Archival Report

Associated Genetics and Connectomic Circuitry in Schizophrenia and Bipolar Disorder

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ABSTRACT

BACKGROUND: Schizophrenia (SCZ) and bipolar disorder (BD) are severe psychiatric conditions that can involve symptoms of psychosis and cognitive dysfunction. The 2 conditions share symptomatology and genetic etiology and are regularly hypothesized to share underlying neuropathology. Here, we examined how genetic liability to SCZ and BD shapes normative variations in brain connectivity.

METHODS: We examined the effect of the combined genetic liability for SCZ and BD on brain connectivity from two perspectives. First, we examined the association between polygenic scores for SCZ and BD for 19,778 healthy subjects from the UK Biobank and individual variation in brain structural connectivity reconstructed by means of diffusion weighted imaging data. Second, we conducted genome-wide association studies using genotypic and imaging data from the UK Biobank, taking SCZ-/BD-involved brain circuits as phenotypes of interest.

RESULTS: Our findings showed brain circuits of superior parietal and posterior cingulate regions to be associated with polygenic liability for SCZ and BD, circuitry that overlaps with brain networks involved in disease conditions ($r = 0.239$, $p < .001$). Genome-wide association study analysis showed 9 significant genomic loci associated with SCZ-involved circuits and 14 loci associated with BD-involved circuits. Genes related to SCZ-/BD-involved circuits were significantly enriched in gene sets previously reported in genome-wide association studies for SCZ and BD.

CONCLUSIONS: Our findings suggest that polygenic liability of SCZ and BD is associated with normative individual variation in brain circuitry.

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Schizophrenia (SCZ) and bipolar disorder (BD) are psychiatric disorders affecting an estimated 3% of the population worldwide (1,2). SCZ is characterized by symptoms of delusions, hallucinations, affective flattening, and cognitive dysfunction, and BD is characterized by periodic symptoms of mania and depression (3). The 2 disorders share mood and psychotic symptoms (4), show high comorbidity (5), are both highly heritable (6), and are believed to overlap in their genetic background (7,8) with a high genetic correlation ($r = 0.7$, $p < .001$) (9) and several overlapping sets of involved risk genes and pathways (10,11).

Their shared genetic background suggests the involvement of common biological mechanisms. Neuropathological and neuroimaging studies have pointed out that SCZ and BD share major pathophysiological changes, such as a loss in dendritic spines of pyramidal neurons in the prefrontal cortex (12), decreased density of interneurons in the parahippocampal cortex (13), and gray matter volume disruptions (14). The 2 conditions further show overlapping pathology in terms of abnormalities in white matter tracts such as the uncinate fasciculus (15) and short-range connections among brain regions relevant to language processing, mood regulation, and working memory (16). Specifying to what extent individual variation in brain connectivity is directly associated with underlying unique and shared polygenic liability can improve our knowledge of the combined genetic and connectomic etiology of psychiatric conditions (17,18).

We first examined polygenic scores (PGSs) that quantitatively estimate an individual’s genetic predisposition for SCZ and BD based on genomic variants (19). Combining genetic and neuroimaging data of the UK Biobank (UKB) (20) with neuroimaging data from disease cohorts (part I) (21,22), we examined structural brain circuits related to combined polygenic effects for SCZ and BD in the healthy brain and demonstrated their relationship to connectivity-based pathology in disease conditions (Figure 1). Second, we examined the genetic-connectomic association by conducting genome-wide association studies (GWASs) on SCZ- and BD-involved brain circuits (part II), stressing that genomic variants associated with brain circuits play a role in psychiatric conditions.

METHODS AND MATERIALS

Compliance With Ethical Standards

The UKB study protocol was approved by the National Research Ethics Service Committee North West Haydock (reference 11/NW/0382), and all procedures were conducted following the ethical principles for medical research declared in the World.
Medical Association Declaration of Helsinki. The COBRE SCZ study protocol was approved by the institutional review board of the University of New Mexico. The MACS BD study was approved by the ethics committees of the medical faculties of the University of Marburg and the University of Münster.

Part I: Examining Associations Between PGSs and Brain Connectivity

Participants From the UKB. Neuroimaging and genotypic data of 38,436 subjects from the UKB (access number 16406; February 2020) (20,23) were used. A hold-out sample of 5000 subjects was selected for validation purposes, making a discovery set of 33,436 participants and a replication set of 5000 participants. Strict quality control was conducted for both neuroimaging and genotypic data to exclude unreliable data samples (Supplemental Methods). Remaining data samples ($n = 26,703$ of 38,436) were divided into a healthy sample ($n = 19,778$; discovery/hold-out sample: 17,189/2589) and a disease sample ($n = 6815$; including 26 patients with SCZ and 124 patients with BD) (Supplemental Methods; Table S1).

Participants From Disease Cohorts. Neuroimaging data from 2 independent cohorts of SCZ and BD were used to assess disease-associated brain circuits. The SCZ dataset included 58 SCZ and 77 age-matched and sex-matched healthy control subjects (HCs), obtained from the open SchizConnect Center for Biomedical Research Excellence (COBRE) dataset (21,22). The BD dataset included 84 BD and 326 age-matched and sex-matched HCs, as part of the Marburg-Münster Affective Disorders Cohort Study (MACS) BD dataset, were used to study connectivity differences between healthy control subjects and patients with SCZ or BD. Spatial correlations between the spatial pattern of PGS-connectivity associations and the pattern of case-control connectivity differences were then validated. Connections showing deficits in disease conditions were identified and were taken as the phenotypes of interest in GWAS analysis, which was conducted using genotype data from the UK Biobank.
included in the current study (27) (Supplemental Methods). Genetic principal components (PCs) were computed within the full UKB sample, based on a set of 145,432 independent $t^2 < 0.1$ autosomal single nucleotide polymorphisms (SNPs) using FlashPCA (28). The first 20 PCs were used as covariates to correct for population stratification (29).

**PGS Calculation.** PGSs were calculated on imputed genotype data for each individual from the UKB, based on summary statistics from GWASs on SCZ and BD (10) (Table S2). PGS regarding combined polygenic effects for SCZ and BD (referred to as SCZ+BD) was computed using the GWAS comparing combined patients with SCZ and BD with HCs (10). PGS for the differentiated polygenic effects between SCZ and BD was also calculated (referred to as SCZ–BD) (10). Summary statistics from the 2 most recent GWASs for SCZ (30) and BD (31) were included for validation purposes. Eleven GWASs on other psychiatric and neurological conditions were used to examine to what extent results relevant to SCZ and BD are specific and/or are generalizable to other conditions (Table S2). PGS calculation was performed using PRSice-2 (19,32) for a range of $p$-value thresholds for inclusions of SNPs ($p < .0005, .001, .005, .01, .05, .1, and .5$). Results derived from $p < .01$ are reported in the main results; results on alternative thresholds are reported in Figures S2–S6. PGSs were also computed based on an optimal threshold [by PRSice-2 (32)] identified according to case prediction within the entire UKB sample (Supplemental Results).

**Magnetic Resonance Imaging Data.** T1-weighted magnetic resonance imaging (MRI) and diffusion weighted imaging data were used for reconstruction of brain connectivity circuits. Scanning parameters and data processing are summarized in (33,34) and Supplemental Methods. A 114 × 114 connectivity matrix describing all reconstructed region-to-region connections was formed for each subject using FreeSurfer (version 6.0) and CATO (version 3.1.2) (35–37) (for details, see Supplemental Methods). Considering a high heritability as evidenced by both twin MRI studies (38) and GWAS (39), mean fractional anisotropy (FA) of reconstructed tractography streamlines was taken as a metric of the strength of connections. Results of streamline density weighted connectivity are summarized in Supplemental Results.

**Linear Regression Analysis.** Linear regression analysis was used on the discovery dataset to identify relationships between polygenic effects for the different contrasts (SCZ, BD, SCZ+BD, and SCZ–BD) and brain connectivity (global-, regional-, and connectionwise). Global connectivity strength (mean strength across connections), regional connectivity strength (mean strength of connections of a region), and strength of single connections were used, respectively, for global-, regional-, and connectionwise analysis. For connectionwise analysis, group thresholding was applied by selecting consistent connections ($N = 1311$) that were mapped in >60% of the subjects (40). PGS-connectivity association was examined using the following formula:

$$y_i = \beta_0 + \beta_x x_i + \beta_{p+1} c_{pi} + \ldots + \beta_{p+1} c_{pi} + \epsilon_i$$

where $x_i$ indicates the standardized PGS of subject $i$, $y_i$ the standardized connectivity strength, $c_{pi}$ the standardized $p$th covariate, and $\epsilon_i$ the residual. Age, sex, genotyping array, assessment center, and 20 ancestry PCs were included as the $p$ covariates in the model. The standardized regression coefficient $\beta$ indicates the effect size, with $t$ tests performed to express the corresponding $p$ value. Network-based statistic (NBS) analysis (41) was used to control familywise error rate and identify subnetworks showing significant PGS-connectivity associations (Supplemental Methods).

**Cross-reference to Disease Conditions.** Connectivity maps were similarly formed for the 26 SCZ and 124 BD cases in the UKB dataset. Two-tailed two-sample t tests were performed on the 1311 connections in the connectivity matrix to assess connectionwise differences for SCZ+BD compared with matched HCs (150 randomly selected HCs, matched for age and sex of the SCZ and BD groups, respectively). Resulting $t$ scores were correlated to the standardized regression coefficient $\beta$ obtained in the PGS-connectivity association analysis across all 1311 connections, with permutation testing performed to rule out the spatial autocorrelation effects (Supplemental Methods). Similar analyses were conducted for the COBRE SCZ and the MACS BD datasets for validation.

**Part II: GWAS Analysis on SCZ-/BD-Involved Brain Circuits**

Abovementioned analyses focused on identifying brain connectivity in relation to PGSs for SCZ and BD in healthy subjects. We further examined the genetic-connectomic association using GWAS analysis on a phenotype capturing subnetworks of connections related to SCZ and BD. SCZ-involved connections and BD-involved connections were selected using the external COBRE SCZ and MACS BD datasets, computed by means of two-sample t tests on all connections between the patients and HCs in these datasets. Disease-involved connections were selected if two-sided $p < .05$ and $t$ score $< 0$ (i.e., connectivity strength reduced in patients, resulting in 46 SCZ-involved connections and 100 BD-involved connections). Next, in the UKB sample ($n = 22,799$), including both healthy and disease samples (results of healthy samples only are shown in Supplemental Results), the mean strength of the selected SCZ- and BD-involved connections was computed and taken as the phenotype of interest in a following GWAS analysis. GWAS was conducted in PLINK version 2.00 (42), using an additive linear regression model controlling for covariates of age, sex, 20 European-based ancestry PCs, genotyping array, assessment center, and 2 quality control metrics of diffusion weighted imaging data (Supplemental Methods). Total brain volume was additionally taken as a covariate to rule out genetic effects that are generally related to the brain. Genetic correlation analysis was conducted between the resulting GWAS summary statistics and the summary statistics for SCZ+BD, SCZ, BD, and SCZ–BD, using linkage disequilibrium score regression (LDSC) (43,44).
RESULTS

Part I: Connectome-wide Associations of the Combined Polygenic Effects for SCZ and BD

Sample Characteristics. PGSs for SCZ, BD, and SCZ+BD were computed for 17,189 UKB healthy subjects. PGSs for SCZ+BD was positively associated with PGS for SCZ ($r = 0.705, p < .001$), PGS for BD ($r = 0.465, p < .001$), and PGS for SCZ–BD ($r = 0.101, p < .001$). UKB SCZ and BD samples showed significantly higher PGSs compared with UKB healthy samples (SCZ+BD PGS: $t_{17,296} = 5.564, p < .001$; SCZ PGS: $t_{17,296} = 2.412, p = .016$; BD PGS: $t_{17,296} = 5.011, p < .001$) (Table S3). Similar results were observed in the entire UKB sample of 641 SCZ and 1455 BD cases (Supplemental Results).

PGS-Connectomic Association in the Healthy Population. PGS for SCZ+BD was negatively associated with global connectivity strength across healthy subjects ($\beta = −0.021, p_{\text{FDR}} = .012$, false discovery rate [FDR] corrected across 4 tests), indicative of healthy individuals with a higher SCZ+BD PGS to show overall lower levels of connectivity strength in their brain network. Follow-up analysis showed significant associations when examining only SCZ PGS ($\beta = −0.023, p_{\text{FDR}} = .011$), but not for PGSs for BD ($\beta = −0.003, p_{\text{FDR}} = .661$) and SCZ–BD ($\beta = −0.008, p_{\text{FDR}} = .274$). Using PGS calculated on the more recent SCZ GWAS (30) revealed similar results ($\beta = −0.021, p_{\text{FDR}} = .012$) (Supplemental Results). Reperforming this analysis with a more recent BD GWAS describing a larger sample (31) did indicate a potential significant effect for BD PGS ($\beta = −0.018, p = .019$). Results on PGS for BD in the following sections are thus based on this recent BD GWAS (31).

Significant associations between SCZ+BD PGS and regional connectivity strength were observed for the left posterior cingulate and superior parietal regions and the right lateral occipital and anterior cingulate regions ($q < .05$, FDR corrected across 114 brain regions) (Figure 2A; Table S4). Similar results were observed for PGSs for SCZ and BD separately (Figure S7). Connectionwise regression analyses revealed 2 subnetworks of a total of 72 connections that showed significant associations with SCZ+BD PGS ($\beta = −0.020$ to $−0.039, p_{\text{NBS}} = .001$ and .006) (Figure 2B). These connections linked intrahemispheric cortical regions including the inferior parietal cortex and insula/superior temporal cortex, supramarginal and lateral orbitofrontal cortex, etc. Post hoc examinations revealed longer connections to show stronger PGS-connectivity associations ($r = −0.240, p < .001$) (Supplemental Results). A stronger PGS-connectivity association was also observed for connections spanning between type 2 Economo cortical areas (i.e., homotypic frontal cortex; $t_{1309} = −3.555, p_{\text{FDR}} = .002$) and connections spanning between regions involved in cognitive domains of cognition and manipulation ($t_{1309} = −3.312, p_{\text{FDR}} = .006$ and $t_{1309} = −2.723, p_{\text{FDR}} = .020$, respectively) (Supplemental Results). Correlating SCZ PGS to connectivity strength showed significant associations in 3 subnetworks of a total of 47 connections ($p_{\text{NBS}} < .05$; 18 connections nested within the above SCZ+BD PGS-identified network). PGS for BD was associated with a subnetwork of 8 connections ($p_{\text{NBS}} = .020$; 6 connections nested within the SCZ+BD PGS-identified network). No specific effects were observed for PGS for SCZ–BD ($p_{\text{NBS}} = .478$).

Post hoc analysis further revealed significant associations between SCZ+BD PGS and within-network connectivity strength of the default mode network (see Supplemental Methods) (45) ($\beta = −0.020, p_{\text{FDR}} = .032$) (Figure 2D). PGS for SCZ+BD was associated with between-network mean connectivity strength among examined networks (Figure 2E), with the highest effect observed for connections spanning between the ventral attention network and dorsal attention network ($\beta = −0.038, p_{\text{FDR}} < .001$). Results of SCZ PGS are shown in Figure S8. No significant...
correlations were observed for PGSs for BD and SCZ–BD. In addition, examining associations between SCZ+BD PGS and network topological properties showed trend-level, nonsignificant associations for the characteristic path length ($\beta = 0.017$, nominal $p = .16$) and the mean clustering coefficient ($\beta = -0.016$, nominal $p = .42$) (Supplemental Results).

The specificity of the association between SCZ+BD PGS and brain circuits was tested by examining PGSs for other mental conditions. The SCZ+BD PGS subnetwork significantly correlated to PGS for attention-deficit/hyperactivity disorder (46) ($\beta = -0.026$, $p_{\text{perm}} = .009$) and major depressive disorder (47) ($\beta = -0.021$, $p_{\text{perm}} = .036$), but not for other examined mental disorders (Supplemental Results).

**PGS-Connectomic Associations Overlapped With Disconnectivity of Psychiatric Disorders.** The spatial pattern of correlations between SCZ+BD PGS and connectivity strength significantly correlated to the pattern of connectivity differences between the groups of patients with SCZ and BD and HCs from the UKB ($r_{1,309} = 0.239$, $p_{\text{perm}} < .001$) (Figure 3). Similar spatial correlations were observed for the patterns of connectivity differences between patients with SCZ and HCs ($r_{1,309} = 0.214$, $p_{\text{perm}} < .001$) and between patients with BD and HCs ($r_{1,309} = 0.216$, $p_{\text{perm}} < .002$). These findings suggest that connections associated with a higher SCZ+BD PGS in the healthy population display larger changes in brain circuitry in clinical groups (SCZ and BD). The association for SCZ remained significant when controlling for polygenic effects of BD ($r_{1,309} = 0.186$, $p_{\text{perm}} < .001$), and vice versa (see Supplemental Results). Outgroup analyses correlating the spatial pattern of PGS-connectivity associations to the pattern of connectivity differences between HCs and non-SCZ and non-BD subjects ($n = 6665$) with other mental conditions showed a nonsignificant effect ($r_{1,309} = 0.028$, $p = .658$). Analyses separately on 4 distinct mental disorders, including depression ($n = 4731$), anxiety ($n = 34$), autism ($n = 31$), and obsessive-compulsive disorder ($n = 112$), similarly resulted in nonsignificant effects (all $p > .3$), suggesting the observed spatial correlation between SCZ and BD PGSs and brain patterns to be relatively specific to SCZ and BD conditions.

**PGSs, Connectivity, and Cognition.** SCZ and BD share a genetic background with genetics of intelligence and cognition (48). Thus, we further investigated potential interactions across PGSs, brain connectivity, and cognitive functions (assessed by means of fluid intelligence [UKB field: 20016], reaction time [UKB field: 20023], pairs matching [UKB field: 399], numeric memory [UKB field: 4282], and prospective memory [UKB field: 20018]) (see Supplemental Methods). The SCZ+BD PGS subnetwork (72 connections) positively associated with higher scores on fluid intelligence test ($\beta = 0.065$, $p < .001$) (Figure 4), suggesting that higher connectivity strength covaried with lower polygenic risk for SCZ/BD and overall higher scores on fluid intelligence tests. Post hoc analysis using permutation testing showed that this observed effect was relatively specific to the SCZ+BD PGS network with effects significantly exceeding the null distribution of effect sizes obtained when we computed this correlation with randomly selected connections across the brain ($p_{\text{perm}} = .025$, 1000 permutations). Mediation analysis showed connectivity strength of the SCZ+BD PGS-derived subnetworks to significantly mediate the relationship between SCZ+BD PGS and cognitive function ($\beta = -0.002$, $p < .001$, effect accounting for 2.5% of the total effect size for the PGS-intelligence association) (Figure 4). The SCZ+BD PGS subnetwork was also significantly associated with cognitive performance in reaction time ($\beta = -0.062$, $p < .001$), pairs matching ($\beta = -0.033$, $p < .001$), and numeric memory ($\beta = 0.044$, $p < .001$), with no effect observed for prospective memory ($\beta = 0.004$, $p = .655$).

**Validation.** The robustness of the observed connectome-wide association with SCZ+BD PGS was tested using the hold-out dataset ($n = 2589$) (see Methods and Materials). First, the spatial pattern of PGS-connectivity association reported using the discovery sample again significantly correlated to the pattern of PGS-connectivity association observed in the hold-out sample ($r_{1,309} = 0.150$, $p < .001$). Second, the pattern of connectome-wide correlations between PGS for SCZ+BD and connectivity strength similarly showed a positive correlation to the pattern of disconnectivity in the combined group of patients with SCZ and BD ($r_{1,309} = 0.160$, $p < .001$), as well as to the pattern of disconnectivity in SCZ ($r_{1,309} = 0.167$, $p < .001$) and BD ($r_{1,309} = 0.135$, $p < .001$).

Using the independent COBRE SCZ dataset (21,22), we further validated the overlapping patterns of SCZ+BD PGS-connectivity correlations (as observed in the UKB healthy sample) and the connectivity differences between SCZ and HCs ($r_{1,309} = 0.18$, $p_{\text{perm}} = .006$) (Figure S9). Analyzing the independent MACS BD dataset (24,25) ($n = 84$ patients, 346 HCs) validated the observation of the overlapping pattern between the PGS-connectivity correlations and connectivity differences between SCZ and BD groups ($r_{1,309} = 0.129$, $p_{\text{perm}} = .014$) (Figure S9).

**Part II: GWASs on SCZ-/BD-Involved Brain Circuits Reveal Genetic Overlaps With the Disorders**

**GWAS on SCZ Circuity.** GWAS results with minor allele frequency $>0.0001$ are shown in Figure 5A. GWAS on SCZ-
involved connections revealed 32 independent significant variants \((p < 5 \times 10^{-8})\), tagging 9 independent genomic loci (Table S5). The SNP-based heritability \((h^2_{SNP})\) estimated by LDSC was 24.0% (standard error = 2.9%). The LDSC intercept of 1.008 was close to 1 and the observed inflation level \((\lambda_{G})\) was 1.099, suggesting that the inflation of genetic signals is mostly due to polygenicity rather than population stratification (49). One of the observed genomic loci \((rs3129171;\) chromosome 6; position 29155749) (Figure 5B) was within the significant loci reported in a recent SCZ GWAS study (50). Five of the 9 observed loci overlapped with the loci reported in a recent GWAS on brainwide FA (39).

The identified SNPs were mapped to 261 genes using positional mapping, expression quantitative trait loci mapping, and chromatin interaction mapping implemented in FUMA (51). Gene enrichment analysis based on previously curated gene sets showed significant enrichment of the identified genes in the GWAS catalog–reported gene sets of autism spectrum disorder or schizophrenia \((\rho_{G} = 1.70 \times 10^{-52})\), schizophrenia \((\rho_{G} = 4.05 \times 10^{-11})\), bipolar I disorder \((\rho_{G} = 1.31 \times 10^{-9})\), and 12 other traits related to sleep, lung cancer, social communication, and blood protein levels (Figure 5D).

LDSC genetic correlation analysis showed a trend-level correlation between our GWAS on SCZ-involved connectivity and previous GWAS on SCZ (10) \((r = -0.111,\) nominal \(p = .015;\) \(\rho_{G} = .058,\) corrected across 4 tests), Controlling for the effect of global FA (which showed phenotypic correlation with SCZ-involved circuits: \(r = 0.730)\), permutation testing (see Supplemental Methods) showed \(r_{G}\) for SCZ and SCZ+BD \((r_{G} = -0.078,\) \(\rho_{G} = .104)\) to significantly exceed the null distribution of \(r_{G}\) yielded by GWAS analysis on same sized random connections \((p_{perm} = .030\) and .045 for SCZ and SCZ+BD, respectively; 200 permutations) (Figure SC). Correlating to GWAS results of BD \((r = -0.052,\) \(\rho_{G} = .208)\) and SCZ–BD (10) \((r = -0.109,\) \(\rho_{G} = .104)\) revealed no additional significant effects.

**DISCUSSION**

Our study provides biological insights into associated brain connectivity and polygenic liability for SCZ and BD. Combining PGS and neuroimaging shows that healthy individuals with a higher PGS for SCZ and BD display relatively lower levels of connectivity strength in brain circuits matching those involved in disease samples.

Our findings suggest that normative variations of macro-scale brain circuitry are associated with combined polygenic effects of SCZ and BD, findings that are in support of a general relationship between polygenic liability and structural (52,53) and functional (54,55) brain organization. SCZ and BD are known to share a common genetic background and several molecular pathways (10,11,56). The observed association between polygenic liability and brain connectivity might be attributable to the role of disorder risk genes in white matter organization (52). Functional studies on disorder risk genes also pinpoint the role of genes in biological processes related to synaptic and oligodendrocytes (10,30), processes that are known to shape the cellular organization (57) and dynamics of brain connectivity (58,59). Our findings converge on cross-scale interactions among genetic, cellular, and macroscale brain organization in the context of shared polygenic effects for SCZ and BD (58,60).

Association analysis on PGSs in a healthy population may identify new brain circuits that are potentially related to disease processes. This corroborates previous observations in functional connectivity, which have indicated that several functional networks are related to SCZ’s PGSs (55). Structural circuits in this study involve the superior and inferior parietal cortex and the posterior cingulate regions of the default mode network, systems that have been broadly reported to be associated with both SCZ (16,61–63) and BD (16,64,65). Combined, these and previous results suggest that accumulating liability for
Figure 5. Genome-wide association study (GWAS) on schizophrenia (SCZ)-involved connections. (A) GWAS results on the mean strength of SCZ-involved connections (top) and of bipolar disorder (BD)-involved connections (bottom). The Miami plot shows $-\log_{10}$-transformed two-tailed $p$ value for all single nucleotide polymorphism (SNP) (y-axis) and base pair positions along the chromosomes (x-axis). Red line indicates Bonferroni-corrected genome-wide significance ($p < 5 \times 10^{-8}$). (B) Regional plot of the lead SNP rs3129171 on chromosome 6 in the GWAS on SCZ-involved connections. (C) Linkage disequilibrium score regression genetic correlation between SCZ-involved connections and SCZ, BD, SCZ and BD, SCZ, BD, and SCZ–BD. Error bar indicates standard error. Orange indicates $r_g$ with $p < .05$ and $p_{perm} < .05$ in permutation testing simultaneously. (D) Enrichment of genes associated with SCZ-involved connections and BD-involved connections in GWAS Catalog terms. Significant terms are displayed (false discovery rate-corrected $p < .05$). ASD, autism spectrum disorder; L, left; R, right.
psychiatric disorders in the healthy population can target particular brain substrates that are vulnerable to disease processes.

Neuroimaging and neurocircuitry analysis may provide valuable new endophenotypes to connect genetics and disease conditions (66). GWAS analyses on SCZ- and BD-involved circuits point to a common genetic architecture of brain white matter integrity and mental health traits (39). Overlapping genes of SCZ-involved circuits and SCZ traits include, for example, ZSCAN31, a gene that regulates pivotal SCZ risk genes such as VIP2R and NPY, as well as the PI3K-AKT and the NOTCH signaling pathways in SCZ (67), and XPNPEP3, PCDHA7, and PCDHA8, genes reported to show altered expressions in SCZ and BD (68).

Several remarks have to be considered when interpreting our results. First, PGSs explain only a small proportion of variance of case-control differences in SCZ (here, 3.2%–11.5%) and BD (2.3%–9.2%) (69), but it should be noted that PGSs explain an even smaller proportion of variance in brain connectivity (~1%), which is similar to previous literature examining other neuroimaging traits (52,70). Second, our samples are all from European ancestry, which limits the generalizability of the results to populations of different ancestry (32). Third, brain connectivity was reconstructed using tractography, which is known to have several limitations regarding the reconstruction of complex oriented white matter fibers, for example, fibers through the corpus callosum (71,72). This might explain why no interhemispheric connection was found to correlate to PGSs for SCZ+BD (12 of the 142 interhemispheric connections showed nominal $\rho < 0.05$, $\beta = -0.017$ to $-0.025$; $p_{BG} > .05$). Fourth, information on antipsychotic treatment and disease duration was not available in the studied data cohorts. Future study on the impact of antipsychotic medication dosage on the reported genetic-connectomic associations is warranted (73).

Conclusions

Our study shows a common genetic background for brain structural connectivity and SCZ and BD, with a combined polygenic liability for the 2 disorders playing a central role in key macroscale brain circuits. The integration of genetics and connectomics may pave an avenue for the transition of the diagnostic practice of psychiatric disorders from a traditional descriptive manner to diagnosis built upon the underlying biological systems of the brain.

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Coders are available from the corresponding author on reasonable request. Data visualization uses the Gramm toolbox (74) and the Simple Brain Plot (75) implemented in MATLAB (version R2021a; The MathWorks, Inc.).

The UKB genotype data and MRI data that support the findings of this study are available in the UKB (accessed under application 18406; https://www.ukbiobank.ac.uk). The Centers for Biomedical Research Excellence dataset that supports the findings of this study is available at http://schizconnect.org. The Marburg-Münster Affective Disorders Cohort Study bipolar disorder data that support the findings of this study are available from the corresponding author on reasonable request.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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