

Mendelian randomization analyses uncover causal relationships between brain structural connectome and risk of psychiatric disorders

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Aims: Growing evidence suggests abnormalities of brain structural connectome in psychiatric disorders, but the causal relationships remain underexplored. Therefore, elucidating the causality is critical for deciphering the neurobiological underpinnings of mental illnesses.

Methods: We conducted bidirectional two-sample Mendelian randomization (MR) analyses to investigate the causal links between 206 white-matter connectivity phenotypes ($n = 26,333$, UK Biobank) and 13 major psychiatric disorders ($n = 14,307$ to $1,222,882$).

Results: Forward MR analyses identified causal effects of five genetically predicted white-matter structural connectivity phenotypes on six psychiatric disorders, with associations being significant or suggestive. For instance, the increase in structural connectivity between the left-hemisphere frontoparietal control network and right-hemisphere default mode network was significantly causally associated with decreased autism spectrum disorder risk, while elevated structural

connectivity between the right-hemisphere frontoparietal control network and hippocampus was significantly causally linked to lower risk of both anorexia nervosa and cannabis use disorder. Reverse MR analyses revealed significantly or suggestively causal relationships between the risk of two psychiatric disorders and four different white-matter structural connectivity phenotypes. For example, the heightened susceptibility to anorexia nervosa was found to be significantly causally associated with diminished structural connectivity between the left-hemisphere visual network and pallidum.

Conclusions: These findings offer new insights into the cause of psychiatric disorders and highlight potential biomarkers for early detection and prevention at the brain structural connectome level.

Keywords: connectome, GWAS, Mendelian randomization, psychiatric disorders.

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Psychiatric disorders are a group of mental illnesses that manifest as dysfunctions in emotional regulation, cognition, or behavior.¹ Due to their high prevalence, mortality and morbidity risk, psychiatric disorders represent a global public health threat that imposes economic burdens worldwide.^{2,3} However, our understanding of the pathogenesis of psychiatric disorders remains limited, which impedes the development of effective therapeutic strategies.

Alterations within the brain structural connectome have been extensively observed among psychiatric disorders, with variations in the direction and anatomical distribution of these changes. Many conditions are associated with reduced structural connectivity. For instance, patients with attention-deficit/hyperactivity disorder (ADHD)⁴ and obsessive-compulsive disorder (OCD)⁵ exhibit decreased structural connectivity in networks involving the frontal–striatal–cerebellar regions and orbitofrontal–striatal–insula–temporo–limbic regions, respectively. Generalized anxiety disorder has been linked to disruptions in a structural subnetwork primarily involving the frontal-subcortical circuits, which may serve as a potential neuroimaging biomarker for diagnosis.⁶ Reduced white-matter connectivity in the default mode network and the frontal–thalamus–caudate regions is reported in patients with depression.⁷ In schizophrenia (SCZ), decreased connectivity in frontal and

temporal regions is observed, along with a diminished central role of frontal hubs in the brain network.⁸ Patients with high-functioning autism spectrum disorder (ASD) show lower white-matter density in the anterior corpus callosum compared with typically developing peers,⁹ and cannabis use disorder (CUD) is linked to disrupted structural connectivity in the fornix, corpus callosum, and commissural fibers.¹⁰ Conversely, increased structural connectivity has been observed in bipolar disorder (BIP)¹¹ and Tourette syndrome (TS),¹² affecting the subgenual cingulate–amygdala–hippocampal complex and the striatal–thalamic–sensorimotor circuits, respectively. Heroin use disorder, a subtype of opioid use disorder (OUD), is similarly linked to enhanced structural connectivity across paralimbic, prefrontal, and temporal regions.¹³ Notably, some disorders display mixed patterns of white-matter alterations. For example, individuals with anorexia nervosa (AN) exhibit decreased subcortical but heightened frontal structural connectivity,¹⁴ while alcohol use disorder (AUD) involves both diminished integrity in the cerebellum and insula and increased connectivity within the default mode network.¹⁵ Posttraumatic stress disorder (PTSD) is associated with altered structural connectivity, including decreased nodal centrality in the medial orbital part of the superior frontal gyrus and increased centrality within the salience

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network.¹⁶ These findings collectively delineate the presence of dysconnectivity within the brain's structural networks in diverse psychiatric disorders. Nonetheless, the causal relationships between these structural network alterations and psychiatric disorders remain largely unexplored.

The gold standard for studying causal relationships is randomized controlled trials (RCTs). However, due to limitations such as cost and ethical concerns, RCTs are not always feasible. With the increasing availability of large-scale genome-wide association studies (GWAS), Mendelian randomization (MR) has gained prominence as a valuable alternative to RCTs.¹⁷ MR utilizes genetic variations (typically single nucleotide polymorphisms, or SNPs) associated with an exposure as instrumental variables (IVs) to evaluate the causal effect of exposure on the outcome.¹⁸ Compared with conventional observational studies, MR analysis offers a methodological advantage by substantially reducing biases arising from confounding factors and eliminating reverse causation. This enhanced validity stems from the fundamental biological principle that genetic alleles undergo random segregation during meiosis, and genetic variants are determined before both exposure and outcome variables.^{17,18} Previous MR studies have primarily focused on examining the relationships between white-matter tract microstructure and psychiatric disorders,^{19,20} revealing putative causal associations between diffusion tensor imaging-derived metrics (e.g. fractional anisotropy, orientation dispersion index, and axial diffusivity) and conditions including SCZ and AN. However, these investigations are limited by the fact that white-matter fiber tracts provide only indirect measures of anatomical connectivity without explicitly characterizing the complex inter-regional relationships within the brain. In contrast, the structural connectome offers a comprehensive representation of whole-brain connectivity, enabling global detection of brain network reorganization.²¹ Therefore, investigating the causal links between interregional brain connectivity and psychiatric disorders shows a remarkable advancement in understanding the neurobiological basis of mental illnesses.

In this study, we conducted a bidirectional two-sample MR analyses to explore the potential causal links between the brain structural connectome and 13 major psychiatric disorders. The brain structural connectome encompasses 206 white-matter connectivity metrics, quantifying the density of white-matter tracts that interconnect cortical hemispheres, cortical networks, and subcortical regions, either internally or across these modules. Our findings might provide novel insights into the neuropathological mechanisms underlying major psychiatric disorders through the lens of brain structural connectomics. These discoveries have significant translational implications, potentially informing the development of: (1) early diagnostic biomarkers, (2) targeted intervention strategies, and (3) personalized treatment approaches based on individual connectome profiles.

Results

Overview of this study

Our study design is briefly illustrated in Fig. 1. To systematically investigate potential causal relationships between brain structural connectome organization and psychiatric disorders, we implemented a comprehensive bidirectional two-sample MR framework. This analyses leveraged the largest GWAS data set currently available, comprising 206 distinct white-matter structural connectivity phenotypes that capture interregional connectivity patterns across multiple brain networks and anatomical divisions.²¹ Furthermore, we incorporated large-scale GWAS summary statistics for 13 psychiatric disorders, selected to minimize sample overlap and restricted to individuals of European ancestry (see Tables 1 and S2 for details). Although there remains a maximum possible sample overlap of approximately 5.29% for AN²² and 2.15% for PTSD,²³ these minimal overlaps are deemed insufficient to significantly bias the study results.^{19,24,25} After rigorous IVs selection and outliers removal, all significant exposure-outcome pairs reported had *F* statistics >30 (see Tables S3 and S4 for details), indicating robust IVs. Forward MR analyses identified six

putative causal associations, while reverse MR analyses revealed four putative causal associations. A series of sensitivity analyses confirmed the robustness of our results. Additionally, we incorporated birth length²⁶ as a negative control to further validate the reliability of causal inferences. No significant causal associations were observed between birth length and either brain structural connectome (after Bonferroni correction) or the 13 psychiatric disorders (even at nominal significance), which supports the specificity of our primary causal findings.

Forward MR results of brain structural connectome on psychiatric disorders

We identified six putative causal links between white-matter structural connectivity phenotypes and risk of psychiatric disorders in the forward MR analyses, as shown in Fig. 2 and Table S7. The inverse-variance weighted (IVW) estimates suggest that an increase of 1 standard deviation (SD) in white-matter structural connectivity between the left-hemisphere dorsal attention network (DAN) and right-hemisphere somatomotor network (SMN) was nominally associated with 36% lower odds of ADHD risk (IVW odds ratio [OR] = 0.64 [95% CI, 0.51–0.81], $P = 1.88 \times 10^{-4}$). The risk of AN decreased by 50% per 1-SD increase in white-matter structural connectivity between the right-hemisphere frontoparietal control network (FPCN) and hippocampus (IVW OR = 0.50 [95% CI, 0.37–0.68], $P = 1.11 \times 10^{-5}$). An increase of 1 SD in the left-hemisphere FPCN to the right-hemisphere FPCN white-matter structural connectivity was nominally associated with 29% higher risk of anxiety disorders (IVW OR = 1.29 [95% CI, 1.12–1.49], $P = 6.35 \times 10^{-4}$). In addition, 1-SD increase in white-matter structural connectivity between the left-hemisphere FPCN and right-hemisphere default mode network (DMN) was found to be significantly associated with 45% lower odds of ASD risk (IVW OR = 0.55 [95% CI, 0.41–0.73], $P = 3.59 \times 10^{-5}$). Moreover, the risk of CUD decreased by 53% per 1-SD increase in white-matter structural connectivity linking the right-hemisphere FPCN with hippocampus (IVW OR = 0.47 [95% CI, 0.35–0.64], $P = 9.66 \times 10^{-7}$). Furthermore, 1-SD increase in cross-hemisphere white-matter structural connectivity was nominally associated with 39% lower risk of SCZ (IVW OR = 0.61 [95% CI, 0.46–0.82], $P = 7.61 \times 10^{-4}$).

Reverse MR results of psychiatric disorders on brain structural connectome

We also identified four putative causal relationships between psychiatric disorders and white-matter structural connectivity phenotypes in the reverse MR analyses, as shown in Fig. 3 and Table S8. A significantly negative causal effect of the susceptibility to AN on white-matter structural connectivity between the left-hemisphere visual network and pallidum was observed (IVW beta = −0.19 [95% CI, −0.26 to −0.11], $P = 7.76 \times 10^{-7}$). Moreover, genetically predicted increased susceptibility to SCZ was nominally associated with the higher white-matter structural connectivity between the left-hemisphere DMN and putamen (IVW beta = 0.04 [95% CI, 0.02–0.06], $P = 2.36 \times 10^{-4}$), nominally associated with the higher white-matter structural connectivity between the left-hemisphere visual network and putamen (IVW beta = 0.04 [95% CI, 0.02–0.07], $P = 2.84 \times 10^{-4}$), and nominally associated with the higher white-matter structural connectivity between the right-hemisphere limbic network and amygdala (IVW beta = 0.03 [95% CI, 0.01–0.05], $P = 6.04 \times 10^{-4}$).

Sensitivity analyses

Six different MR methods—MR-Egger, weighted median, weighted mode, MR robust adjusted profile scores (MR-RAPS), contamination mixture, and debiased IVW—yielded consistent causal effect directions with IVW, further supporting the robustness of the causal inference (see Tables S7 and S8, and Figs S1–S10). Not all MR methods

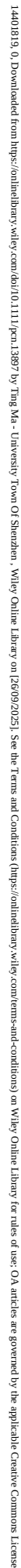


Table 1. Overview of the GWAS summary data for psychiatric disorders

Psychiatric disorder	Abbreviation	Sample sizes	Ancestry	References	PubMed ID
Attention-deficit/hyperactivity disorder	ADHD	38,691 cases and 186,843 controls	European	Demontis <i>et al.</i> ⁹⁶	36702997
Anorexia nervosa	AN	16,992 cases and 55,525 controls	European	Watson <i>et al.</i> ²²	31308545
Anxiety disorders	ANX	50,486 cases and 330,460 controls	European	Kurki <i>et al.</i> ⁹⁷	36653562
Autism spectrum disorder	ASD	18,381 cases and 27,969 controls	European	Grove <i>et al.</i> ⁹⁸	30804558
Alcohol use disorder	AUD	113,325 cases and 639,923 controls	European	Zhou <i>et al.</i> ⁹⁹	38062264
Bipolar disorder	BIP	40,463 cases and 313,436 controls	European	Mullins <i>et al.</i> ¹⁰⁰	34002096
Cannabis use disorder	CUD	42,281 cases and 843,744 controls	European	Levey <i>et al.</i> ¹⁰¹	37985822
Depression	Depression	53,313 cases and 394,756 controls	European	Kurki <i>et al.</i> ⁹⁷	36653562
Obsessive-compulsive disorder	OCD	2490 cases and 403,817 controls	European	Kurki <i>et al.</i> ⁹⁷	36653562
Opioid use disorder	OUD	15,251 cases and 538,935 controls	European	Deak <i>et al.</i> ¹⁰²	35879402
Posttraumatic stress disorder	PTSD	137,136 cases and 1,085,746 controls	European	Nievergelt <i>et al.</i> ²³	38637617
Schizophrenia	SCZ	53,386 cases and 77,258 controls	European	Trubetskoy <i>et al.</i> ¹⁰³	35396580
Tourette syndrome	TS	4819 cases and 9488 controls	European	Yu <i>et al.</i> ¹⁰⁴	30818990

produced statistically significant results, likely due to their lower statistical power compared with the IVW method.^{27,28}

Additional sensitivity analyses validated the reliability of the results. MR-Egger regression and the MR pleiotropy residual sum and outlier (MR-PRESSO) global test detected no evidence of horizontal pleiotropy or outliers in the reported significant exposure-outcome pairs in bidirectional MR analyses. Moreover, Cochran Q test revealed no significant heterogeneity across different IVs. The leave-one-out analyses indicated that no single IV disproportionately influenced the results, and the causal effects remained consistent when each IV was excluded. The sensitivity analyses results are available in Tables S5 and S6, with the exception of the leave-one-out analyses, which are presented in Figs S1–S10.

Discussion

This MR study provides novel insights into the bidirectional causal relationships between brain structural connectome organization and psychiatric disorders. Leveraging publicly available GWAS summary statistics, we conducted systematic bidirectional two-sample MR analyses encompassing 206 white-matter structural connectivity phenotypes and 13 major psychiatric disorders. Our investigation revealed significant causal associations, including: (1) five specific white-matter connectivity patterns showing causal effects on six distinct psychiatric disorders, and (2) two psychiatric disorders demonstrating causal influences on four different white-matter structural connectivity profiles. To ensure the robustness of our findings, we implemented a rigorous series of sensitivity analyses, including consistency checks of causal directions across multiple MR methods, pleiotropy detection, heterogeneity testing, and leave-one-out analyses, all of which reliably supported the validity of our primary results.

ADHD, marked by difficulties in sustaining attention or by impulsive and hyperactive behaviors, is increasingly conceptualized as a brain dysconnectivity disorder. In our forward MR analyses, we

identified that decreased bilateral brain structural connectivity between the DAN and the SMN was positively associated with the risk of ADHD. The DAN, comprising key regions including the dorsal and lateral prefrontal cortex, superior parietal lobule, and intraparietal sulcus, has been consistently implicated in ADHD pathophysiology, with disrupted microstructural properties serving as established connectomic signatures of the disorder.²⁹ Meanwhile, microstructural characteristics in the SMN have been reported to play a crucial role in attention and impulsivity in the ADHD population.³⁰ In addition to WM structural connectivity findings, functional interconnections between DAN and SMN have been reported to be associated with impulsive behaviors in children with ADHD.³¹ Notably, prior meta-analytic evidence suggests a developmental shift in the neural correlates of ADHD, with childhood manifestations primarily characterized by SMN hypoactivation that transitions to predominant DAN hypoactivation in adulthood.³² Further longitudinal clinical studies focusing on these two brain networks may help to confirm this developmental variation and elucidate its implications for patients with ADHD. Altogether, our MR-based evidence indicates that altered structural connectivity between the DAN and the SMN may play a vital role in ADHD.

Our bidirectional MR analyses revealed a complex neurobiological interplay underlying AN, characterized by energy restriction behaviors and distorted body perception. The forward MR demonstrated that decreased connectivity between the FPCN and hippocampus confers heightened AN risk. The hippocampus is thought to be involved in the energy intake and weight-regulation processes,³³ and may thus contribute to the alterations of eating behaviors in patients with AN,^{34,35} alongside other contributing factors. Congruently, anatomical magnetic resonance imaging studies also reported volume reduction in the hippocampus^{36–38} and disrupted microstructures of white-matter fiber (e.g. fornix, cingulum) linking to the hippocampus in patients with AN.^{35,39–41} Of note, a recent study has suggested that

Fig. 1 Study flowchart for bidirectional MR analyses between brain structural connectome and psychiatric disorders. A total of 206 white-matter structural connectivity phenotypes and 13 major psychiatric disorders were included for causality inference. IVs were selected based on their strong association with the exposure and independence after clumping to remove linkage disequilibrium, excluding any SNPs associated with confounders or the outcome. Outliers showing significant heterogeneity were further discarded. Bidirectional MR analyses were performed to investigate causal links between white-matter structural connectivity phenotypes and psychiatric disorders. To validate the reliability and consistency of the MR findings, a series of sensitivity analyses were conducted. The top left chord plot visualizes the average values of the brain structural connectivity measures across GWAS participants. The top right Manhattan plot visualizes the GWAS summary data of 13 psychiatric disorders. Acc, accumbens; ADHD, attention-deficit/hyperactivity disorder; Amy, amygdala; AN, anorexia nervosa; ANX, anxiety disorder; ASD, autism spectrum disorder; AUD, alcohol use disorder; BIP, bipolar disorder; Cau, caudate; CUD, cannabis use disorder; DAN, dorsal attention network; DMN, default mode network; FPCN, frontoparietal control network; GWAS, genome-wide association studies; Hip, hippocampus; IV, instrumental variable; LH, left hemisphere; LIM, limbic network; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; OCD, obsessive-compulsive disorder; OUD, opioid use disorder; Pal, pallidum; PTSD, posttraumatic stress disorder; Put, putamen; RH, right hemisphere; SMN, somatomotor network; SNP, single nucleotide polymorphism; Tha, thalamus; TS, Tourette syndrome; VAN, ventral attention network; VIS, visual network.

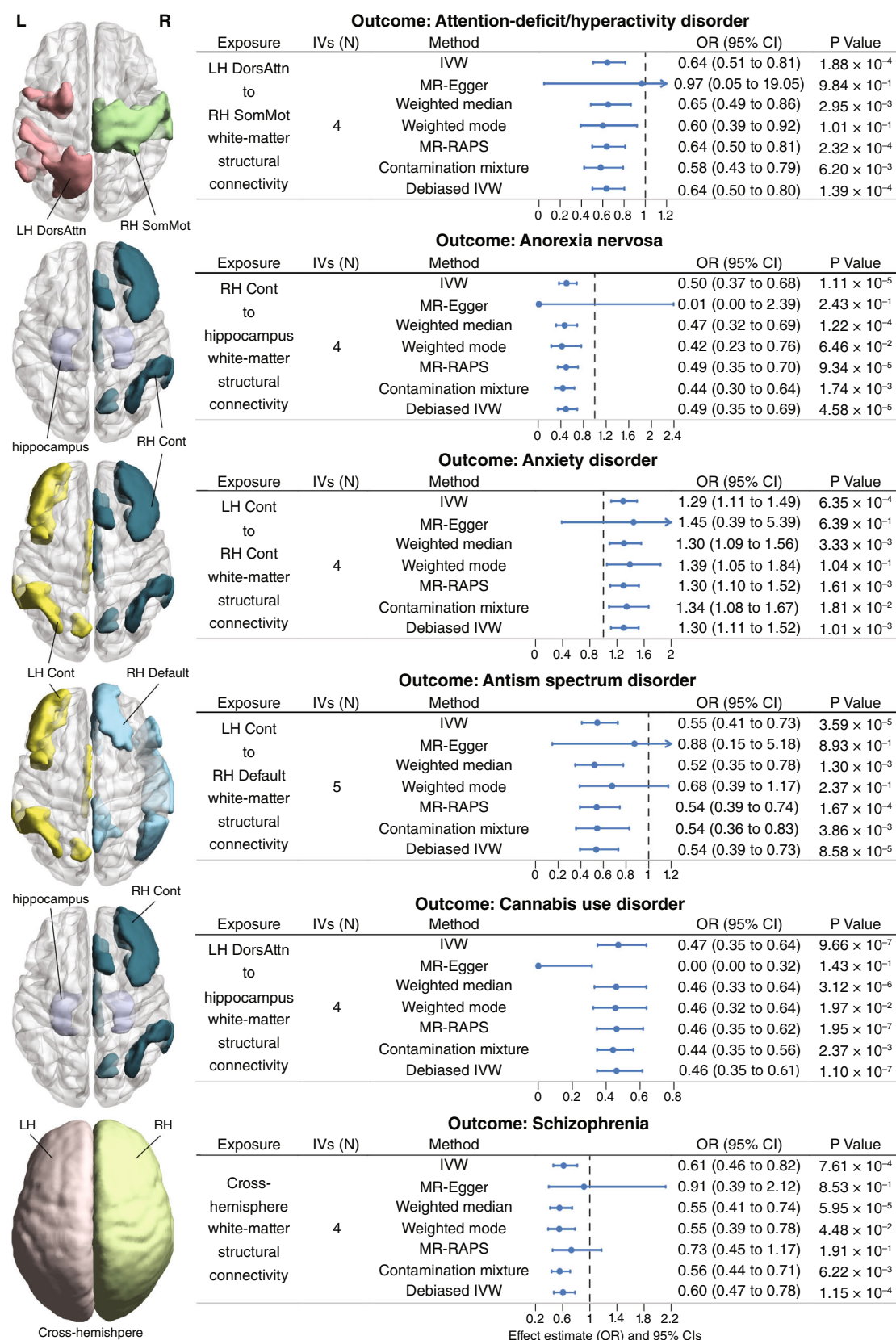


Fig. 2 Significant results of forward MR analyses. Left: axis view (dorsal side) of related functional networks and subcortical structures. Right: forest plot illustrates the Bonferroni-corrected significant ($P < 1.2316 \times 10^{-4}$) and nominally significant ($P < 1 \times 10^{-3}$) IVW results for the causal effects of white-matter structural connectivity on psychiatric disorders, along with the results from six additional methods: MR-Egger, weighted median, MR-RAPS, contamination mixture, debiased IVW. Arrows indicate the extension of the maximum interval on the x-axis. The error bars represent the 95% CIs. *P*-values were from each MR analyses method, and all statistical tests were two-sided. CI, confidence interval; IV, instrumental variable; IVW, inverse-variance weighted; LH, left hemisphere; MR, Mendelian randomization; MR-RAPS, Mendelian randomization robust adjusted profile score; OR, odds ratio; RH, right hemisphere.

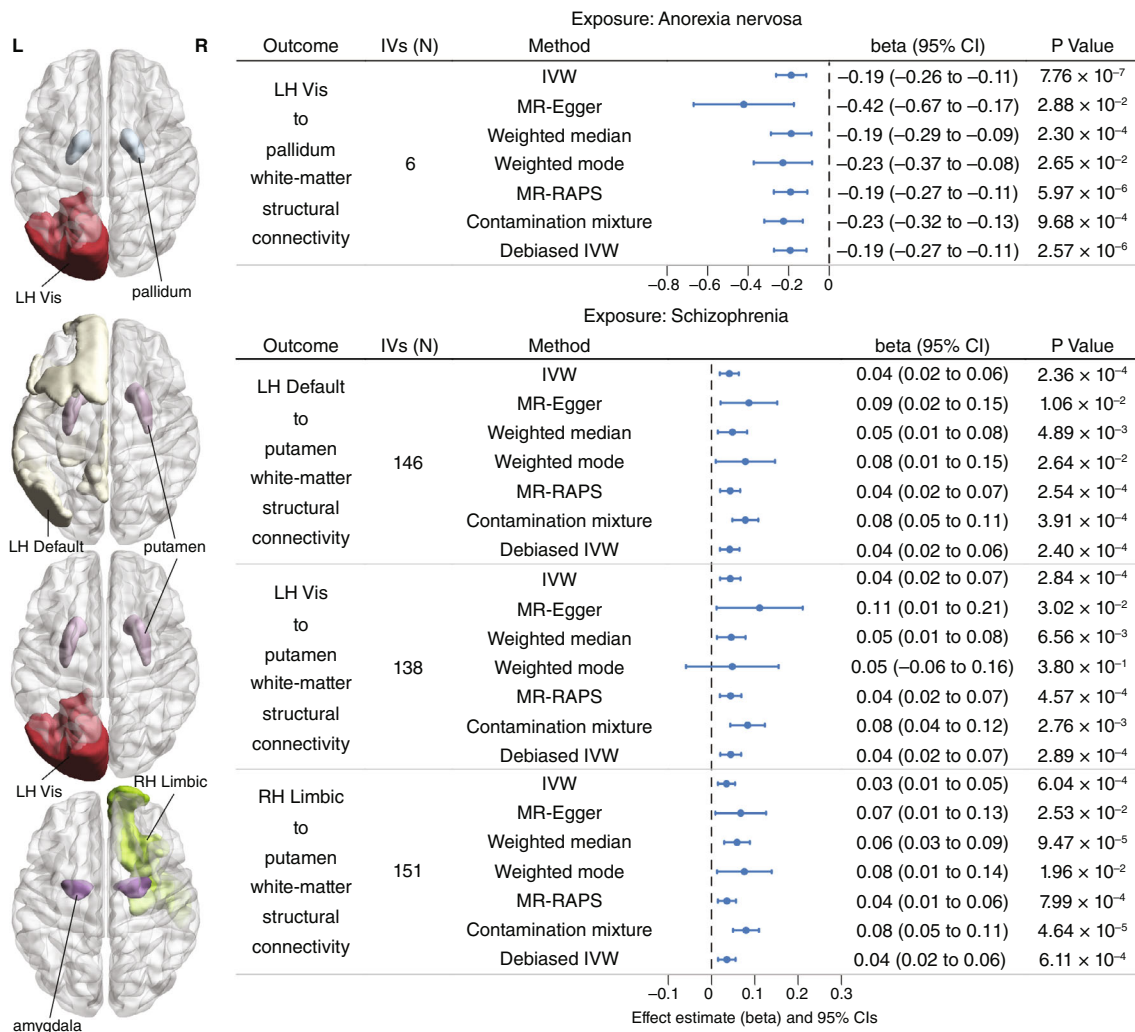


Fig. 3 Significant results of reverse MR analyses. Left: axis view (dorsal side) of related functional networks and subcortical structures. Right: forest plot illustrating the Bonferroni-corrected significant ($P < 1.2316 \times 10^{-4}$) and nominally significant ($P < 1 \times 10^{-3}$) IVW results for the causal effects of psychiatric disorders on white-matter structural connectivity, along with the results from six additional methods: MR-Egger, weighted median, weighted mode, MR-RAPS, contamination mixture, and debiased IVW. The error bars represent 95% CIs. P -values were from each MR analyses method, and all statistical tests were two-sided. CI, confidence interval; IVW, inverse-variance weighted; LH, left hemisphere; MR, Mendelian randomization; MR-RAPS, Mendelian randomization robust adjusted profile score; RH, right hemisphere.

brain activity within the FPCN may function as a biomarker to predict treatment response in individuals with AN.⁴² Cortical thinning of these regions observed in AN populations,³⁶ combined with our findings regarding structural connectivity, indicates that the functional aberrations of the FPCN in AN may come from the underlying structural damages. The reverse MR analyses further identified AN-induced hypoconnectivity between the pallidum and the visual network. Although no direct evidence has been reported linking the pallidum-visual connection to AN, decreased structural connectivity within this neural pathway has been primarily associated with obsessive-compulsive personality disorder, which is often comorbid with AN.⁴³ Based on the neural basis of the ventral pallidum in regulating food motivation and reward,^{44,45} as well as the role of the ventral visual network in subserving the visual perception of the body,^{46,47} we can infer that the compulsive disorder-related behavior may be induced after the onset of AN through the disruption of the pallidum-visual connection. In sum, our results revealed a complex pattern of connectomic signatures in AN, offering novel insights into the pathophysiology of AN.

Anxiety disorders, characterized by maladaptive fear responses and stimulus avoidance patterns, demonstrate associations with

disruptions in brain network connectivity. Our forward MR analyses identified increased structural connectivity within bilateral FPCN as a causal factor for higher risk of anxiety disorders. Neuroimaging evidence implicates the central role of the prefrontal cortex in both the pathophysiology⁴⁸ and prediction⁴⁹ of anxiety disorders. In social anxiety disorder, the genu of the corpus callosum, which bridges bilateral prefrontal cortical regions, exhibits elevated white-matter density when seeded in the right medial prefrontal cortex.⁵⁰ In addition, the dorsal anterior cingulate cortex, anatomically anterior to the genu and functionally connected with the FPCN,⁵¹ plays a key role in attentional control and emotional regulation.⁵⁰ Abnormally heightened thickness in FPCN areas^{52,53} and prefrontal-limbic hyperconnectivity patterns^{49,54} have been observed in patients with anxiety disorders, although these findings are not entirely consistent among studies.^{6,55–57} Our results contribute to addressing this heterogeneity and offer a potential neural connectivity basis for anxiety disorders, particularly in relation to interhemispheric hyperconnectivity within the FPCN. The heightened structural connectivity, as indexed by streamline density,²¹ might indicate impaired axonal pruning during critical developmental periods⁵⁸ or aberrant myelination triggered by neurobiological dysfunction.⁵⁹ This could reflect inefficiency in

FPCN connectivity during anxiety-related cognitive processes or maladaptive adaptation to underlying neurobiological deficits.

ASD is characterized by social communication deficits and restricted/repetitive behaviors, with emerging evidence implicating brain network reorganization in its pathophysiology. Our forward MR analyses identified a potential causal relationship between diminished structural connectivity linking the left FPCN with the right DMN and increased ASD susceptibility. This finding aligns with longitudinal neuroimaging evidence demonstrating divergent developmental trajectories of FPCN-DMN connectivity: neurotypical individuals demonstrate normative age-associated strengthening of these internetwork connections, while high-functioning patients with ASD experience a progressive decline of FPCN-DMN interconnection.⁶⁰ Moreover, volumetric variations within FPCN and DMN regions correlate with intelligence quotient development in ASD, suggesting network-specific neuroanatomical biomarkers.⁶¹ Complementary literature reveals that ASD is linked to abnormalities in white-matter integrity within tracts connecting regions associated with executive control functions (e.g. the FPCN) and socioemotional processing (e.g. the DMN).⁶² Specifically, diffusion magnetic resonance imaging studies have highlighted disruptions in several critical white-matter pathways, including the cingulum bundle,⁶³ corpus callosum, uncinate fasciculus, and superior longitudinal fasciculus.⁶⁴ These convergent brain structural reorganization patterns provide mechanistic context for our MR-derived hypothesis of bilateral FPCN-DMN hypoconnectivity contributing to ASD pathogenesis.

In our forward MR analyses, reduced white-matter connectivity between the FPCN and hippocampus was found to be causally associated with an elevated risk of CUD. Consistent with this, previous studies have reported structural impairments in both the frontoparietal^{65,66} and hippocampus^{67,68} areas among cannabis users. Researchers further postulate that the shift from voluntary to habitual drug consumption may stem from disruptions in brain regions governing executive control and behavioral inhibition.⁶⁹ The FPCN, which plays a crucial role in decision-making and inhibitory regulation,^{70,71} might be among these affected regions. Interestingly, our study discovered that the structural connectivity between right-hemisphere FPCN and hippocampus converges as a negative causal factor influencing the risks of both AN and CUD. Consistent with our MR findings that implicate shared neural pathways, epidemiological studies have reported a 14% prevalence of cannabis use and a 6% prevalence of CUD in patients with AN,⁷² suggesting a possible comorbid relationship between the two conditions. Genetic analyses further suggest that individuals with a genetic predisposition to AN may exhibit a similar vulnerability to developing CUD.⁷³ Emerging evidence has proposed cannabis use as a potential therapeutic intervention for AN symptoms, particularly in addressing weight restoration and associated physiological complications.^{74,75} However, the potential adverse effects of cannabis use in this context warrant careful consideration, including the risk of precipitating binge episodes and subsequent compensatory behaviors, especially when individuals experience postconsumption guilt regarding their eating patterns.⁷⁶ An alternative hypothesis posits that symptoms of cannabinoid hyperemesis syndrome might be misdiagnosed as compensatory behaviors in individuals with binge-eating/purging subtype AN, due to their overlapping clinical presentations.⁷⁷ These findings underscore the need for future clinical research to resolve existing inconsistencies and to develop personalized cannabis dosing strategies that maximize therapeutic efficacy while minimizing potential adverse effects.

The current study identified potential causal associations between genetic liability to SCZ and widespread disturbances in both cortico-cortical and cortico-subcortical structural connectivity. In the forward MR, we found that interhemispheric hypoconnectivity was associated with the risk of SCZ, echoing the well-recognized lateralized hemispheric dysfunction in this psychotic disorder.^{78–80} In line with our findings, a recent functional magnetic resonance imaging study observed a dissociable network signature of SCZ, characterized by the coexistence of preserved intrahemispheric connectivity

organization and interhemispheric connectivity disruptions,⁸¹ underscoring the potential functional deficits in interhemispheric information exchanges in SCZ. The corpus callosum is a major white-matter tract that facilitates efficient interhemispheric neurosignal transmission. Similar to our results, a previous MR study suggested that one SD decrease in the orientation dispersion index of the forceps major, and one SD increase in the mean diffusivity of the tapetum, were associated with 32% and 35% higher odds of schizophrenia risk, respectively.¹⁹ In the reverse MR, we observed putative causal effects of SCZ on long-range cortico-subcortical hyperconnectivity, including enhanced connectivity between the putamen and the DMN, the putamen and the visual network, as well as within the amygdala-limbic circuitry. Nevertheless, the disruption landscape of the cortico-subcortical connection in SCZ reported in previous observational studies remains elusive,^{82–85} partly due to the inability to fully control for confounding factors. According to the connectome architecture of SCZ from a recent worldwide ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) study,⁸⁶ our findings may be partially explained by network-spreading pathological processes propagating from subcortical epicenters (e.g. the putamen and amygdala) to distal cortical regions. Therefore, our MR results may provide novel insights to elucidate the association between structural dysconnectivity and SCZ.

Our MR analyses suggest potential causality between brain structural connectome and major psychiatric disorders. A previous MR study examined the causal relationships between the brain functional connectome and psychiatric disorders,⁸⁷ but given that functional connectivity is closely linked to and dependent on the structural connectivity,⁸⁸ investigating the causal relationships between brain structural connectome and psychiatric disorders remains of significant importance. Furthermore, two MR studies^{89,90} have explored the structural and functional connectivity within the “Yeo 7” functional networks⁹¹ and their causal relationships with depression. However, these studies did not examine the structural connectivity between pairs of functional networks or between functional networks and subcortical structures, nor did they address other common psychiatric disorders. In parallel to our work, a contemporaneous study also investigated the causal links between the white-matter structural connectome and psychiatric disorders.⁹² While both studies share a broadly similar aim, our study differs in several important aspects, including the analytic pipeline, GWAS sources, and disease coverage. By applying stricter criteria for instrument selection, incorporating multiple recently developed MR methods, performing negative control analyses, and utilizing more curated, large-scale, multicohort GWAS data sets, as well as examining a broader range of psychiatric conditions, our study offers a complementary perspective with enhanced causal resolution and a more mechanistically oriented contribution to the literature.

Our study has several limitations that should be acknowledged. First, the GWAS for brain structural connectome was based on cohorts from the UK Biobank. Although we meticulously selected large-scale GWAS data sets that did not include UK Biobank participants to minimize sample overlap, a potential maximum overlap rate of approximately 5.29% for AN²² and 2.15% for PTSD²³ still exists. Due to the inaccessibility of detailed participants' information, we were unable to exclude overlapping participants. Second, differences in the age distributions between the cohorts used in the GWAS for brain structural connectome and those for psychiatric disorders may introduce bias, particularly for age-related psychiatric disorders. Third, all GWAS summary data used in this study were derived from populations of European ancestry. Therefore, the generalizability of our findings to other populations requires further investigation. Fourth, while we excluded SNPs associated with common confounders (e.g. income, education, drinking, and smoking) during IV selection, it is plausible that some of these variables may act as mediators rather than confounders in the associations explored. By excluding SNPs linked to these variables to control for confounding, we cannot rule out the possibility that this approach might have reduced

statistical power or inadvertently adjusted for pathways that are part of the causal mechanism. In addition, some unmeasured confounders may persist. Potential biases could arise from unobserved confounding factors such as population stratification and assortative mating.⁹³ Furthermore, MR analysis relies on the principle of gene–environment equivalence, which assumes genetic variation–induced changes in exposures have identical downstream effects on outcomes as environmental changes.^{17,94} However, genetic variations may not accurately mimic environmental changes. MR estimates also reflect the lifetime effects of exposures on outcomes, which could lead to larger effect sizes compared with estimates derived from RCTs or other approaches that measure effects over specific time frames.¹⁷ Therefore, despite rigorous IV selection and sensitivity analyses, our findings should be interpreted with caution in clinical contexts. Future work would benefit from formal mediation analyses to clarify whether variables such as income, education, and lifestyle act as confounders or mediators, alongside longitudinal and multiethnic studies to validate and extend these insights clinically.

In conclusion, we explore the causal relationships between brain structural connectome and major psychiatric disorders by conducting bidirectional two-sample MR analyses with 206 white-matter structural connectivity phenotypes and 13 psychiatric disorders. The results shed light on the pathogenesis of major psychiatric disorders at the level of brain structural connectome, as well as provide insights into potential biomarkers for detection and prevention of psychiatric disorders.

Methods

GWAS of brain structural connectome

We used the GWAS summary statistics of human brain structural connectome from 26,333 participants of European ancestry in the UK Biobank, processed from Wainberg *et al.*²¹ Specifically, the density and connectivity of white-matter fibers between pairs of brain regions were quantified based on 214 predefined regions, which include 200 cortical parcels from the Schaefer atlas⁹⁵ and 14 subcortical parcels from the Harvard-Oxford atlas. A GWAS was subsequently conducted on the brain structural connectome to investigate the associations between 206 white-matter structural connectivity measures—which collectively represent the brain structural connectome—and the 9,423,516 variants present in the imputed genotypes of the UK Biobank.

The 206 white-matter structural connectivity measures include: (1) three hemisphere-level connectivity measures, including left intrahemisphere, right intrahemisphere, and interhemisphere connectivity; (2) a total of 105 cortical network-level connectivity measures, encompassing white-matter structural connectivity within the seven functional networks⁹¹ of both hemispheres. Specifically, 14 measures were derived from within-network connectivity, while 91 measures were derived from between-network connectivity; and (3) a total of 98 cortical-to-subcortical connectivity measures, including white-matter structural connectivity between the seven functional networks⁹¹ of both hemispheres and seven subcortical structures: the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens.

GWAS of psychiatric disorders

In our study, we collected publicly available GWAS summary statistics for 13 psychiatric disorders, which were selected based on their high prevalence, strong neurobiological relevance, availability of large, high-quality GWAS data sets, and their frequent inclusion in MR research, including ADHD⁹⁶ (38,691 cases and 186,843 controls), AN²² (16,992 cases and 55,525 controls), anxiety disorders⁹⁷ (50,486 cases and 330,460 controls), ASD⁹⁸ (18,381 cases and 27,969 controls), AUD⁹⁹ (113,325 cases and 639,923 controls), BIP¹⁰⁰ (40,463 cases and 313,436 controls), CUD¹⁰¹ (42,281 cases and 843,744 controls), depression⁹⁷ (53,313 cases and 394,756 controls), OCD⁹⁷ (2490 cases and 403,817 controls), OUD¹⁰² (15,251 cases and 538,935 controls), PTSD²³ (137,136 cases and 1,085,746 controls), schizophrenia¹⁰³ (53,386 cases and 77,258 controls), and

TS¹⁰⁴ (4819 cases and 9488 controls). Given that the GWAS of brain structural connectivity was conducted in the European-ancestry population of the UK Biobank, we tried to avoid participant overlap between the psychiatric disorder GWAS and brain structural connectome GWAS. There was no sample overlap with the UK Biobank in 11 of the psychiatric disorders, except for AN and PTSD. In the case of AN, the largest obtainable GWAS sample was utilized, exhibiting a maximum overlap rate of 5.29% with the brain structural connectome sample. PTSD was also examined using the largest accessible GWAS sample, featuring an overlap rate of approximately 2.15% and a sample size in the millions. Given these parameters, the likelihood of introducing meaningful bias into the results is considered minimal.^{19,24,25} To minimize confounding due to genetic ancestry differences and other contextual factors that could inflate MR results, we restricted all psychiatric disorder GWAS data sets utilized the study to European-ancestry samples. Detailed information on these GWAS samples is summarized in Tables 1 and S2.

Selection of IVs

For MR analysis to be valid, three fundamental assumptions must be satisfied: (1) the IVs must be strongly associated with the exposure; (2) the IVs must be independent of confounders that influence both the exposure and the outcome; and (3) the IVs must affect the outcome only through the exposure, without exerting any direct effect on the outcome or through alternative pathways, which is also referred to as the absence of horizontal pleiotropy.¹⁰⁵

To satisfy these assumptions, we first selected SNPs that are strongly associated with the exposure ($p\text{-val} < 5 \times 10^{-8}$). Clumping was then performed using the “TwoSampleMR” R package,¹⁰⁶ with parameters $r^2 = 0.001$ and a window size of 1000 kb, using the 1000 Genomes European data as the reference panel. Incompatible SNPs (those that do not follow the principle of complementary base pairing) were checked and removed, and palindromic SNPs with a minor allele frequency close to 0.5 were excluded to avoid potential ambiguity. The harmonization procedure was performed using the “TwoSampleMR” R package¹⁰⁶ to ensure that the SNPs in the exposure and outcome GWAS summary statistics were consistent and came from the same DNA strand. Afterward, SNPs associated with the outcome were removed ($p\text{-val} < 5 \times 10^{-5}$), and the Steiger test¹⁰⁷ was performed to reduce the risk of potential reverse causality. Previous studies have shown that factors such as income,^{108,109} education,^{110,111} smoking,^{112,113} and drinking^{114,115} may influence both brain structural connectome and psychiatric disorders. Therefore, we used the NHGRI-EBI Catalog¹¹⁶ (<https://www.ebi.ac.uk/gwas/home>) to search for and remove SNPs associated with potential confounders ($p\text{-val} < 5 \times 10^{-5}$). Quality control was conducted to enhance the robustness of the IVs. We used the “IVW_radial” method from the “RadialMR” R package¹¹⁷ to perform a Cochran Q test for the IVW model, and outliers were removed ($p\text{-val} < 5 \times 10^{-5}$).

The F statistic was calculated to assess the strength of the IVs using the following formula,^{118,119}

$$F = \frac{R^2 \times (n - k - 1)}{(1 - R^2) \times k} \quad (1)$$

where R^2 (the variance in the exposure explained by the IVs), n (the sample size of the exposure GWAS), and k (the number of IVs) are parameters in the calculation. The R^2 statistic can be calculated using the following formula,^{118,119}

$$R = \frac{\beta^2}{\beta^2 + se^2 \times n} \quad (2)$$

where β (effect size of the exposure) and se (standard error of the exposure) are parameters in the calculation. For multiple IVs, the R^2 is the sum of R^2 of each individual IV.

Bidirectional MR analyses

Bidirectional two-sample MR analyses were conducted to investigate the causal relationships between brain structural connectome and psychiatric disorders. In the forward MR analyses, the brain structural connectome served as the exposure, with psychiatric disorders as the outcome. Conversely, in the reverse MR analyses, psychiatric disorders were considered the exposure, and the brain structural connectome was regarded as the outcome.

The IVW regression with multiplicative random effects was applied as the primary causal inference method due to its highest statistical efficiency.¹²⁰ However, the IVW method may yield biased results if there is an average pleiotropic effect that deviates from zero. Therefore, six additional MR methods were employed to strengthen the robustness of our findings. The MR-Egger method, particularly useful when there is directional pleiotropy among IVs, provides a consistent causal effect estimate through its slope.¹²¹ The weighted median method yields reliable causal effects even in the presence of invalid IVs, under the assumption that at least half of the IVs are valid.¹²² The weighted mode method groups IVs based on similar causal effects and provides consistent estimates if the majority of IVs in the largest cluster are valid.²⁸ MR-RAPS accounts for systematic and idiosyncratic pleiotropy and enables robust causal inference with many weak IVs.¹²³ The contamination mixture method offers reliable estimates for causal analysis using hundreds of IVs with the presence of invalid IVs.¹²⁴ Debiased IVW effectively reduces bias related to weak IVs and enhances robustness in situations with multiple weak IVs.¹²⁵ All the above methods were conducted using the “TwoSampleMR”,¹⁰⁶ “mr.raps”,¹²³ and “MendelianRandomization”.¹²⁶ R package.

Considering that the white-matter structural connectivity phenotypes of the brain structural connectome are continuous and unitless normalized indices reflecting the relative strength of connectivity between brain regions, while psychiatric disorder phenotypes are binary (case/control) variables, we utilized ORs and beta coefficients to quantify the effect sizes in the forward and reverse MR analyses, respectively. Furthermore, we adhered to the Strengthening the Reporting of Mendelian Randomization Studies (STROBE-MR) guidelines¹²⁷ (see Supporting Information Note for details).

Sensitivity analyses

To account for multiple comparisons, our study applied a Bonferroni-corrected significance threshold of 1.2316×10^{-4} ($0.05/206/2$, with 206 denoting the number of white-matter structural connectivity phenotypes and 2 representing bidirectional MR analyses). In addition, we set a nominal significance threshold of 1×10^{-3} , as results that do not quite meet the Bonferroni threshold may still be of suggestive value. To ensure the reliability of our MR analyses, we only considered causal links that met the following criteria: the SNPs were sufficient for sensitivity analyses (i.e. at least four IVs),⁸⁷ the directions of estimates from different MR methods were consistent, and the *P*-value from the IVW method was below the nominal significance threshold.

A series of sensitivity analyses were conducted to further verify the significant MR results. First, we employed MR-Egger intercept test¹²¹ to detect potential directional pleiotropy ($P < 0.05$). Then, we performed a MR-PRESSO global test¹²⁸ to detect potential bias of horizontal pleiotropy ($P < 0.05$). In addition, a Cochran Q test¹²⁹ was utilized to assess heterogeneity in the causal estimates across different IVs ($P < 0.05$). Finally, we conducted leave-one-out analyses to identify whether any single IV was disproportionately influencing the results or whether the causal effects remained consistent when each IV was excluded.¹⁷ The MR-PRESSO global test was conducted with the “MR-PRESSO” R package,¹²⁸ while all other analyses were performed using the “TwoSampleMR” R package.¹⁰⁶

Because the GWAS summary data utilized in this study are publicly available, no additional ethical approval or participant consent was necessary. Details regarding ethical approval and participant consent can be found in the respective original GWAS publications.

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Disclosure statement

The authors declare no competing interests.

Author contributions

Data acquisition and analyses were conducted by K.X. and X.C. The initial manuscript draft and figures were prepared by K.X. and C.Y. C.Y. and J.S. critically revised the work for important intellectual content. C.Y., J.S., Z.Z. and T.M. contributed to the conception and design of the study. All authors have read and approved the final version of the manuscript.

Data availability statement

All GWAS summary statistics utilized in this study are publicly available. The GWAS summary statistics of 206 brain white-matter structural connectivity (GCST90302648 ~ GCST90302853) can be downloaded from the GWAS catalog (<https://www.ebi.ac.uk/gwas/>). The GWAS summary statistics for anxiety disorders, depression, and OCD are obtained from the FINNGEN R11 release (to access these data, please follow the FINNGEN R11 release guidance: <https://finngen.gitbook.io/documentation/data-download>). The GWAS summary statistics for the three substance use disorders (AUD, CUD, OUD) can be accessed at <https://medicine.yale.edu/lab/gelernter/stats/>. Summary statistics for other psychiatric disorders are available from the PGC (<https://pgc.unc.edu/for-researchers/download-results/>). The GWAS summary statistics for birth length can be downloaded from <https://www.decode.com/summarydata/>.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.