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Genome-Transcriptome-Functional Connectivity-Cognition Link Differentiates Schizophrenia From Bipolar Disorder

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***Background and Hypothesis*: Schizophrenia (SZ) and bipolar disorder (BD) share genetic risk factors, yet patients display differential levels of cognitive impairment. We hypothesized a genome-transcriptome-functional connectivity (frontoparietal)-cognition pathway linked to SZ-versus-BD differences, and conducted a multiscale study to delineate this pathway. *Study Designs*: Large genome-wide studies provided single nucleotide polymorphisms (SNPs) conferring more risk for SZ than BD, and we identified their regulated genes, namely SZ-biased SNPs and genes. We then (a) computed the polygenic risk score for SZ (PRS_{SZ}) of SZ-biased SNPs and examined its associations with imaging-based frontoparietal functional connectivity (FC) and cognitive performances; (b) examined the spatial correlation between ex vivo postmortem expressions of SZ-biased genes and in vivo, SZ-related FC disruptions across frontoparietal regions; (c) investigated SZ-versus-BD differences in frontoparietal FC; and (d) assessed the associations of frontoparietal FC with cognitive performances. *Study Results*: PRS_{SZ} of SZ-biased SNPs was significantly associated with frontoparietal FC and working memory test scores. SZ-biased genes' expressions significantly correlated with SZ-versus-BD differences in FC across frontoparietal regions. SZ patients showed more reductions in frontoparietal FC than BD patients compared to controls. Frontoparietal FC was significantly associated with test scores of multiple cognitive domains including working memory, and with the composite scores of all cognitive domains. *Conclusions*: Collectively, these multiscale findings support the hypothesis that SZ-biased genetic risk, through transcriptome regulation, is linked to frontoparietal dysconnectivity, which in turn contributes to differential cognitive deficits in SZ-versus BD, suggesting that potential biomarkers for more precise patient stratification and treatment.**

Key words: SNP/polygenic risk score/gene expression/functional connectivity/working memory

Introduction

Debates continue on the categorical classification between schizophrenia (SZ) and bipolar disorder (BD) where symptoms across diagnostic boundaries. The move from syndromes to diseases requires knowledge of underlying etiology and pathology.[1] Although large-scale genome-wide association studies (GWASs) demonstrates a strong genetic correlation of 0.68,[2–5] molecular, neurobiological, and phenotypic differences remain between SZ and BD, including differential genetic effects,[6,7] greater frontal, temporal and parietal gray matter reduction,[8,9] as well as more severe global and frontal dysconnectivity in SZ than BD.[10,11] Compared to BD, individuals with SZ show more severe and pervasive cognitive impairments, notably preceding illness-onset.[12–14] Understanding the connections between molecular, neurobiological, and phenotypic differences may shed light on etiologies and aid in the deconstruction of psychiatric disorders in a dimensional manner. To this end, the current study focuses on whether and how SZ-versus-BD biased genetic variants (ie, conferring more risk for SZ than BD) relate to differential cognitive deficits noted between these 2conditions.

Genetics and cognition are bridged by the brain, where epigenetics, transcriptomics, proteomics, and neurobiology play a role in the functional pathway.[15] Recent findings converge to suggest that SZ-associated genetic variants exert their effects more through regulation of gene expression than alteration of protein structure.[3,16,17] A recent study further revealed that the overlap in gene expression dysregulation across psychiatric disorders aligns with the overlap in polygenic risk, indicating that transcriptome comprises a substantial component in the functional pathways of genetic risk.[18]

Integrating transcriptomics into cohort-based studies is challenging, given its tissue and region specificity, and the difficulty in obtaining neurological tissues. This has motivated the strategy to link imaging to transcriptomic features based on spatial-level rather than subject-level variation. For instance, Romme *et al.*[19] showed that transcriptomic profiles of SZ risk genes derived from the Allen Human Brain Atlas (AHBA) data correlated with the macroscale functional dysconnectivity profiles across cortical regions in SZ but not the patients with BD. Anderson *et al.*[20] demonstrated that depression-related brain phenotypes spatially correlated with expressions of SST, CORT, and NPY genes, which are 3 transcriptomic markers of somatostatin interneurons implicated as pathophysiological features of depression. These imaging transcriptomic findings support that brain regions carrying higher expressions of risk genes may be more disrupted in a psychiatric condition.

The current work studied a pathway underlying SZ-versus-BD differences, linking genetics to cognition through ex vivo transcriptomic and in vivo neuroimaging data. At the genetic level, we leveraged the psychiatric genomic consortium (PGC) GWAS findings to identify SZ-biased single nucleotide polymorphisms (SNPs) conferring more risk for SZ than BD.[3,4,6,21] At the transcriptomic level, we identified SZ-biased genes as those regulated by SZ-biased SNPs, ie, expression quantitative trait loci (eQTL), based on the PsychENCODE database,[22] and then obtained their postmortem transcriptomic profiles from the AHBA data.[23] *At the neurobiological level, considering that the limited sample sizes might not support blind brain-wide tests, we focused on frontoparietal regions that comprise a primary component underlying cognition*[24–26] *and have been highlighted by the triple network model for cognitive dysfunction in psychopathology.*[27] *Reduced frontoparietal functional connectivity (FC) has been more consistently observed in SZ than BD.*[28,29] *This echoes the observed graded frontoparietal FC reductions, increasing in severity in patients suffering from more extreme forms of psychopathology.*[30,31] *Notably, significantly lower frontoparietal FC was noted in psychotic patients with cognitive dysfunction compared to those with intact cognition*.[32] Herein, we characterized frontoparietal FC as the primary brain phenotype based on resting-state functional magnetic resonance images (rsfMRI). At the cognitive level, we relied on MATRICS Consensus Cognitive Battery (MCCB) and Computerized Multiphasic Interactive Neurocognitive System (CMINDS) scores. We then investigated intermodality associations as well as SZ-versus-BD differences in individual modalities. The key point lies in bridging between SZ-biased genetic risk and cognitive deficits with transcriptomic and neuroimaging data, by showing that expressions of genes regulated by SZ-biased SNPs correlate with disruptions in frontoparietal FC, which is more impaired in SZ than BD and underlies cognition.

Materials and Methods

We integrated PGC GWASs, PsychENCODE eQTLs, AHBA postmortem gene expressions, rsfMRI, neuropsychiatric data of controls and SZ and the patients with BD, to conduct a multiscale analysis. figure 1 provides an overview, where 6 tests were performed sequentially. table 1 provides the demographic information.

Test_A. SZ-Biased and Alternative SNP/Gene Sets

The PGC SZ, SZ-versus-BD, and BD GWAS results[3,4,6] were leveraged to identify SZ-biased SNPs. In brief, 740 SZ-biased SNPs were selected which showed: (1) SZ-versus-control differences ($P < 5 \times 10^{-5}$, uncorrected)[3]; (2) SZ-versus-BD differences ($P < 1 \times 10^{-5}$, uncorrected, risk alleles consistent with the SZ GWAS)[33]; and (3) no BD-versus-control differences ($P > .05$, uncorrected).[34] We used more stringent thresholds than commonly accepted suggestive associations ($P < 1 \times 10^{-4}$)[34,35] for SZ relevance and SZ-BD differences, expecting to achieve better functional homogeneity. To avoid false-positive

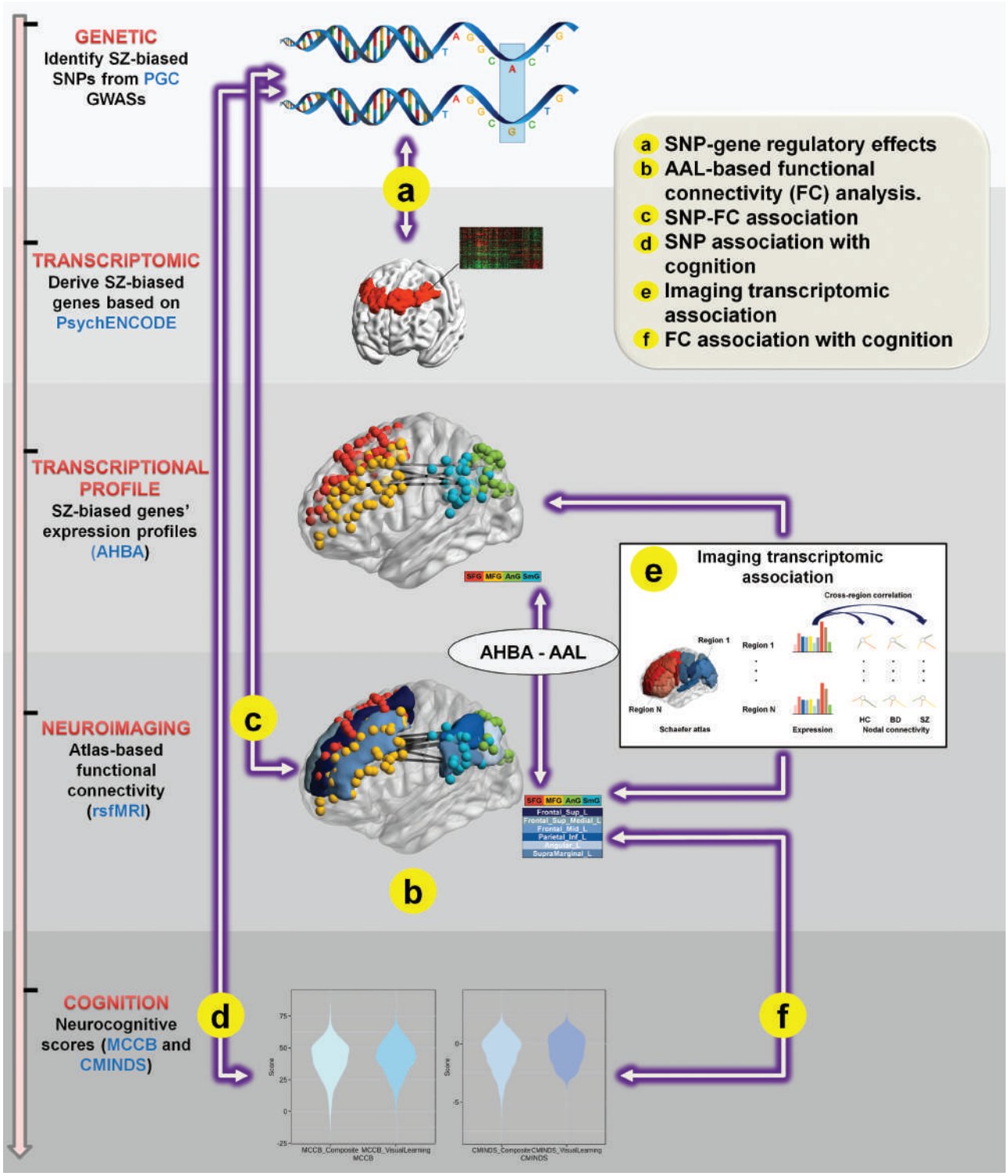

Fig. 1. Method overview for integrating information from genetic, transcriptomic, neuroimaging, and cognitive domains. A step-by-step overview visually depicts the process of linking SZ-biased genetic risk to cognitive deficits through transcriptomics and neuroimaging. The seven tests are coded sequentially. **A**. Derive SZ-biased SNPs and genes. **B**. Resting fMRI functional connectivity (FC) analysis based on the AAL atlas, where the 4 AHBA annotations map to six AAL regions. **C**. Association between SZ-biased SNPs and frontoparietal FC. **D**. Association between SZ-biased SNPs and neurocognitive performance. **E**. Imaging transcriptomic association based on the Schaefer atlas. **F**. Association of frontoparietal FC with neurocognitive performance.

Table 1. Participant Demographics. An Overview of Available Data Modalities in Individual Studies

Study	rsfMRI	SNP	Neurocognitive	Diagnosis Groups
COBRE	√	√	√ (MCCB)	HC, SZ
Local BD study*	√	×	√ (MCCB)	BD
FBIRN	√	√	√ (CMINDS)	HC, SZ
TOP	√	×	×	HC, BD, SZ
UMD	√	√	×	HC, SZ
UKBiobank	√	√	×	HC

*The imaging data of the COBRE and local BD study were collected at the same institution.

findings due to selection bias, we also examined SZ-biased SNPs yielded by other thresholds up to $P < 1 \times 10^{-3}$ (see *other supporting tests*).

The genes regulated by SZ-biased SNPs were defined as SZ-biased genes, leveraging the PsychENCODE eQTLs of the prefrontal cortex,[22] which aligned with our hypothesis to focus on frontoparietal regions and excelled in sample size compared to the Genotype-Tissue Expression database.[36] We obtained 15 SZ-biased genes with eQTL $P < 1 \times 10^{-4}$ (uncorrected), 8 of which were probed in the AHBA data.

We further created alternative SNPs as "controls" for comparison with SZ-biased SNPs. Following a similar rationale, we obtained (1) 536 SNPs conferring top SZ risk and no SZ-versus-BD differential risk to contrast with SZ-biased, denoted as SZ-top; (2) 236 SNPs showing both SZ and BD relevance, denoted as SZ-BD-common; and (3) 382 SNPs conferring top BD risk, denoted as BD-top. The GWAS thresholds were adjusted to yield roughly comparable numbers of SNPs between these sets. *These SZ-top, SZ-BD-common, and BD-top SNPs yielded 50, 29, and 24 regulated genes based on eQTL P < 1 × 10^{-4}, with 32, 14, and 18 genes probed in the AHBA data, respectively*. More details are in Supplementary Text 1 (ST1). Supplementary Table S1 summarizes the selection thresholds. Supplementary Table S2 and Supplementary Table S3 provide the complete lists of SNPs and genes.

Test_B. FC Differences Between Diagnosis Groups

While at the genetic and transcriptomic level, the SZ specificity was grounded by large-scale GWASs and eQTLs, it remained a question whether the targeted frontoparietal regions would show SZ-biased disruptions. We analyzed rsfMRI-based frontoparietal FC in two independent cohorts. As shown in table 1, Cohort1 consisted of 168 controls, 134 patients with SZ, and 58 patients with BD, aggregated from the FBIRN, COBRE, and local BD studies. Cohort2 consisted of 498 controls, 208 patients with SZ, and 58 patients with BD, aggregated from the TOP and UMD studies. The institutional review board at each site approved the study, and all participants provided written informed consent. Details regarding recruitment and data collection can be found in the previous publications[37–41] and Supplementary Text ST2.

The rsfMRI data went through an SPM12-based preprocessing pipeline,[42,43] including realignment, normalization, resampling (3mm × 3mm × 3mm), and smoothing (6mm FWHM Gaussian kernel), followed by temporal filtering (0.01–0.15Hz), and regression of head motion, white matter and cerebrospinal fluid signals (see Supplementary Text ST2 for more details). Subsequently, 116 regions of interest (ROIs) were defined using the automated anatomical labeling (AAL) atlas.[44] Each ROI or node was then characterized by its mean time course across voxels. An FC matrix was constructed for each participant based on Pearson correlations of time courses between pairs of ROIs.

Focusing on frontoparietal FC, we identified frontoparietal ROIs by mapping AHBA postmortem tissue samples to the AAL atlas, to assure consistency between the FC and imaging transcriptomic analysis (explained later). We first identified all the AHBA tissue samples with the following annotations: Superior frontal gyrus (SFG), middle frontal gyrus (MFG), angular gyrus (AnG), and supramarginal gyrus (SMG). Based on their MNI coordinates, the AHBA SFG samples roughly mapped to Frontal_Sup and Frontal_Sup_Medial in AAL; MFG to Frontal_Mid; AnG to Angular and Parietal_Inf; and SMG to SupraMarginal, as shown in figure 2. This led to nine frontoparietal FC pairs in AAL.

Differences between diagnosis groups in the 9 pairs of frontoparietal FC were evaluated in 2 independent cohorts (table 2) with a two-sample t-test (two-tailed) after age, sex, and site (dummy-coded) were regressed out. Meta-analysis was then conducted using Stouffer's Z-score method (two-tailed),[45] followed by false discovery rate (FDR) correction[46] to identify significant group differences. *For a subset of SZ patients with medication records available, we examined the FC correlation with chlorpromazine equivalent dose, controlled for age, sex, and site.*

Test_C. SNP-FC Associations

Two independent cohorts were used to examine associations between SZ-biased SNPs and frontoparietal FC

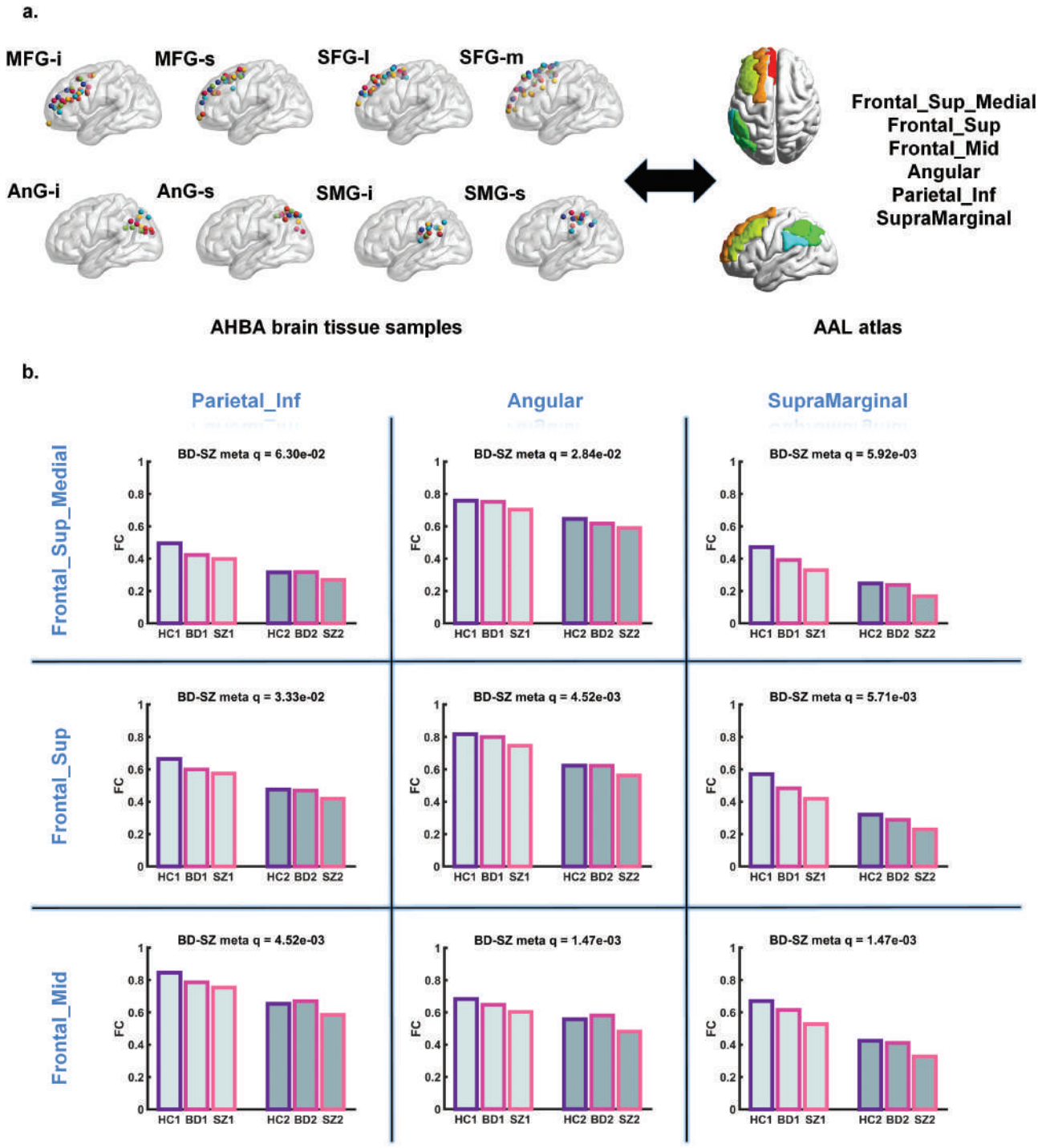

Fig. 2. Group differences in functional connectivity. A. Mapping between AHBA frontoparietal brain tissue samples and AAL frontoparietal ROIs. **B**. Bar plots of averaged frontoparietal functional connectivity (9 pairs of the left hemisphere) within individual diagnosis groups of Cohort 1 and Cohort 2, respectively, where *q* reflects the FDR corrected significance level obtained from the meta-analysis (Stouffer's z-test) of 2 cohorts, thresholded at 0.05 for statistical significance.

(table 3): The COBRE+FBIRN cohort consisting of 109 controls and 80 SZ patients of European Ancestry (EA); and the UMD cohort consisting of 69 controls and 35 SZ patients (EA). The COBRE+FBIRN SNP data went through the standard imputation and quality control as described in our previous work.[47] The UMD SNP data were collected and imputed as described in Bhat *et al.*[48] and followed the same quality control as COBRE+FBIRN[47] (preprocessing details in Supplementary Text ST3). *We then leveraged the PGC SZ GWAS*[3] *to compute the polygenic risk score for SZ (PRS_{SZ}) of 29 SZ-biased SNPs yielded*

Table 2. Participant Demographics. Cohort-Wise Demographics for FC Analysis (Test_B).

Group	Sample Size	Sex (M/F)	Age (Mean ± SD)	Age (Min–Max)
Cohort1				
HC	168	121/47	37.72 ± 11.26	19–63
BD	58	35/23	41.50 ± 13.54	20–69
SZ	134	115/19	37.76 ± 12.62	18–64
Cohort2				
HC	498	298/200	36.37 ± 12.47	18–79
BD	58	27/31	32.17 ± 11.57	18–65
SZ	208	90/118	35.15 ± 13.02	18–63

Table 3. Participant Demographics. Cohort-Wise Demographics for SNP-FC Analysis (Test_C)

Cohort	Sample Size	Sex (M/F)	Age (Mean ± SD)	Age (Min–Max)	Diagnosis (HC/SZ)
COBRE+FBIRN	189	148/41	39.10 ± 12.04	18–65	109/80
UMD	104	35/69	40.86 ± 12.83	18–66	69/35
UKBiobank	34 833	16 444/18 389	63.71 ± 7.52	44–81	34 833/0

by applying linkage disequilibrium pruning ($r < 0.2$) on 740 SZ-biased SNPs. In the following text, PRS_{SZ} refers to the risk score for SZ of 29 SZ-biased SNPs unless otherwise specified. The PRS_{SZ} association with each of the nine frontoparietal FC pairs was assessed with two-tailed partial correlation, controlling for age, sex, site, diagnosis, and the top 20 principal components (PCs) of the genomic SNP data.[3] Meta-analysis was conducted on COBRE+FBIRN and UMD using Stouffer's Z-score method followed by FDR correction. *Given the relatively small sample sizes of COBRE+FBIRN and UMD, the identified SNP-FC associations were further verified in the UKBiobank data consisting of 34 833 healthy EA individuals (see* Supplementary Text ST3 *for more details).*

Test_C. SNP-Cognition Associations

We examined PRS_{SZ} associations with MCCB scores in 60 COBRE EA participants, and with CMINDS scores in 110 FBIRN EA participants, using two-tailed partial correlation, controlling for age, sex, site, diagnosis, and the top 20 SNP PCs. Meta-analysis was conducted on the MCCB and CMINDS results of the composite scores and 6 comparable cognitive domains (ie, speed of processing, attention/vigilance, working memory, verbal learning, visual learning, and reasoning/problem solving) using Stouffer's Z-score method (two-tailed) followed by FDR correction (see Supplementary Text ST4 for more details).

Test_E. Imaging Transcriptomic Associations

Following Romme *et al.*,[19] we examined the spatial correlation between postmortem transcriptomic profiles of SZ-biased genes and macroscale dysconnectivity profiles across frontoparietal regions. For this purpose, we leveraged Schaefer's 200-region atlas[49,50] to obtain a fine parcellation of the targeted frontoparietal regions, where the AHBA frontoparietal tissues (as listed in Test_b) mapped to 32 Schaefer ROIs (see Supplementary Text ST5 for more details). Compared to 6 AAL ROIs, 32 Schaefer ROIs provided improved power for spatial correlation analysis. Then as shown in figure 1E, for each Schaefer ROI, we created a transcriptomic profile as the mean expression across all the SZ-biased genes and across all the mapped AHBA samples.[19] In parallel, using the same rsfMRI data and approach as Test_b, we constructed the FC matrix for each participant based on the Schaefer atlas. We then computed nodal connectivity measures for each ROI. For this purpose, an adjacency matrix was generated from the FC matrix, using a connectivity threshold of $|r| > 0.45$ (more stringent than uncorrected $P < 1 \times 10^{-4}$).[51] We then computed the nodal mean connectivity strength (MCS) for each of the 32 frontoparietal ROIs, defined as the mean connectivity of the edges connected to a node in the adjacency matrix.[52] Macroscale functional dysconnectivity was computed as the ratio of change in mean MCS of individual diagnosis groups, as shown below:

SZ-HC dysconnectivity = (SZ_mean_MCS–Control_mean_MCS)/Control_mean_MCS
BD-HC dysconnectivity = (BD_mean_MCS–Control_mean_MCS]/Control_mean_MCS
SZ-BD dysconnectivity = (SZ_mean_MCS–BD_mean_MCS)/Control_mean_MCS.

Pearson correlations (two-tailed) were computed between the transcriptomic and dysconnectivity profiles across 32 ROIs. We further conducted permutation tests using BrainSmash,[53] which generated surrogate

expression/connectivity maps with comparable spatial autocorrelation patterns to avoid inflation in significance levels. The surrogate expression/connectivity maps were then correlated with the original connectivity/expression maps to generate the null distribution, whose tail probability was computed as the permutation *P*-value. Note that AHBA has more donors and better coverage for the left hemisphere than the right. Hence, we restricted our imaging transcriptomic analysis to the left hemisphere. For consistency, this restriction extended to the whole study. *Finally, we repeated the imaging transcriptomic correlation test across all the ROIs of the left hemisphere, across 32 randomly selected ROIs, and across 27 ROIs assigned to the default mode network (DMN) in Schaefer's atlas, which would be compared with the frontoparietal results to assess spatial specificity.*

Test_F. FC-Cognition Associations

Finally, we investigated associations of frontoparietal FC with MCCB scores in 171 COBRE and BD participants, and with CMINDS scores in 151 FBIRN participants using two-tailed partial correlation controlling for age, gender, site, and diagnosis. Meta-analysis was conducted on the MCCB and CMINDS results of the composite scores and 6 comparable cognitive domains (as listed in Test_d) using Stouffer's *z*-score method (two-tailed) followed by FDR correction.

Other Supporting Tests

We conducted supporting tests to examine the impact of selection thresholds. First, we tested SZ-biased SNPs yielded by GWAS thresholds from 1×10^{-3} to 1×10^{-5} for SZ relevance and SZ-versus-BD differences. Second, we examined SZ-biased genes yielded by various eQTL thresholds up to $P < 5 \times 10^{-3}$. *Third, we investigated how different connectivity thresholds for the adjacency matrix (from 0.3 to 0.45) might affect the results of Test_e. Fourth, we leveraged the PsychENCODE postmortem data*[22] (http://resource.psychencode.org/) *to examine whether the mean expression of SZ-biased genes showed differences between diagnosis groups (more details in* Supplementary Text ST6*).*

Results

Test_b. FC Differences Between Diagnosis Groups

figure 2A *shows the mapping between AHBA frontoparietal samples and AAL frontoparietal ROIs.* Meta-analysis of 2 cohorts indicated that SZ patients showed significant FC reductions compared to controls in all the nine frontoparietal pairs, with *p*-values ranging from 2.80×10^{-6} to 3.71×10^{-17}, which remained significant after FDR correction. We also observed FC reductions in SZ compared to BD, where the FDR corrected meta-analysis *q*-values were significant for eight out of nine FC pairs with the remaining pair being marginal, as highlighted in figure 2B. No significant BD-versus-control difference was noted in any of the nine FC pairs after FDR correction. Complete results are in Supplementary Table_S4. No significant FC association was noted with chlorpromazine equivalent dose.

Test_C. SNP-FC Association

We observed consistent negative associations between PRS_{SZ} and Frontal_Sup_Medial - Angular FC: $r = -0.21$, $P = 4.34 \times 10^{-3}$ in COBRE+FBIRN; and $r = -0.26$, $P = 7.63 \times 10^{-3}$ in UMD, yielding a meta-analysis *P* of 9.49×10^{-5} and *FDR q* of 8.54×10^{-4}. This PRS_{SZ}-FC association was further validated in the UKBiobank data ($r = -0.041$, $P = 3.94 \times 10^{-13}$). Supplementary Table_S5 provides the complete results of 9 FC pairs. No significant association was noted for alternative SNPs.

Test_D. SNP-Cognition Associations

For the 29 SZ-biased SNPs, its PRS_{SZ} showed no significant association with any MCCB cognitive domain nor the composite score, but a significant association with CMINDS_working memory ($r = -0.27$, $P = 4.78 \times 10^{-3}$, $q = 3.35 \times 10^{-2}$). See Supplementary Table_S6 for complete results.

Test_e. Imaging Transcriptomic Associations

figure 3A shows the Schaefer ROIs mapped from the AHBA frontoparietal samples. For the 8 SZ-biased genes with regulatory effects $P < 1 \times 10^{-4}$, their transcriptomic profiles showed a marginal correlation with the SZ-versus-BD dysconnectivity profiles across 32 frontoparietal ROIs in Cohort1 ($r = -0.34$, $P = 5.85 \times 10^{-2}$), and a significant correlation in Cohort2 ($r = -0.51$, $P = 2.77 \times 10^{-3}$), yielding a meta-analysis *P* of 5.53×10^{-4}. In the BrainSmash permutation, the null distribution yielded by 1000 surrogate expression maps resulted in a two-tailed *P*-value of .067 for Cohort 1 and .005 for Cohort 2 (meta-analysis $P = 1.00 \times 10^{-3}$). In parallel, with surrogate connectivity maps, we obtained a *P*-value of .041 and .001 for Cohort 1 and 2, respectively (meta-analysis $P = 1.62 \times 10^{-4}$). figure 3B presents the scatter plots of gene expression versus dysconnectivity. In contrast, the correlation with SZ-versus-HC dysconnectivity was less consistent (meta-analysis $P = 1.63 \times 10^{-2}$), with no association noted for BD-versus-HC dysconnectivity (meta-analysis $P = .71$). *Furthermore, no significant imaging transcriptomic association was observed across the left-hemisphere ROIs or across the 27 DMN ROIs.* For 32 randomly selected left hemisphere ROIs, the chance of observing $r < -0.34$ in Cohort1 was 0.001, and observing $r < -0.51$ in Cohort2 was < 0.001 given 1000 tests. The chance decreased to < 0.001 for both cohorts

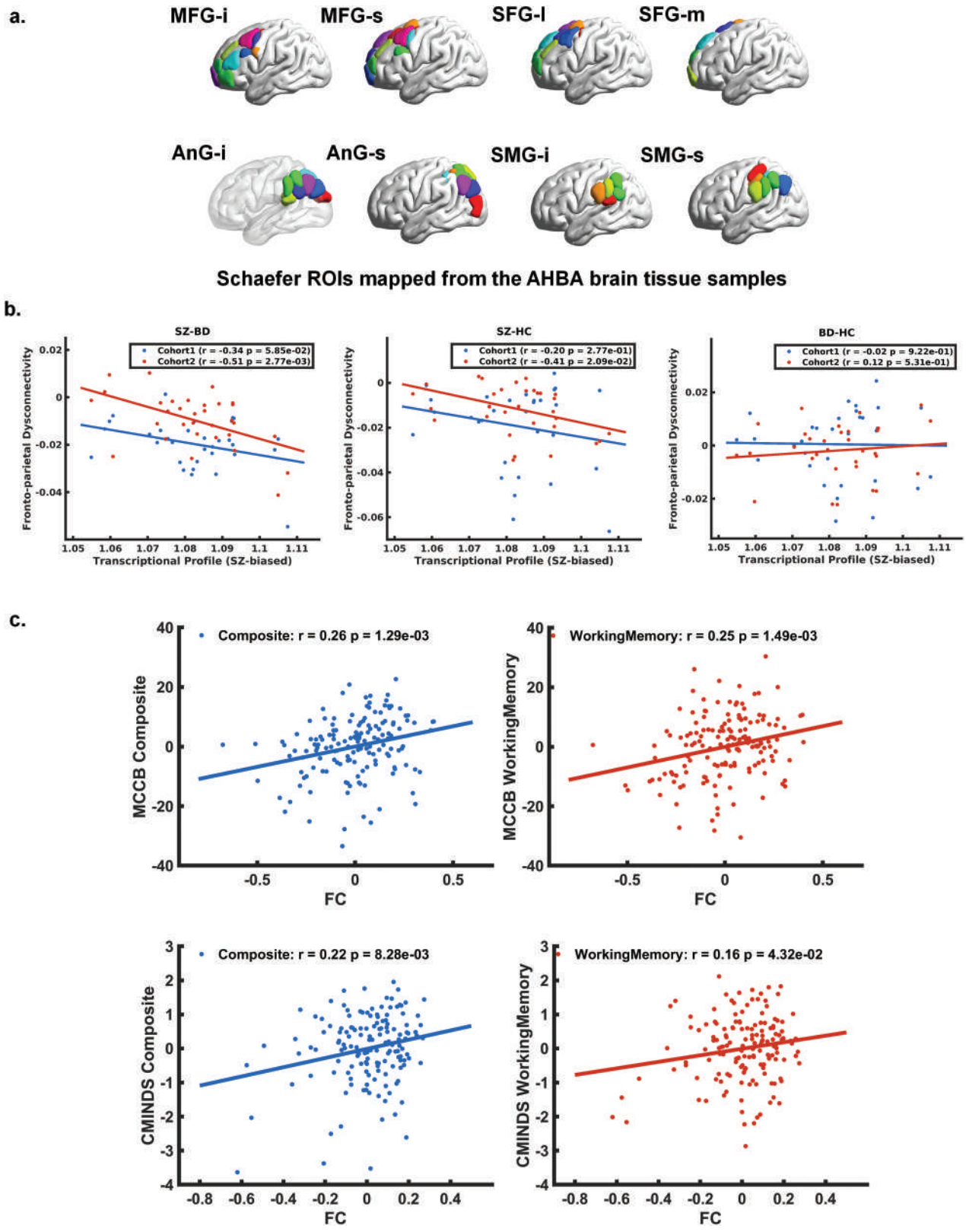

Fig. 3. Frontoparietal imaging transcriptomic associations and associations between frontoparietal connectivity and neurocognitive performance. **A**. Schaefer ROIs mapped from the AHBA frontoparietal tissue samples. **B.** Frontoparietal imaging transcriptomic associations between SZ-biased gene expression and functional dysconnectivity of SZ-BD, SZ-HC, and BD-HC, respectively. Each dot represents one of the 32 ROIs in the scatter plot. **C**. Frontoparietal functional connectivity associations with neurocognitive performance.

when the random selection was restricted to ROIs outside frontoparietal regions. There was no consistently significant association for SZ-top, SZ-BD-common, or BD-top genes. Complete results are in Supplementary Table_S7.

Test_f. FC-Cognition Associations

In the meta-analysis, the composite score of all cognitive domains showed the most significant associations with Frontal_Sup_Medial - Angular FC and Frontal_Sup - Angular FC (FDR $q = 1.08 \times 10^{-3}$ and 5.09×10^{-4}, respectively). Note that these two FC pairs also presented the most significant PRS_{SZ} associations (Test_c). Coincidentally, among individual cognitive domains, the most significant FC association was observed from working memory, pointing to Frontal_Sup_Medial - Angular FC and Frontal_Sup - Angular FC again (FDR $q = 4.96 \times 10^{-3}$ and 8.11×10^{-3}, respectively). figure 3C presents the scatter plots between Frontal_Sup_Medial - Angular FC and MCCB/CMINDS composite and working memory scores. Significant FC associations were also noted for other cognitive domains, including processing speed. Results of individual batteries are in Supplementary Table_S8.

Other Supporting Tests

For SZ-biased SNP sets yielded by various GWAS thresholds, their risk scores showed consistent negative associations with Frontal_Sup_Medial - Angular FC in both cohorts, as summarized in Supplementary Table_S9. For eQTL thresholds ranging from $P < 5 \times 10^{-3}$ to $P < 1 \times 10^{-4}$, again we observed consistent negative imaging transcriptomic correlations, while overall stronger correlations were observed with more stringent eQTL thresholds (see Supplementary Table_S10). Consistent imaging transcriptomic correlations were also observed for the tested adjacency matrix thresholds (from $|r| > 0.30$ to $|r| > 0.45$), where SZ-biased genes showed stronger correlations with SZ-versus-BD differences in nodal MCS if only more strongly connected edges were included. Supplementary Table_S11 summarizes the complete results. *In the PsychENCODE data, we found that the mean expression of SZ-biased genes were significantly higher in SZ than controls or BD ($P = 3.46 \times 10^{-2}$ and 3.91×10^{-3}, respectively, see* Supplementary Table_S12*).*

Discussion

More severe frontoparietal FC reductions were observed in SZ than BD compared to controls (Test_b), showing potential as biomarkers for differentiating SZ from BD. Furthermore, the FC measures are also related to cognitive performances evaluated by MCCB and CMINDS composite scores (Test_f), which reflect general cognitive ability with impairment reliably observed in SZ patients.[54] We also observed frontoparietal FC associations with working memory. The frontoparietal regions have been found to integrate bottom-up representations of perceptual features and top-down task-selective signals, playing an important role in the control of attention.[55] The frontoparietal regions also constitute a primary component in working memory, consistently activated in tasks of diverse modalities and paradigms.[25] Echoing the notion that attention and working memory deficits are core to SZ and BD[56] with more severity in SZ[57] and more phase-dependency in BD,[58,59] frontoparietal dysconnectivity has been broadly identified in SZ patients using various brain measures, including functional dysconnection[60] and altered white matter integrity in superior longitudinal fasciculus.[61] Meanwhile, for BD, the existing findings of frontoparietal dysconnectivity are less conclusive and more phase-dependent.[58,62] Our results align with the literature while highlighting working memory as the most associated cognitive domain. Collectively, these results suggest that differential frontoparietal FC contributes to differential cognitive deficits between SZ and BD.

PRS_{SZ} was directly associated with frontoparietal FC in both cohorts (Test_c) and with CMINDS_working memory (Test_d), which provides evidence for genetic effects in the pathway. The most significant PRS_{SZ}-FC association was presented by the Frontal_Sup_Medial - Angular pair, indicating a higher load of SZ-biased risk relates to lower FC. A PRS_{SZ}-FC association was also noted for the Frontal_Sup - Angular pair. Notably, these 2 FC pairs were also highlighted as showing stronger associations with cognitive composite scores and working memory scores. PRS_{SZ} was also associated with CMINDS_working memory, but not MCCB_working memory. Given the small sample size of the MCCB test (60 EA participants), this is not surprising. Future replication tests with large cohorts are necessary for verifying this promising result. Taken together, our results uphold that SZ-biased risk contributes to disruptions in frontoparietal FC that likely underlie cognitive deficits.

While cross-subject imaging transcriptomic studies are not achievable at present, some inferences may still be drawn from the spatial correlation between ex vivo transcriptomic and in vivo FC profiles (Test_e), which could not be attributed to spatial autocorrelation, as indicated by the permutation test. First, more significant imaging transcriptomic correlations tended to be observed with strengthened regulatory effects (eQTL threshold decreased from 5×10^{-3} to 1×10^{-4}), suggesting that genes are more regulated by SZ-biased SNPs are better correlated with SZ-versus-BD dysconnectivity in frontoparietal regions, upholding genetic influence. Second, the negative correlations reasonably indicate that, in general, the brain regions carrying higher expressions of SZ-biased genes tend to show more SZ-versus-BD reductions in frontoparietal FC. Third, no significant correlation was noted across the whole left hemisphere or the DMN regions, lending support for a certain level of spatial

specificity to the targeted frontoparietal regions for the impact of SZ-biased genes, which distinguishes our findings from those of Romme *et al.*[19] Fourth, alternative genes did not show similarly significant correlations, indicating that the observations were exclusively between SZ-biased genes and SZ-biased dysconnectivity. Collectively, these results encourage us to connect biological specificity (to SZ) with spatial specificity (to frontoparietal) and support that SZ-biased genetic risk affects frontoparietal FC through transcriptomics.

We argue that caution should be exercised in examining a specific SZ-biased SNP or gene as they warrant refinement and confirmation from more solid lab experiments. However, the inferences drawn from the lumped set are expected to be valid, particularly given the robust associations under various selection thresholds. The SZ-biased SNP set covered some major histocompatibility complex (MHC) SNPs. At the transcriptomic level, MHC genes (eg, ZKSCAN3 and ZSCAN23) were still noted, reflecting regulatory effects in the frontal cortex. Our previous work found the MHC SNPs to present cross-cohort, cross-tissue convergent associations with gray matter density in the inferior parietal regions.[47] In the present study, the functional impact was further delineated to emphasize risk specificity to SZ and frontoparietal regions. Other highlighted SZ-biased genes included the DRG2 gene which showed opposite directions of effects in SZ and educational attainment[63]; the MDK gene (also known as NEGF2, neurite growth-promoting factor 2) which has been found up-regulated under disease conditions, particularly those diseases affecting the nervous system[64]; and the TOM1L2 gene whose reduced expression might be related to increased synaptic protein levels and resilience to psychosis in Alzheimer's disease.[65] Overall, our findings mirror the literature that brain regions preferentially expressing these SZ-biased genes are more vulnerable compared to other areas in SZ conditions.

Our findings should be interpreted in light of the following limitations. *First, we could not examine regulatory effects in the parietal cortex due to unavailability of eQTL databases*, and the eQTL threshold was limited by the current sample size. This could be one reason why the SZ-biased and SZ-top gene sets were not exclusive of each other (SNPs were exclusive of each other). It remains unclear whether improvement in the derivation of SZ-biased genes would lead to stronger SZ specificity. Second, no cell type information is available for further interpretation in the AHBA data. According to PanglaoDB,[66] none of our SZ-biased genes happened to be a canonical marker of dopaminergic, glutamatergic, GABAergic neurons or pyramidal cells.[67] Dissection of cell type specific effects will be explored in our future work. Third, given the current data, we could not investigate differences between SZ and subgroups of BD, eg, with and without psychotic symptoms.[68] Fourth, despite no significant FC associations with chlorpromazine equivalent dose, we could not exclusively rule out the medication influence. *Fifth, due to data unavailability, how environmental factors might stratify the identified PRS_{SZ}-FC associations remains unknown*. All these await further investigation.

The current study represents a multiscale framework for elucidating functional pathways from genetics to phenotypes. First, partitioning the genetic risk based on disease-specificity may improve functional homogeneity and facilitate capturing genetic effects on focal brain abnormalities. Second, linking postmortem gene expressions with neuroimaging features based on spatial variation posits a valuable strategy for drawing inferences regarding transcriptomic correlates of brain phenotypes. The current study demonstrates an application of these concepts to distinguishing SZ from BD. Our results provide evidence for a reasonable genetic risk—frontoparietal expression—frontoparietal connectivity—cognition pathway, and more precisely provide plausible mechanisms to explain SZ-versus-BD differences. Such a framework can be applied to other clinical syndromes, such as the overlap between SZ and autism spectrum disorder, and the distinction between BD and major depressive disorder, facilitating more precise patient stratification and treatment.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Author Contributions

J.C., J.L., and V.D.C. designed the research; J.C. conducted analyses and wrote the paper. The remaining authors contributed to the recruitment, data collection, or processing of the participating cohorts of the study. All authors critically reviewed the content and approved the final version for publication.

Data Availability

The COBRE data and FBIRN imaging data are available through COINS (https://coins.trendscenter.org). Other imaging and genetic data were shared privately by individual PIs.

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