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Polygenic risk score for five major psychiatric disorders associated with volume of distinct brain regions in the general population

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ABSTRACT

Risk genes and abnormal brain structural indices of psychiatric disorders have been extensively studied. However, whether genetic risk influences brain structure in the general population has been rarely studied. The current study enrolled 483 young Chinese adults, calculated their polygenic risk scores (PRS) for psychiatric disorders based on Psychiatric Genomics Consortium GWAS results, and examined the association between PRSs and brain volume. We found that PRSs were associated with the volume of many brain regions, with differences between PRS for different disorder, calculated at different threshold, and calculated using European or East Asian ancestry. Of them, the PRS for Major Depressive Disorder based on European ancestry was positively associated with right temporal gyrus; the PRS for schizophrenia based on East Asian ancestry was negatively associated with right precentral and postcentral gyrus; the PRS for schizophrenia based on European ancestry was positively associated with right superior temporal gyrus. All these brain regions are critical for corresponding disorders. However, no significant associations were found between PRS for Autism Spectrum Disorder / Bipolar Disorder and brain volume; and the association between PRS for Attention Deficit Hyperactivity Disorder at different thresholds and brain volume was inconsistent. These findings suggest distinct brain mechanisms underlying different psychiatric disorders.

1. Introduction

According to World Health Organization (WHO), psychiatric disorders are characterized by "a combination of abnormal thoughts, perceptions, emotions, behaviors and relationships with others" (WHO, 2017), which have long been recognized as the leading cause of global disability in children and adults (Erskine et al., 2015). Without intervention, people with psychiatric disorders are most likely to have severe emotional, behavioral and physical health problems throughout lifespan. Considering the urgency of preventing further increases in psychiatric disorders, it is crucial to understand the etiologies, including genetic architecture and brain structure, underlying psychiatric disorders.

The genetic and neural basis of psychiatric disorders have been extensively studied. Regarding the genetic influences, the Psychiatric Genomics Consortium have assembled published genome-wide association studies (GWAS) results for a large-scale meta-analysis on 12 disorders. Five major psychiatric disorders, including Bipolar Disorder, Major Depressive Disorder, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Schizophrenia, have been frequently examined in the literature for shared and distinct genetic effects (Consortium, 2013; Leppert et al., 2020; Schlag et al., 2022; Wang et al., 2017). Meta-analysis based on large European ancestry population of Bipolar Disorder(Mullins et al., 2021), Major Depressive Disorder (Howard et al., 2019), Autism Spectrum Disorder (Grove et al., 2019) and Attention Deficit Hyperactivity Disorder (Demontis et al., 2019) had identified 64, 101, 5, and 12 risk loci, respectively. A meta-analysis combining European and East Asian populations on Schizophrenia has reported 255 risk loci (Trubetskoy et al., 2022). A meta-analysis of a large East Asian sample on Major Depressive Disorder reporting 1 novel

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risk loci is also available on the PGC website (Giannakopoulou et al., 2021).

Similarly, psychiatric disorders have been linked to brain dysfunction or abnormal structures (Alfredo, 2018). The ENIGMA Consortium (http://enigma.ini.usc.edu/) has conducted large-scale meta-analysis to explore brain indices associated with these disorders, and found abnormal cortical and subcortical thickness/volume associated with Bipolar Disorder (Hibar et al., 2018), Schizophrenia (Van Erp et al., 2018), Major Depressive Disorder (Schmaal et al., 2016), Autism Spectrum Disorder (Postema et al., 2019), and Attention Deficit Hyperactivity Disorder (Hoogman et al., 2019). In addition, previous reviews on the neural basis of psychiatry have also confirmed structural changes in the brain associated with these disorders (Qiu & Li, 2018; Rubia et al., 2014).

Despite of these findings on specific risk genes and abnormal brain structure for each psychiatric disorder, there is also evidence of shared pleiotropic loci and high levels of shared heritability (Lee et al., 2019), as well as common brain functional activation patterns (Sprooten et al., 2017) and brain structural abnormalities (Opel et al., 2020) among the disorders. These results are consistent with the fact of high comorbidity rates among different psychiatric disorders, and raise the questions about the specificity of psychiatric disorders and underlying etiologies among different psychiatric disorders (Prata et al., 2019).

Exploring and comparing effect of risk gene(s) on brain among disorders helps understand the common and specific etiologies underlying different psychiatric disorders. Previous work suggests that the brain structure serve as an important endophenotype connecting genes and psychiatric disorders (Meyer-Lindenberg & Weinberger, 2006). Some studies had focused on general subjects at risk (i.e., people with risk genotypes, or relatives of patients), which offers the opportunity to study risk and resilience underlying psychiatric disorders, and help inform early diagnosis and intervention (Cattarinussi et al., 2021). This approach eliminates confounding factors such as comorbidity, medications and illness duration and has been validated by previous work. For example, PRS for Alzheimer's Disorder have been associated with the volume of hippocampus in children (Axelrud et al., 2018) and young adults (Foley et al., 2017), such that children and young adults with higher PRS showed smaller volume of hippocampus; PRS for schizophrenia has been associated with hippocampus activation during memory task in healthy adults (Chen et al., 2018). These studies demonstrate the feasibility of examining the influence of PRS for psychiatric disorders on the brain using general subjects. PRS for multiple disorders have also been associated with brain functional connectivity (Wang et al., 2017), white matter microstructure (Jansen et al., 2019), volume of whole brain or subcortical regions (Alemany et al., 2019), or pattern of whole brain grey matter (Ranlund et al., 2018), although results are not consistent across studies. However most of these studies focuses on participants of European ancestry.

Building upon the latest GWAS data of five psychiatric disorders, including Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Bipolar Disorder, Major Depressive Disorder and schizophrenia, in the Psychiatric Genomics Consortium, the current study aims to examine the associations between PRS for five psychiatric disorders and brain structure volume in healthy Chinese subjects (N = 483). Specifically, we investigate: (a) whether PRS for five distinct psychiatric disorders are associated with brain structure volume in general subjects, (b) whether PRS for five distinct psychiatric disorders are associated with the volume of shared or distinct brain regions among five psychiatric disorders, and (c) whether PRS calculated based on different ancestry for the same disorder are associated with volume of the same or different brain regions.

2. Method

2.1. Subjects

This study enrolled 483 undergraduate and graduate students (237 men, mean age=21.41 +2.24, range=16.58–29.17). All subjects were Han Chinese self-reported not having a neurological or psychiatric history, and capable of attending MRI scan. This study was approved by the Institutional Review Board (IRB) of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, and was performed in accordance with relevant guidelines and regulations. All subjects signed written informed consent and were paid for participation.

2.2. Structural MRI acquisition and preprocessing

MR images were acquired using a Siemens Trio 3 T scanner in the Brain Imaging Center of Beijing Normal University. Foam pads were used to minimize head motion. Structural MRI images were acquired using a T1-weighted, three-dimensional, gradient-echo pulse sequence. Parameters for this sequence were as follows: repetition time/echo time/flip angle = 2530 ms/3.39 ms/7°, field of view = 256 × 256 mm, matrix = 256 × 256, slice thickness = 1.33 mm. One hundred and forty-four sagittal slices were acquired to provide a high-resolution structural image of the whole brain.

MRI data were analyzed with the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library voxel-based morphometry (FSL-VBM), a VBM style analysis toolbox (Good et al., 2001) implemented in FSL. Brains from the structural images were extracted, tissue-type segmented, and then aligned to the gray-matter template in the MNI152 standard space. The spatially normalized images were then averaged to create a study-specific template, to which the native gray matter images were registered again using both linear and nonlinear algorithms. The registered partial volume images were then modulated by dividing them with the Jacobian of the warp field to correct for local expansion or contraction. The modulated segmented images, which represented the gray matter volume, were then smoothed with an isotropic Gaussian kernel with 3 mm standard deviation. Visual inspection was taken after each step and all had good quality.

2.3. Genotyping

The genotype of this dataset was reported with details previously (Chen et al., 2020). Briefly, DNA were extracted from blood using Axypre Blood Genomic DNA Kit (Corning Life Sciences cat. no.11313KC3) and genotyped using Infinium Human Omni-Zhonghua-8 chips or Infinium Human Omni2.5–8 exome chips or Infinium OminiExpress-12 chips (Illumina, San Diego, CA, USA), all according to the manufacturer's specifications, all with call rate larger than 98%. Autosome genotype data were first cleaned with PLINK2 then imputed using Michigan Imputation Server (https://imputationserer.sph.umich.edu/index.html) following their protocol using 1000 G Phase 3 EAS population as reference. Imputed data were cleaned again to keep only SNPs with imputation quality $r^2 > 0.8$, MAF> 0.05, HWE> 1E-6, retaining 4856,474 SNPs. No duplicated or related subjects were identified (maximum PI_HAT=0.0537, calculated with PLINK2). No clear population stratification problem or outlier subjects were found by principal component analysis (Chen et al., 2020), since this study only enrolled Han Chinese subjects.

2.4. Statistical Analysis

GWAS summary statistics of the five psychiatric disorders based on European ancestry (Demontis et al., 2019; Grove et al., 2019; Howard et al., 2019; Mullins et al., 2021; Trubetskoy et al., 2022), Major Depressive Disorder (Giannakopoulou et al., 2021) and Schizophrenia

(Trubetskoy et al., 2022) on East Asian ancestry were downloaded from Psychiatric Genomics Consortium website on November 21, 2022 (https://pgc.unc.edu/for-researchers/download-results/). Details can be found in supplementary table S1. PRS for each disorder was calculated with PRSice-2 software (Choi & O'Reilly, 2019; Euesden et al., 2015), following this protocol (https://choishingwan.github.io/PRS-Tutorial/) (Choi et al., 2020). Briefly, these GWAS summary statistics were used as base file, standardized by removing SNPs with imputation information < 0.8 or MAF< 0.01 when the information available, deleting duplicated SNPs or Ambiguous SNPs. Imputed genotype data of the current sample was the target data, quality controlled as described above, used to estimate LD pattern and calculate PRS score at threshold of 5E-2,5E-3,5E-4,5E-5,5E-6,5E-7,5E-8. The correlation among PRSs were calculated using Matlab (version R2018b).

Association of each PRS with brain structure was calculated using FSL randomise (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide), with 4D brain image data as input, PRS as predictor, and age, sex and 10 principal components of genetic ancestry as covariates. Resulting maps were corrected with Gaussian Random Field (GRF) correction, with voxel-level threshold of $p < 0.001$ and cluster-level threshold of $p < 0.05$ (Eklund et al., 2016). Volume of the significant clusters were extracted, and regressed on corresponding PRS while controlling those covariates to estimate effect size of PRS.

3. Result

3.1. Correlations among PRS

Correlations of the PRSs on our sample were shown in Fig. 1 (lower triangle), p values significant after Bonferoni correction ($p < 0.05/1176$) were shown in upper triangle. PRSs for the same disease calculated at different thresholds were highly correlated; PRSs for different disease were less correlated. PRSs for each disease at 7 threshold were then averaged, and the correlations of mean PRSs only significant between Schizophrenia on East Asian and European ancestry ($r(483) = 0.202$, $p < .001$), and between Schizophrenia and Bipolar Disorder on European ancestry ($r(483) = 0.268$, $p < .001$). One thing needs to point out is, PRS for Schizophrenia based on East Asian and European ancestry significantly correlated, but that for Major Depressive Disorder did not, suggesting that ancestry influence differs among diseases. Controlling age, gender and 10 genomic principal components did not change the pattern (supplementary Fig. S1).

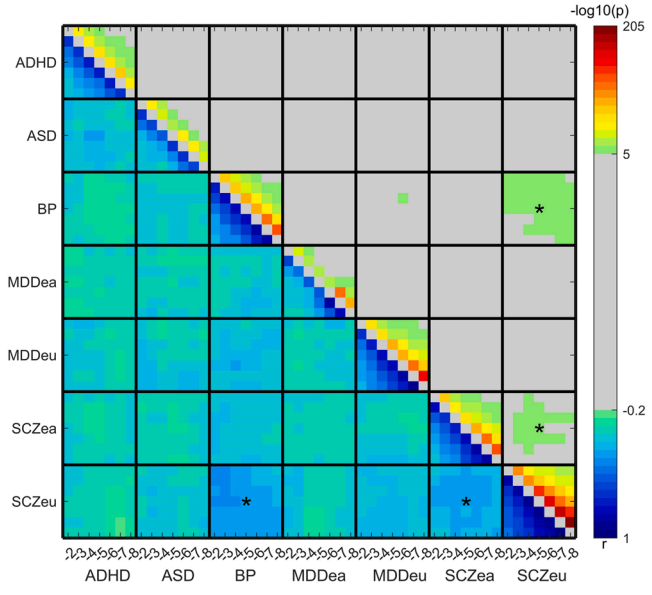

Fig. 1. Correlation between PRSs for each disease at each threshold (in the order of E-2, E-3, E-4, E-5, E-6, E-7, E-8 within each block for a disorder) were shown in the lower triangle, corresponding p value were presented at the upper triangle, with only p values significant after Bonferoni correction were shown. Correlation of mean PRS among disorders only significant between SCZeu and SCZea/BP (marked with asterisk). Note: ADHD=Attention Deficit Hyperactivity Disorder, ASD=Autism Spectrum Disorder, BP=Bipolar Disorder, MDDea=Major Depressive Disorder on East Asian, MDDeu=Major Depressive Disorder on European ancestry, SCZea=Schizophrenia on East Asian, SCZeu=Schizophrenia on European ancestry.

3.2. Association between PRSs and brain structure

Next, we examined the associations between the PRSs for the five psychiatric disorders and the brain volume controlling age, gender and 10 principal components of genetic ancestry. After the multiple comparison corrections, the results indicated that PRSs for the five psychiatric disorders were associated with the volume of distinct brain regions, and the results also changed among PRSs for the same disorder calculated at different threshold (Table 1). Specifically, the PRS for Attention Deficit Hyperactivity Disorder were positively associated with the volume of left inferior temporal gyrus and negatively correlated with left caudate, left fusiform and cerebellum, such that people with higher PRS showed larger brain volumes in left inferior temporal gyrus but smaller left caudate, left fusiform and cerebellum. Effect size of PRS were presented in Table 1, with the standardized regression coefficient (Beta) represents change of brain volume per unit increase in PRS, ΔR^2 and p represents the unique contribution of PRS on brain volume variance after controlling those covariant. The PRS for Major Depressive Disorder based on East Asian were positively correlated with left middle cingulum and negatively correlated with right lingual, such that people with higher PRS showed larger volume of left middle cingulum but smaller right lingual. The PRS for Major Depressive Disorder base on European ancestry were positively correlated with brain regions of right inferior and middle temporal gyrus, such that people with higher PRS showed larger volume of this region. The PRS for Schizophrenia base on East Asian were negatively correlated with right precentral and postcentral gyrus and positively correlated with bilateral cerebellum, such that people with higher PRS showed smaller volume of right precentral and postcentral gyrus and larger volume of cerebellum. The PRS for Schizophrenia base on European ancestry were positively correlated with right superior temporal gyrus, right inferior temporal gyrus, and left middle cingulum, such that people with higher PRS showed larger volume of these brain regions. The PRS for Autism Spectrum Disorder and Bipolar Disorder did not show any significant correlation with brain volume. As shown in Table 1, effects of all PRS on brain volume were 3–6% and very significant.

PRSs calculated at different threshold associated with diverse brain regions (Table 1). There might be two possible reasons. First, these results may be false positive. Second, PRS calculated at different threshold captured distinct genetic effect thus associated with different brain regions. Still, the association between PRS for Major Depressive Disorder base on European ancestry and right inferior and middle temporal gyrus, between PRS for Schizophrenia base on East Asian and right precentral and postcentral gyrus, between PRS for Schizophrenia base on European ancestry and right Superior temporal gyrus are consistent across PRSs calculated at different thresholds (Table 1 and Fig. 2). These results were robust thus deserved more investigation in future studies.

4. Discussion

The aim of this study was to investigate and compare the brain structure volume associated with PRSs for five distinct psychiatric disorders in the general population. We found that the PRSs for each psychiatric disorder were associated with the volume of distinct brain regions: the PRS for Major Depressive Disorder based on European ancestry was positively associated with right temporal gyrus; the PRS for

Table 1
Details of brain regions associated with PRS for each psychiatric disorder and the effect size of corresponding PRS.

Psychiatric disorder	Threshold for PRS	Regional correspondence of the maximum	Maximum t value within cluster	MNI Coordinates at maximum	Number of voxels	Beta	ΔR^2	p
ADHD	5E-2	Left inferior temporal gyrus	4.10	-64 –26 –18	264	0.18	0.03	< .001
	5E-3	Left caudate	4.03	-16 14 6	579	-0.18	0.03	< .001
		Left fusiform, cerebellum	4.13	-28 –40 –20	428	-0.21	0.04	< .001
MDDea	5 E-5	Left middle Cingulum	4.41	-8 –6 36	217	0.18	0.03	< .001
	5 E-6	Right Lingual	4.75	6 –36 2	208	-0.21	0.04	< .001
MDDeu	5 E-4	***Right inferior and middle temporal gyrus***	5.54	52 –46 –16	687	0.26	0.06	< .001
	5 E-5	**Right inferior and middle temporal gyrus**	4.43	62 –58 –6	464	0.21	0.04	< .001
	5 E-6	**Right inferior and middle temporal gyrus**	4.45	60 –50 –4	382	0.20	0.04	< .001
SCZea	5 E-3	**Right Precentral Gyrus**	4.19	20 –24 62	218	-0.20	0.04	< .001
	5 E-4	Right Cerebellum	4.06	36 –64 –22	846	0.18	0.03	< .001
		Left Cerebellum	4.04	-36 –60 –50	467	0.23	0.05	< .001
	5 E-5	**Right Precentral/ Postcentral Gyrus**	4.46	32 –28 72	223	-0.21	0.04	< .001
	5 E-6	***Right Precentral/ Postcentral Gyrus***	4.57	34 –24 64	291	-0.21	0.04	< .001
	5 E-8	Right Precentral/ Postcentral Gyrus	4.29	36 –14 38	220	0.18	0.03	< .001
SCZeu	5 E-2	***Right Superior Temporal Gyrus***	4.39	70 –20 –2	454	0.21	0.04	< .001
	5 E-3	**Right Superior Temporal Gyrus**	4.40	70 –20 –2	245	0.20	0.04	< .001
	5 E-6	Right inferior temporal gyrus	4.83	62 –62 –8	230	0.21	0.04	< .001
	5 E-8	Left middle Cingulum	3.96	-8 14 40	195	0.21	0.04	< .001

Note: Brain regions in bold are those consistent across PRS calcualted at mutiple thresholds. Brain regions in italic were those shown in Fig. 2. ADHD=Attention Deficit Hyperactivity Disorder, MDDea=Major Depressive Disorder on East Asian, MDDeu=Major Depressive Disorder on European ancestry, SCZea=Schizophrenia on East Asian, SCZeu=Schizophrenia on European ancestry.

schizophrenia based on East Asian ancestry was negatively associated with right pre- and post-central gyrus; the PRS for schizophrenia based on European ancestry was positively associated with right superior temporal gyrus. Some other brain regions were also identified based on PRSs calculated at different thresholds. However, no significant associations were found between the PRS for Autism Spectrum Disorder / Bipolar Disorder and brain volume. The identified brain regions play a critical role in each corresponding disorder as discussed below. Considering the high genetic correlation of disorders in previous research, these results suggest that although psychiatric disorders may share a common genetic basis, the brain regions associated with each psychiatric disorder can still differ.

The current study found that the PRS for Major Depressive Disorder was positively associated with the volume of right inferior and middle temporal gyrus. This finding is supported by previous research, such as a meta-analysis by the ENIGMA Major Depressive Disorder Working Group, which found the thinner cortical gray matter in many brain regions including the inferior and middle temporal gyrus in adult patients with Major Depressive Disorder compare to controls (Schmaal et al., 2017). A meta-analysis of functional brain activity during emotion processing also found hyperactivation in middle temporal gyrus in Major Depressive Disorder patients compare to controls (Li & Wang, 2021). Moreover, we found that the PRS for schizophrenia based on East Asian ancestry was negatively associated with the right Precentral/ Postcentral Gyrus, while that based on European ancestry was positively associated with Right Superior Temporal Gyrus. A recent meta-analysis of resting state regional homogeneity in schizophrenia revealed reduced homogeneity in precentral and postcentral regions in schizophrenia patients (Cai et al., 2022). Another recent meta-analysis by ENIGMA found that the severity of positive symptoms of schizophrenia was negatively associated with bilateral superior temporal gyrus thickness (Walton et al., 2017). All these previous findings are consistent with the findings of the current study.

One thing to note, previous research has typically found decreased brain volume in patients compare to controls. However, the current study found that some PRSs for Attention Deficit Hyperactivity Disorder, Major Depressive Disorder, and Schizophrenia showed positive correlations with brain volume, meaning that higher genetic risks were associated with increased volume. This inconsistency was also found in previous work. There are two possible explanations. One is inflammation and the release of inflammatory cytokines, which were often found in mental disorders (Felger, 2018), can stimulate astrocytes to facilitate neurogenesis, thus increasing cortex volume (Jones et al., 2019). The other is illness resilience (Perry et al., 2019), such that individuals with higher genetic risk have increased the volume of critical brain regions to maintain good health.

It is important to emphasize that our samples were healthy Chinese individuals. The current study provides additional support for previous work that found genetic influences on the brain in the general population and contributed to the understanding of the pathology of disorders (e.g. Cattarinussi et al., 2019; Raum et al., 2015). However, previous work has mainly focused on healthy European individuals. Ancestral difference is a fundamental concern in genetic research that should be carefully dealt with from the data processing to results explanation. The current study found that the PRS for Major Depressive Disorder calculated based on East Asian and European sample GWAS were not significantly correlated, but that for Schizophrenia were. However, the brain regions were not consistently identified across PRSs based on different ancestry for both diseases. Thus, the picture of ancestral differences is complex and varies depending on the phenotype being studied.

The following limitations should be considered when interpreting the results of this study. First, the findings regarding the morphological changes in brain regions of individuals with high genetic risk require further examination through replications and longitudinal studies. Second, we did not find brain regions significantly associated with PRS for Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, suggesting that the effect of PRS on brain may not be strong in the general population, or that the sample size was not large enough to detect all PRS effect on brain. Future studies with larger sample size may reveal more associated brain regions with stronger effects. Third, the identified brain regions differed for PRS calculated at different thresholds. This is because PRS calculated at looser threshold may capture more genetic effects. Usually, PRS was calculated at

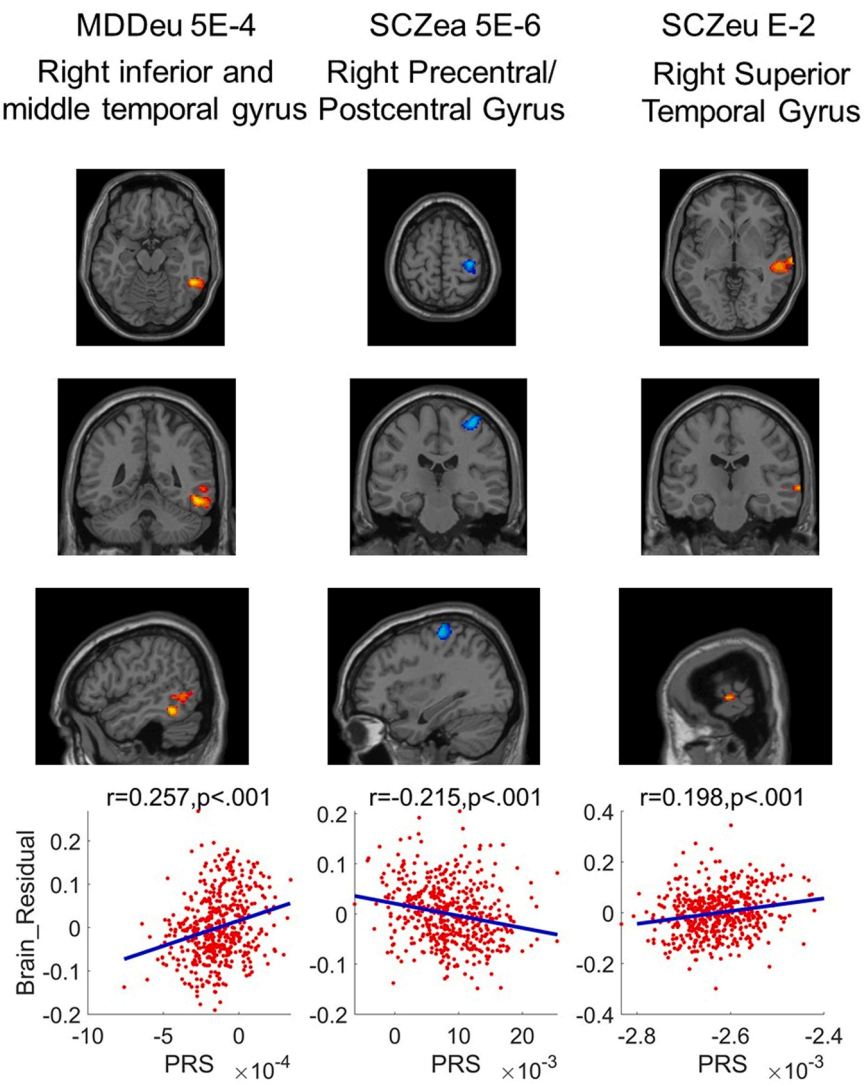

Fig. 2. Brain regions significantly correlated with PRS for Major Depressive Disorder on European ancestry at $p < 5E\text{-}4$ (left column), for Schizophrenia on East Asian at $p < 5E\text{-}6$ (middle column), and for Schizophrenia on European ancestry at $p < 5E\text{-}2$ (right column) after controlling age, gender and 10 principal components of genetic ancestry. Upper: T map of significant clusters after GRF correction; lower, scatter of brain volume (residual after controlling covariates) again PRS.

multiple thresholds and only the one with best prediction was reported. We reported results of all PRS calculated at 7 thresholds, some of the results could be false positive and should be further examined in other studies. Fourth, the study was limited by a self-reported healthy population of young adults, more stringent screening methods and a wider age range should be used in future studies.

CRediT authorship contribution statement

Ziyi Wang: Formal analysis , Writing – original draft. **Chang Liu:** Writing – review & editing. **Qi Dong:** Conceptualization, Funding acquisition. **Gui Xue:** Conceptualization. **Chunhui Chen:** Conceptualization, Formal analysis, Funding acquisition, Writing – review & editing.

Conflict of interest

The authors declare no conflict of interest.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2023.108530.

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