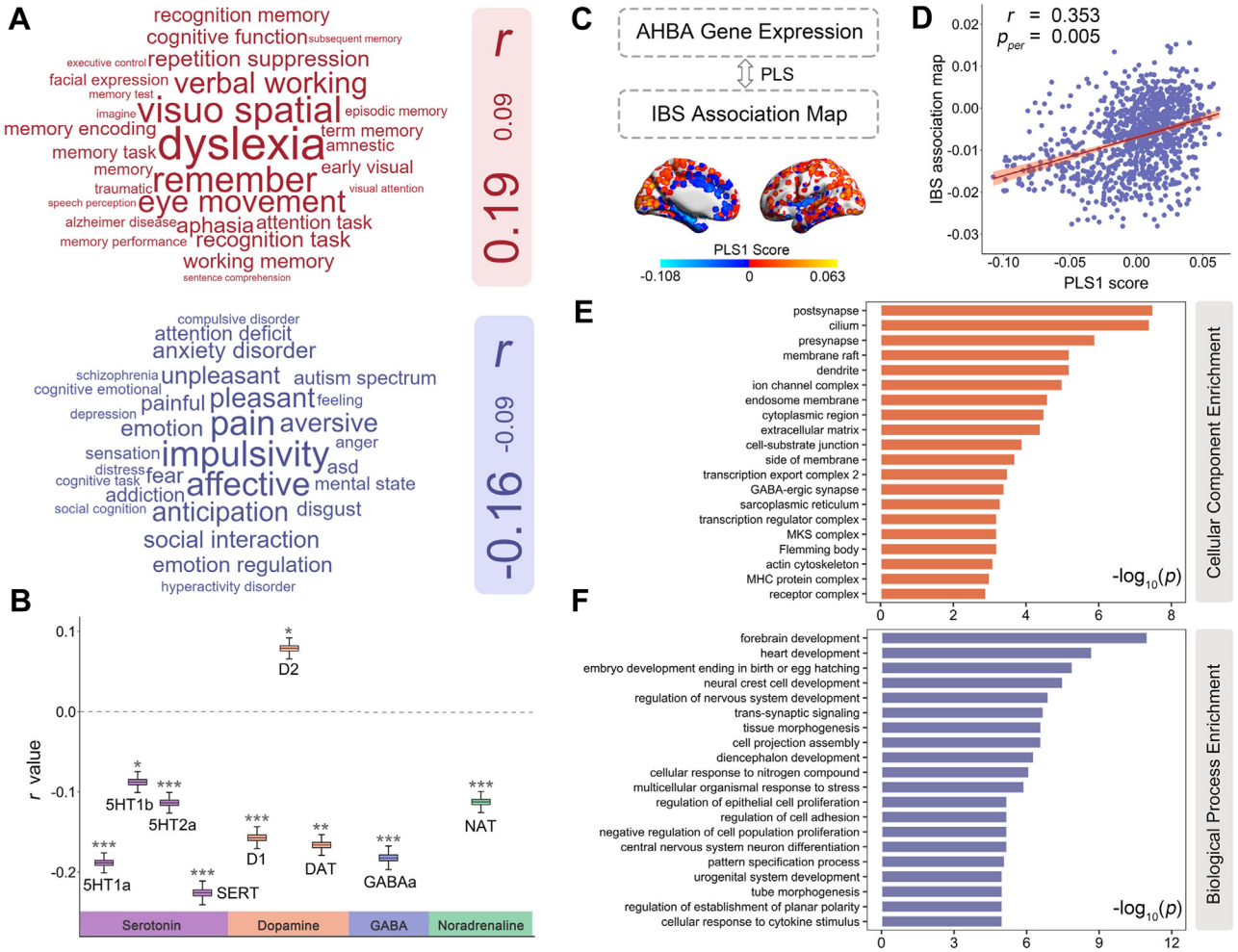

Figure 4. Functional annotation, transmitter architecture, and transcriptomic profile related to irritable bowel syndrome (IBS)–associated brain map. **(A)** Word-cloud plots showing emotion and cognition terms associated with the IBS-associated brain map. The color of the word clouds denotes positive correlation (red) or negative correlation (blue) of the IBS-associated brain map with the meta-analytic map of that term generated by Neurosynth. The font size of a given term corresponds to the Spearman correlation coefficient (r value). The boxes to the right of word clouds indicate the correspondence between the font size and the correlation coefficient. **(B)** Box-line plot showing the Spearman correlation of the brain neurotransmitter distribution map with the IBS-associated brain map (false discovery rate–corrected ps: *$p < .05$, **$p < .01$, ***$p < .005$). **(C)** Plot showing the association between the IBS-associated brain map and the Allen Human Brain Atlas (AHBA) gene expression map using partial least squares (PLS) regression analysis. Brain map showing the spatial distribution of PLS1 scores. **(D)** Scatterplot showing the spatial correlation between the IBS brain map and the PLS1 score map. Lines are fitted to linear models, and shaded areas are 95% CIs. **(E)** Significant enrichment of gene ontology terms associated with cellular components was observed for bottom genes with low weights for the PLS1 component. **(F)** Significant enrichment of gene ontology terms associated with biological processes was observed for bottom genes with low weights for the PLS1 component. Terms with $p < .01$, a minimum count of 3, and an enrichment factor > 1.5 (the enrichment factor is the ratio between the observed counts and the counts expected by chance) were collected and grouped into clusters based on their membership similarities. The top 20 clusters with their representative enriched terms (1 per cluster) are shown in the figure. DAT, dopamine transporter; GABA, gamma-aminobutyric acid; MHC, major histocompatibility complex; MKS, Meckel-Gruber syndrome; NAT, noradrenaline transporter; SERT, serotonin transporter.

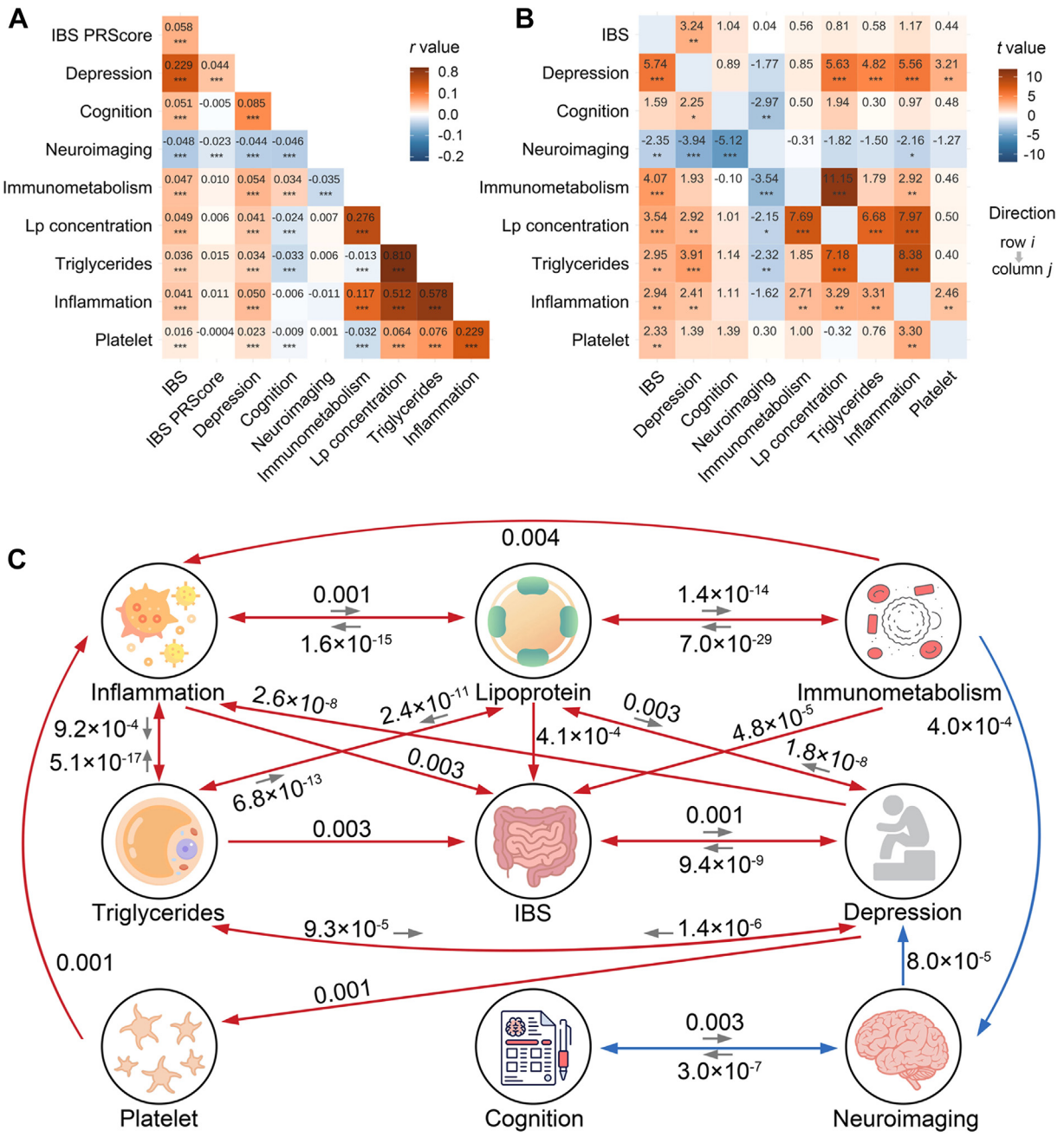

Figure 5. Causal link between irritable bowel syndrome (IBS) and brain health revealed by Mendelian randomization analyses. **(A)** Phenotypic associations between IBS, the IBS symptom severity score polygenic risk score (PRScore), depression, cognition, neuroimaging, immunometabolism, lipoprotein (Lp) concentration, triglycerides, inflammation (glycoprotein acetyls), and platelets. **(B)** Genetic association between IBS, depression, cognition, neuroimaging, immunometabolism, Lp concentration, triglycerides, inflammation, and platelets using the Mendelian randomization inverse-variance weighting method. The *t* value was calculated by dividing the beta by the standard deviation. The direction of (*i*, *j*) is row *i* to column *j*. (*$p < .05$, **false discovery rate–corrected $p < .05$, ***$p_{Bonferroni} < .05$). **(C)** Mendelian randomization with a false discovery rate–corrected *p* value < .01 in **(B)**. The color of the arrow indicates the positive (red) or negative (blue) beta value. The number on the arrow represents the *p* value. In the above analyses, cognition included fluid intelligence, reaction time, and pairs matching; neuroimaging included significant voxels associated with IBS; immunometabolism included C-reactive protein, glucose, HbA1c, apolipoprotein a, apolipoprotein b, cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, direct, and triglycerides; lipoprotein particle concentrations included concentration of chylomicrons and extremely large very low-density lipoprotein (VLDL), very large VLDL, large VLDL, small VLDL, intermediate-density lipoprotein, very large HDL, and large HDL particles; triglycerides included total triglycerides, triglycerides in VLDL, very large VLDL, large VLDL, medium VLDL, small VLDL, very small VLDL, LDL, large LDL, medium LDL, small LDL, HDL, medium HDL, small HDL, and intermediate-density lipoprotein; inflammation only included glycoprotein acetyls; platelets included platelet count, mean platelet volume, and platelet crit.

and 20 biological processes, such as forebrain development and neural crest cell development, which were significantly enriched at the bottom of the gene list (false discovery rate correction, $p < .05$) (Tables S24, S25 in Supplement 2).

Genetic Association Between IBS and Brain Health, Brain Structure, and Biochemical Markers Revealed by MR Analysis

As shown in Figure 5A, IBS symptoms had significant associations with each category, including IBS-SSS PRS ($r = 0.058$, $p = 3.16 \times 10^{-19}$), depression symptoms ($r = 0.229$, $p < 1 \times 10^{-300}$), cognitive function ($r = 0.051$, $p = 5.42 \times 10^{-37}$), neuroimaging ($r = -0.048$, $p = 9.81 \times 10^{-17}$), immunometabolism ($r = 0.047$, $p = 7.45 \times 10^{-70}$), lipoprotein particle concentrations ($r = 0.049$, $p = 3.35 \times 10^{-23}$), triglycerides ($r = 0.036$, $p = 3.43 \times 10^{-13}$), inflammation ($r = 0.041$, $p = 1.05 \times 10^{-16}$), and platelets ($r = 0.016$, $p = 5.97 \times 10^{-11}$), among which depression had the largest effect size. In addition, higher associations were obtained between any 2 of immunometabolism, lipoprotein particle concentrations, triglycerides, and inflammation.

Then we performed 2-sample MR analyses in each pair of 9 categories (excluding IBS-SSS PRS) (Figure 5B, C; Table S26 in Supplement 2). A bidirectional association was observed between depressive symptoms and IBS (IVW: depression to IBS, $\beta = 0.30$, $p = 9.4 \times 10^{-9}$; IBS to depression, $\beta = 0.25$, $p = 1.2 \times 10^{-3}$). Inflammation, as measured by glycoprotein acetyls, was more likely to be an exposure to (cause of) IBS than an outcome of depression, serving as a mediator in the depression-to-IBS pathway. Triglycerides and lipoprotein showed bidirectional associations with depression and were an exposure to IBS, which suggests involvement of both a depression-triglycerides/lipoprotein-IBS pathway and a triglycerides/lipoprotein-depression-IBS pathway. Another finding is the relationship between immunometabolism and IBS, with immunometabolism being directly associated with IBS as well as indirectly associated through the immunometabolism-neuroimaging-depression-IBS pathway. Finally, blood markers including triglycerides, inflammation, lipoprotein, and immunometabolism influenced each other.

DISCUSSION

Utilizing a large-scale dataset from the UKB, we elucidated the associations between IBS and brain health by analyzing multidimensional data. Individuals with more severe IBS symptoms exhibited poorer brain health, including higher anxiety and depression levels, poorer cognitive performance, and lower brain volumes in regions related to emotion and cognition. Meanwhile, IBS was associated with dysregulated lipid metabolism and altered inflammatory indicators, supporting the hypothesis of a complex and multifactorial pathogenesis of IBS. Finally, MR analysis provided evidence regarding the potential causal relationships between IBS and brain health (especially concerning measures of depression), where IBS was more likely to manifest as an outcome trait, with dysregulated lipid metabolism and inflammation playing mediating roles. Taken together, these findings suggest several conclusions, which are discussed below.

Consistent with previous findings, phenome-wide association analysis demonstrated a range of phenotypes that showed a significant association with the severity of IBS, among which mental health and cognitive function showed the greatest effect sizes (3,27). Across the whole population, cognitive ability (e.g., fluid intelligence) exhibited a weaker effect size of association with IBS symptoms than mental health, which is consistent with previous research (27,28) and supported by the indirect genetic association of cognition with IBS symptoms demonstrated in our MR analysis. In contrast, participants who met the diagnostic criteria for IBS showed much lower cognitive ability with a stronger effect size. This difference in effect size could stem from the smaller sample size in the case-control analysis despite meeting the recommended sample size required for robust results (29). It also raises the possibility that the impact of IBS on cognitive ability may not follow a linear pattern once people meet the diagnostic criteria, which warrants further investigation. Meanwhile, our findings complement previous neuroimaging studies by demonstrating that more severe IBS was associated with lower brain volumes in regions related to emotional, cognitive, and social functions (13,30). For example, the anterior and mid-cingulate cortices are known to be related to affective and interoceptive processing and pain modulation (30,31,32), which are associated with IBS symptoms (33). Also, lower brain volume in the hippocampus was observed, which further emphasizes impairments such as problems with memory processing and language skills in patients with IBS (34). Furthermore, IBS-associated brain regions were correlated with gene expression profiles enriched in biological processes closely linked to forebrain development, further suggesting the influence of IBS on cognitive performance.

Regarding biochemical mechanisms, our exploratory analysis identified triglycerides, lipoprotein, inflammatory cells, platelets, and immunometabolic markers as being closely related to IBS. Although less investigated, we identified dyslipidemia (characterized by higher triglycerides and lower HDL) as being associated with IBS, which has been established as a risk factor for diabetes mellitus (35,36). Because greater signs of future diabetes were also found in IBS, our findings provide clues that targeting dyslipidemia may prevent future diabetes in patients with IBS (35,36). Moreover, animal studies of diabetes have found changes in bowel serotonin receptors, implicated in the pathogenesis of IBS (37,38). Alterations to serotonin signaling pathways could lead to gastrointestinal dysmotility, visceral hypersensitivity, and secretomotor disorders in the gut (39). Because most serotonin is stored in platelets and platelet counts are highly correlated with serum serotonin levels (40,41), it was not surprising that we found higher platelet counts with more severe IBS symptoms. Together with our findings that the IBS-associated brain map correlated with serotonin architecture, our study demonstrated clear roles for central and peripheral serotonin signaling pathways in IBS. Moreover, because HDL has antioxidative and anti-inflammatory activity (42), together with associations found in inflammatory cells and immunometabolic markers, our results support the participation of inflammation in the pathophysiology of IBS.

MR analysis suggested that genetically predicted variables, such as depression; metabolites including triglycerides, lipoprotein, and glycoprotein acetyls; and immunometabolic indicators, were associated with IBS. We found 2 possible

genetic associations. First, our findings are consistent with the currently prevailing view that IBS and mental health (especially depression) have a reciprocal association (7). A recent study using MR analysis for gastrointestinal disorder also demonstrated bidirectional pathways between major depression and IBS (43,44). We also observed a stronger causal relationship from depression to IBS, indicating that depression affects the development or manifestation of IBS more significantly than the reverse. Our second hypothesis was that the relationship between depression and IBS may be genetically influenced by metabolism and inflammatory status. In our study, an increase in immunometabolic dysregulation showed a genetically negative correlation with brain volumes, and lower brain volumes would genetically predict increased depressive symptoms, which finally aggravated IBS. This is supported by a previous finding that immunometabolic dysregulation in the serum was correlated with reduced thickness of the rostral anterior cingulate cortex (45). These potential genetic causalities suggest the potential for future clinical applications aimed at developing treatment options for IBS or mental health through the manipulation of peripheral biochemical markers.

The main strength of the current study lies in the integration of multiple dimensional data with a large sample size, which provides systematic novel insights into the association between IBS and brain health. Moreover, this study systematically described altered brain regions associated with IBS and explored its underlying molecular architecture and gene expression profile, providing a more detailed and objective basis for the role of the brain-gut axis in IBS. Furthermore, the current study provides a strong research framework that is applicable to different intestinal diseases and is poised to advance our understanding of the imaging and genetic foundations of various gastrointestinal conditions in future research. Nevertheless, some limitations should be acknowledged. First, the UKB is composed predominantly of White participants, which limits the generalizability of the findings to other ethnic groups. Second, while our study utilized various omics data, future research could integrate proteomics and artificial intelligence algorithms to identify biomarkers specific to IBS with extensive datasets. Third, given the heterogeneity of phenotypes exhibiting diverse symptom profiles, it remains possible that specific IBS symptoms would be associated with specific depressive domains, which requires further exploration. Fourth, the main analyses were based on IBS-SSS rather than diagnostic IBS because of the large interval between making diagnoses and measurement of brain health–related phenotypes. Nevertheless, our main findings could be replicated for participants diagnosed with IBS.

Conclusions

In conclusion, the current study provides a comprehensive understanding of associations between IBS and a wide range of phenotypes, highlighting the role of brain health-related phenotypes in IBS pathogenesis. More severe IBS symptoms were linked to worse mental health status and cognitive performance. IBS was associated with lower brain volumes in regions involved in emotional regulation and higher-order cognition. Biochemical alterations including dyslipidemia and inflammation were also related to IBS. Further MR analysis revealed a bidirectional pathway between IBS and brain health, suggesting a dual impact of the brain-gut axis wherein brain health may play more of an exposure role than IBS. Taken together, our findings support the hypothesis that IBS is associated with a wide range of brain health phenotypes, where genetic predisposition toward poorer mental health is associated with more severe IBS, and dysregulated lipid metabolism and inflammation may play a mediating role in the causal relationship. Additional research on whether targeting brain health or the related central and peripheral biochemical mediators will benefit patients with IBS is warranted.

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WC, ETR, and JF designed the study. ZL and QM conducted the main analyses. ZL, QM, and YD wrote the manuscript. QM and YD critically revised the manuscript. CS, YL, and WZ contributed to the data collection. CS, WZ, and SX contributed to the data analyses. WC, JF, ETR, J-TY, CL, BJS, and TWR critically supervised improvement of the manuscript. All authors reviewed and approved the final version.

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ARTICLE INFORMATION

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