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Polygenic risk for five psychiatric disorders and cross-disorder and disorder-specific neural connectivity in two independent populations

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ABSTRACT

Major psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), autism (AUT), bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SZ), are highly heritable and polygenic. Evidence suggests that these five disorders have both shared and distinct genetic risks and neural connectivity abnormalities. To measure aggregate genetic risks, the polygenic risk score (PGRS) was computed. Two independent general populations (N = 360 and N = 323) were separately examined to investigate whether the cross-disorder PGRS and PGRS for a specific disorder were associated with individual variability in functional connectivity. Consistent altered functional connectivity was found with the bilateral insula: for the left supplementary motor area and the left superior temporal gyrus with the cross-disorder PGRS, for the left insula and right middle and superior temporal lobe associated with the PGRS for autism, for the bilateral midbrain, posterior cingulate, cuneus, and precuneus associated with the PGRS for BD, and for the left angular gyrus and the left dorsolateral prefrontal cortex associated with the PGRS for schizophrenia. No significant functional connectivity was found associated with the PGRS for ADHD and MDD. Our findings indicated that genetic effects on the cross-disorder and disorder-specific neural connectivity of common genetic risk loci are detectable in the general population. Our findings also indicated that polygenic risk contributes to the main neurobiological phenotypes of psychiatric disorders and that identifying cross-disorder and specific functional connectivity related to polygenic risks may elucidate the neural pathways for these disorders.

1. Introduction

Major psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), autism (AUT), bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SZ), are highly heritable and polygenic. Previous studies suggested that these disorders share genetic risks (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a, 2013b; Green et al., 2010; International Schizophrenia Consortium, 2009). Specifically, both shared and specific risk loci for five major psychiatric disorders have been identified (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013b). Another study (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a) estimating genetic variation within and covariation between these disorders found that SNPs explained 17–29% of the variance in liability. Thus, these studies (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a, 2013b; Green et al., 2010; International Schizophrenia Consortium, 2009) supported shared and specific genetic etiologies for these five disorders. However, in addition to significant SNPs associated with these disorders identified by GWAS (Franke et al., 2009; Glessner et al., 2014; Hawi et al., 2015; Major Depressive Disorder Working Group of the Psychiatric Gwas Consortium, 2013; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Ripke et al., 2013; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011), a number of SNPs whose individual effects are very small and do not reach a genome-wide significance level collectively contribute a large proportion to genetic risk and

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explain a substantial part of the heritability of these mental disorders(International Schizophrenia Consortium, 2009).

The polygenic risk score (PGRS), calculated by summing the logarithms of the odds ratios of the associated alleles (International Schizophrenia Consortium, 2009), was introduced to summarize the effects of a set of SNPs based on the GWAS summary statistics of a training dataset (International Schizophrenia Consortium, 2009). This method has proven effective in conveying polygenic risks (Dudbridge, 2013; International Schizophrenia Consortium, 2009) and has been applied in many studies, especially cross-disorder studies. This method was first proposed to find common polygenic variation between schizophrenia and bipolar disorder (International Schizophrenia Consortium, 2009). Another study that examined the five major psychiatric disorders also applied PGRS to find common polygenic risk between pairs of disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013b). PGRS is also a useful and important method in imaging genetics (Dima and Breen, 2015), in which PGRS is utilized to examine the impact of genetic risk on the underlying neurobiology. A cross-disorder imaging genetics study using the PGRS model found that abnormal frontal activation was related to an increased risk for schizophrenia (Whalley et al., 2015).

Previous evidence consistently showed disrupted neural connectivity in major psychiatric disorders (Just et al., 2007; Khadka et al., 2013; Konrad and Eickhoff, 2010). Resting-state fMRI is a powerful method for evaluating regional interactions in clinical populations. Aberrant functional connectivity is associated with psychiatric disorders (Just et al., 2007; Khadka et al., 2013; Konrad and Eickhoff, 2010) and many brain networks, including the salience (Goodkind et al., 2015; Mamah et al., 2013; Manoliu et al., 2014b; Palaniyappan et al., 2011; Uddin et al., 2013), central executive control (Lin et al., 2015; Manoliu et al., 2014b), and default mode network (Garrity et al., 2007; Manoliu et al., 2014b; Ongur et al., 2010), have been found to be affected. For example, the salience network is associated with all of these disorders (Aizenstein et al., 2009; Castellanos and Proal, 2012; Choi et al., 2013; Goodkind et al., 2015; Hamilton et al., 2009; Just et al., 2007; Mamah et al., 2013; Manoliu et al., 2014b; Palaniyappan et al., 2011; Uddin et al., 2013), the central executive network is associated with schizophrenia (Manoliu et al., 2014b) and the default mode network is associated with BD and schizophrenia(Garrity et al., 2007; Manoliu et al., 2014b; Ongur et al., 2010). Functional connectivity and the brain network have been widely used as promising endophenotypes to establish the link between specific genetic variants and psychiatric disorders (Esslinger et al., 2009; Liu et al., 2015; Liu et al., 2014; Meyer-Lindenberg, 2009; Tost et al., 2012). However, few studies investigated the relationship between polygenic risk for psychiatric disorders and functional connectivity. A previous study (Whalley et al., 2015) detected effects of polygenic risk on brain activation for specific ones of these five disorders. However, altered functional connectivity patterns associated with the cross-disorder PGRS and disorder-specific functional connectivity patterns associated with the PGRS for these five disorders remain unrevealed. To address this issue, we studied the functional connectivity alterations associated with cross-disorder PGRSs and disorder-specific altered functional connectivity patterns associated with the PGRSs for these five disorders using young healthy subjects in two independent datasets. First, we calculated the cross-disorder PGRSs and PGRSs for these five psychiatric disorders separately in the 2 independent populations using summary statistics from the PGC GWAS Cross Disorder group (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013b) as training data. Then, we generated a functional connectivity profile for each subject. Next, we performed a voxel-wise statistical analysis to examine the relationships between the PGRSs and the functional connectivities separately in the two independent datasets. After that, we performed conjunction analyses to investigate the overlapping shared and disorder-specific functional connectivity alterations between these two datasets. Finally, we tried to find whether PGRS calculated using other thresholds produced similar results.

2. Materials and methods

2.1. Demographics of participants

Dataset 1: Dataset 1 included 360 healthy young Chinese subjects (Table 1). The subjects and their relatives within the third-degree had no history of psychiatric disorders. None of the participants had a history of psychiatric treatment, drug or alcohol abuse, traumatic brain injury, or visible brain lesions on conventional magnetic resonance imaging (MRI). They all gave full written informed consent to join the study. The Ethics Committee of the School of Life Science and Technology at the University of Electronic Science and Technology of China approved this study.

Dataset 2: 323 healthy young Chinese subjects were included in Dataset 2 (Table 1). None of the subjects nor their first-degree relatives had a history of psychiatric diagnoses, of neurological or metabolic illnesses, or of drug or alcohol abuse. They all gave full written informed consent to participate in the study. The Ethics Committee of Tianjin Medical University approved this study.

2.2. Genotyping and quality control

We collected whole blood and extracted genomic DNA using the EZgene Blood gDNA Miniprep Kit for all subjects. Next we performed whole-genome genotyping using the standard Illumina genotyping protocol on Illumina Human OmniZhongHua-8 BeadChips. Plink (Purcell et al., 2007) was used to perform quality control, using the same procedure for both datasets. First, the individuals, 1 from Dataset 1 and 3 from Dataset 2, whose missing genotype rates were >0.05 were excluded. Then, we removed the one with the greater missing genotype rate from each pair that had more similar genotypes identified by estimating the pairwise identity-by-descent (IBD) than we would have expected in a random sample, removing 2 individuals from Dataset 1 and 5 individuals from Dataset 2. Next, SNPs with missing genotype rates >0.05, a minor allele frequency <0.01, or a significant departure from Hardy-Weinberg Equilibrium ($P < 0.001$) were excluded. Finally, a principal component analysis (PCA) was performed to control for population stratification using EIGENSTART (Patterson et al., 2006; Price et al., 2006) on a linkage disequilibrium (LD) pruned set of autosomal SNPs obtained by carrying out LD pruning with PLINK and removing 5 long-range LD regions with the HapMap phase 3 reference dataset.(Thorisson et al., 2005) We removed the outliers of the sample (>6 SD) after we identified 10 principle components. A Q-Q plot was applied and showed that the population stratification was well controlled with $\lambda = 1.03043$ (Supplementary Fig. 1). After these quality control procedures, 356 and 311 subjects respectively in Datasets 1 and 2 were included for subsequent analyses. Additionally, >700.000 SNPs survived the pruning procedures.

2.3. Imputation and PGRS generation

The genome coordinates were converted from hg19 to hg18 assembly using liftOver (https://genome.ucsc.edu/cgi-bin/hgLiftOver) to be

Table 1
Demographic characteristics of the participants.

	Dataset 1	Dataset 2
Number of subjects	360	323
Male	186	157
Age	19.4 ± 1.1	22.7 ± 2.5
Age range	18–24	18–31
Education	12.3 ± 0.8	15.5 ± 2.7

consistent with the reference dataset used to perform imputation and the training dataset used to calculate the PGRS. Ungenotyped SNPs were imputed using SHAPEIT (Delaneau et al., 2012) and IMPUTE2 (Marchini et al., 2007) with an HapMap phase 3 reference dataset. After imputation, 1,381,116 SNPs were included for the following analysis. We removed the SNPs with imputation quality scores <0.8, missing genotype rates >0.05, a minor allele frequency <0.01, or significant departure from Hardy-Weinberg Equilibrium ($P < 0.0001$). About 960,000 SNPs survived the pruning procedures and were used to calculate the PGRSs. The GWAS data used to calculate the PGRS was pruned for linkage disequilibrium ($r^2 < 0.25$) at thresholds of $P^T < 0.01$, $P^T < 0.05$, $P^T < 0.1$ and $P^T < 0.5$.

It is important to choose an appropriate P-threshold to define PGRS and methods (Euesden et al., 2015) are proposed to choose the threshold. However, since this is a data driven study without predefined phenotypes, this method could not work on our study.

A more stringent threshold generates a SNP set with less SNPs being truly associated with the disorders. With a more liberal threshold, more SNPs will be included, which will help increase the statistical power (International Schizophrenia, C, 2009). But too liberal threshold will include SNPs that are too weakly associated with the disorders. So the statistical power will decrease (Liu et al., 2016). Among these four thresholds, $P^T < 0.05$ could be a balance of statistical power and the number of SNPs. So our research was primarily based on the PGRS calculated at $P^T < 0.05$, and we analyzed PGRS at other thresholds based on the results of $P^T < 0.05$.

We calculated the PGRS using the method described in a previous paper (International Schizophrenia Consortium, 2009). First we calculated the cross-disorder PGRSs and then calculated PGRSs for each of these five disorders (ADHD, autism, BD, MDD, schizophrenia) separately. The summary GWAS results from the PGC GWAS Cross Disorder group (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013b) were used as training datasets.

2.4. fMRI image acquisition and preprocessing

The image acquisition from each scanner was finished within six months. There were no hardware or system upgrades for either scanner, and the sequence and protocols for each subject were kept constant in each scanning period. The subjects from Dataset 1 were scanned on a MR750 3.0T magnetic resonance scanner (GE Healthcare, Milwaukee, WI). Resting-state functional imaging data was obtained using a gradient-echo echo-planar-imaging (GRE-EPI) sequence with the following configuration: echo time (TE) = 30 ms, repetition time (TR) = 2000 ms, flip angle = 90°, field of view (FOV) = 240 × 240 mm^2, matrix = 64 × 64, voxel size = 3.75 × 3.75 × 4.00 mm^3, 39 slices and 255 volumes. The subjects from Dataset 2 were scanned using a Signa HDx 3.0T scanner (GE Healthcare, Milwaukee, WI). We used a single-shot gradient-echo echo-planar imaging (SS-GRE-EPI) sequence to perform resting-state functional imaging with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, field of view (FOV) = 240 × 240 mm^2, matrix = 64 × 64, flip angle = 90°, voxel size = 3.75 × 3.75 × 4.00 mm^3, 40 slices, and 180 volumes. All participants were asked to close their eyes and avoid movement, think about nothing in particular, and avoid sleeping. After scanning, the subjects were asked if they fell asleep to ensure that they had all remained awake. The same preprocessing procedures were applied to each dataset, and DPARSFA (Data Processing Assistant for Resting State fMRI Advanced Edition, http://www.restfmri.net/forum/DPARSF) was used to preprocess the images. The preprocessing procedures included: (1) removing the first 10 volumes; (2) slice timing; (3) head motion correction; (4) spatial normalization; (5) smoothing with a 6 mm Gaussian kernel; (6) removing the influence of the whole brain signals, head motions, and linear trends; and (7) temporal band-pass filtration (0.01–0.08 HZ). After preprocessing, 28 and 14 subjects respectively from Datasets 1 and 2 were excluded due to a maximum displacement >2 mm or a spin >2° in any of the cardinal directions.

2.5. ROI definition

Since cross-disorder PGRS indicates shared genetic risks for these five psychiatric disorders, brain regions that showed disruption in all five major psychiatric disorders were chosen as a ROI to investigate the associations between functional connectivity and cross-disorder PGRS and contributions of subscores for each of these five disorders to the cross-disorder impacts using resting-state fMRI. We used statistical inference maps acquired from Neurosynth (Yarkoni et al., n.d.) (http://neurosynth.org/) to define the region of interest (ROI) for further functional connectivity analysis. We searched the meta-analysis results from Neurosynth (Yarkoni et al., n.d.) (http://neurosynth.org/) for the 5 major psychiatric disorders, separately using ADHD, autism, bipolar, depression, and schizophrenia as search terms. If a study used one of the searched keywords, we obtained statistical inference maps displaying z-scores according to the probability of a region's being activated. In other words, these maps displayed the brain regions that were consistently activated in studies that loaded highly on a specific term. A large z-score means that this region was reported more often than expectation under the hypothesis that activations in the brain would be equally likely (Yarkoni et al., 2011). These maps were thresholded at a false discovery rate (FDR) of 0.01 (Fig. 1). The brain regions affected by all 5 disorders were defined as an ROI. This ROI primarily included the bilateral insula, which is reasonable since the insulae have been suggested as being affected by all five major psychiatric disorders (Goodkind et al., 2015). Then we resampled the voxel size of the ROI to 3 × 3 × 3 mm^3 to match the voxel size of the fMRI images we acquired after preprocessing (Fig. 1).

2.6. Functional connectivity calculation

Based on the defined ROI, we calculated voxel-wise bilateral insular functional connectivity maps for each subject throughout the whole brain. These functional maps were calculated by computing the Pearson's correlation coefficient between the average BOLD time series in the ROI and the time series from all the voxels within a gray matter mask of the whole brain. The correlations were transformed to a Gaussian distribution using Fisher's z-transformation.

2.7. Statistical analysis

We performed a second-level analysis using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) with the subjects in the two independent datasets, separately. We applied a multiple regression model and voxel-wise *t*-test to test for significant correlations between the PGRSs and the voxel-wise functional connectivity. Age, sex, and the 3 top principle components were included in the model as covariates. To correct for multiple comparisons, an Alphasim algorithm implemented in REST (Song et al., 2011) was applied. Statistical maps were thresholded at a voxel-level of $p < 0.05$ and cluster size > 90 voxels to reach a cluster-level significance of alpha < 0.05. After correcting for multiple comparisons, we conducted conjunction analyses. First we performed a conjunction analysis to find consistent functional connectivity alterations associated with cross-disorder PGRS between these two datasets. Then we conducted another two conjunction analyses to find disorder-specific functional connectivity alterations, first performing a conjunction analysis for each dataset to find disorder-specific functional connectivity alterations and then conducting the second conjunction analysis to find consistent disorder-specific functional connectivity patterns with the bilateral insula in both datasets. Clusters larger than 10 voxels were retained.

Then to find whether PGRSs calculated using other thresholds produce similar results, we conducted the same analysis as above using

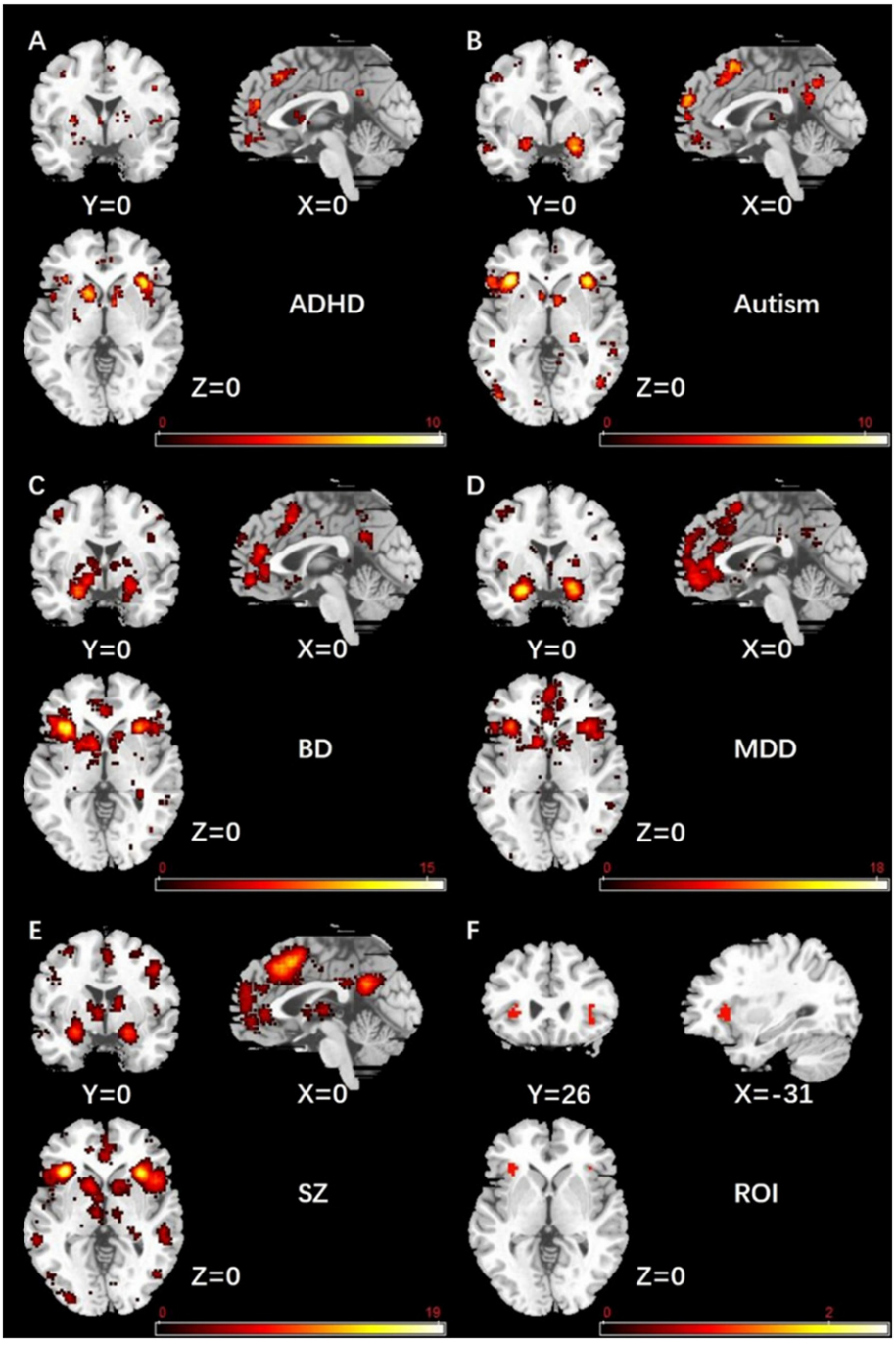

Fig. 1. *Z*-score maps of the meta-analysis for five major psychiatric disorders: (A) ADHD, (B) autism, (C) BD, (D) MDD, (E) schizophrenia. (F) is a binary image of our ROI displaying the overlap between the five maps. MNI coordinates were used.

PGRS calculated with $P^T < 0.01$, 0.1 and 0.5 separately, but only considering the significant voxels at $P^T < 0.05$, not the voxels in the whole brain. To correct for multiple comparisons, an Alphasim algorithm implemented in REST (Song et al., 2011) was applied. Statistical maps were thresholded at a voxel-level of $p < 0.05$ and cluster size > 12 voxels for autism, 9 voxels for BD and 7 voxels for schizophrenia to reach a cluster-level significance of alpha < 0.05.

3. Results

Using healthy subjects in both datasets, we first investigated the consistent functional connectivity alterations associated with cross-disorder PGRSs at $P^T < 0.05$. Statistical maps and statistical tables for clusters survived multiple comparison correction for each dataset are included in the Supplementary materials (Supplementary Table 1, Supplementary Fig. 2). We found that the cross-disorder PGRSs were negatively related to functional connectivity for left supplementary motor area and left superior temporal gyrus with bilateral insula consistently in both datasets (Table 2 and Fig. 2).

Then we studied the consistent disorder-specific functional connectivity alterations associated with PGRSs at $P^T < 0.05$ for each of these five disorders using healthy subjects in both datasets. Statistical maps and statistical tables for clusters survived multiple comparison correction for each dataset are included in the Supplementary Materials (Supplementary Table 1, Supplementary Fig. 2). We found consistent specific functional connectivity patterns associated with the PGRS for three of

Table 2
Statistics for clusters that have consistent altered functional connectivity related to cross-disorder and disorder-specific PGRS ($P^T < 0.05$) across two datasets.

Disorder	Cluster size	Peak MNI coordinates	Peak *t*-value	Peak MNI coordinate region
AUT	34	(57,−11,−11)	2.9347	Temporal_Mid_R
	87	(−36,13,−11)	2.5448	Insula_L
	1	(9,28,22)	1.8169	Cingulum_Ant_R
	1	(−6,16,34)	1.7014	Cingulum_Mid_L
BD	2	(−30,−11,−23)	−1.6619	ParaHippocampal_L
	17	(−12,−17,−23)	−2.7021	Left Pons
	14	(12,−17,−20)	−2.1886	Right midbrain
	1	(18,−14,−11)	−1.7669	Right midbrain
	10	(−3,−56,7)	1.8777	Precuneus_L
	41	(−9,−83,31)	2.0736	Cuneus_L
	9	(21,13,67)	1.8024	Frontal_Sup_R
SZ	20	(−42,46,13)	−2.3668	Frontal_Mid_L
	15	(−54,−62,28)	2.2003	Angular_L
	2	(−30,28,34)	−1.9412	Frontal_Mid_L
Cross-disorder	11	(−57,−20,7)	−1.984	Temporal_Sup_L
	1	(−18,55,28)	−1.7596	Frontal_Sup_L
	20	(−3,4,52)	−2.0877	Supp_Motor_Area_L
	7	(−3,−11,70)	−1.9129	Supp_Motor_Area_L

the five disorders: autism, BD, and schizophrenia, but not for ADHD and MDD. An increasing PGRS for autism was associated with increasing functional connectivities for the right middle and the superior temporal lobe and left insula with the bilateral insula. An increasing PGRS for bipolar disorder was associated with increasing functional connectivities for the bilateral cuneus, precuneus, and posterior cingulate with bilateral insula and decreasing functional connectivities for the bilateral midbrains with bilateral insula. We also observed that an increasing PGRS for schizophrenia was associated with increasing functional connectivities for the left angular gyrus and decreasing functional connectivities for the left dorsolateral prefrontal cortex (DLPFC), both with the bilateral insula (Table2 and Fig. 3).

Considering different PGRS thresholds, we found that when $P^T < 0.1$, cross-disorder PGRS was related to the functional connectivity between the bilateral insula and the left superior temporal lobe and the left supplementary motor area negatively. PGRS for autism was positively related to the functional connectivity between the bilateral insula and the right middle and superior temporal lobe when $P^T < 0.01$ and the functional connectivity for left insula and the right middle and superior temporal lobe with the bilateral insula when $P^T < 0.1$ (Supplementary Table 2 and Supplementary Fig. 3). And we did not find consistent altered functional connectivity related to PGRS for other disorders or PGRS calculated using other thresholds.

4. Discussion

Using young healthy subjects in two independent datasets, we revealed distinct altered bilateral insular functional connectivity patterns associated with the cross-disorder PGRS and the PGRS for three of five major psychiatric disorders. As far as we know, this is the first study to concentrate on associations between functional connectivity patterns and the cross-disorder PGRS and the PGRS for specific ones of these five diseases applying an imaging genetics method. Shared and disorder-specific brain networks, such as the default mode, salience, and central executive networks, showed functional connectivity alterations associated with the cross-disorder PGRSs and PGRSs for specific ones of these disorders. Our findings imply that cross-disorder and disorder-specific functional connectivity alterations are related to the PGRS and, thus, could also be genetically modulated.

Many case-control studies have indicated that the PGRSs for specific disorders are associated with disease status and disorder severity (Clarke et al., 2016; Dudbridge, 2013; Hamshere et al., 2013; International Schizophrenia Consortium, 2009; Robinson et al., 2016; Stergiakouli et al., 2015; Whalley et al., 2012). Furthermore, this model was applied to datasets consisting only of healthy controls to quantify the polygenic risk for schizophrenia (Lancaster et al., 2016; Liu et al., 2016) as well as being applied to a cross-disorder analysis

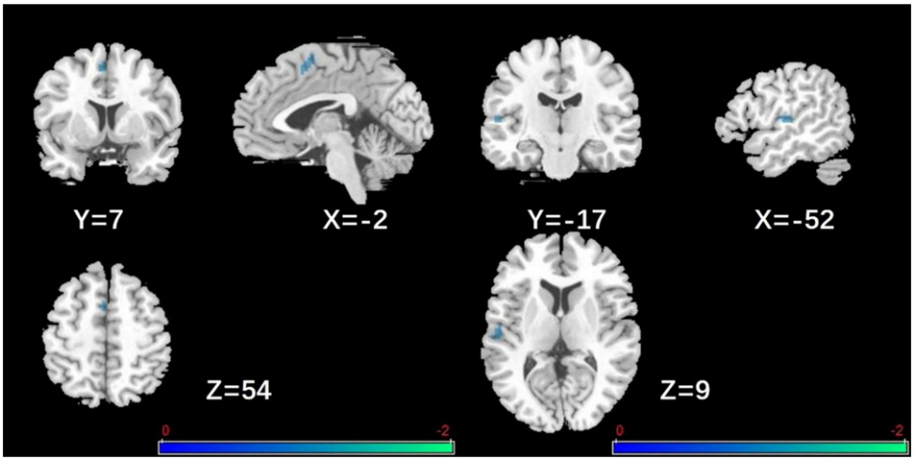

Fig. 2. Consistent functional connectivity alterations with the bilateral insula associated with the cross-disorder PGRSs ($P^T < 0.05$) using Dataset 1 and Dataset 2. The values of each voxel in these maps are only 0, −1 (blue). A value of −1 indicates significant negative associations separately between functional connectivity in these regions with the defined ROI and PGRS. Only clusters with >10 voxels are displayed. MNI coordinates are used.

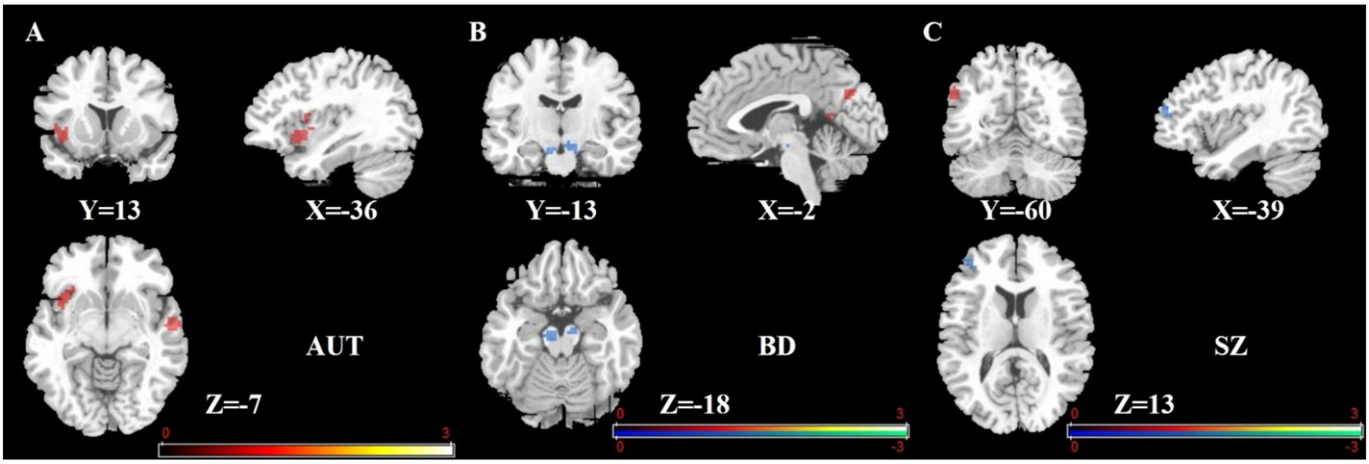

Fig. 3. Consistent disorder-specific functional connectivity alterations associated with the PGRSs($P^T < 0.05$) for: (A) autism, (B) BD and (C) schizophrenia, with the bilateral insula using Datasets 1 and 2. The values of each voxel in these maps are only 0, −1 (blue), and 1 (red). A value of 1 and −1 indicates significant positive and negative associations separately between functional connectivity in these regions with the defined ROI and PGRS. Only clusters with >10 voxels are displayed. MNI coordinates are used.

(Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013b; Ruderfer et al., 2014; Vorstman et al., 2013; Whalley et al., 2015; Wiste et al., 2014). We calculated the cross-disorder PGRSs and the PGRSs for each of these five disorders using healthy subjects in 2 independent datasets. Cross-disorder PGRSs indicate shared genetic risks among these disorders and are related to PGRSs for each of these five disorders. We used the PGRSs to detect the additive effects of a large set of SNPs in this study. The PGRS model evaluated the cumulative effects of the SNPs associated with disease status in each subject and provided a tool that allowed us to utilize the power of the GWAS results (Dima and Breen, 2015). Correlations between the PGRSs and functional connectivity alterations discovered in our study indicated that functional connectivity alterations were related to specific genetic variants. Our findings seem to support the hypothesis that common genetic variants can explain the functional alterations associated with the risk for these disorders and may partially further explain the neurobiological mechanisms of psychiatric disorders. Although we did not find studies that had previously detected such associations between functional connectivity and the PGRS, some studies(Kauppi et al., 2015; Lancaster et al., 2016; Tesli et al., 2015; Walton et al., 2014; Whalley et al., 2015; Whalley et al., 2012) that focused on the associations between abnormal patterns of activation and PGRSs provided evidence for that hypothesis. Most of these focused on the PGRS for schizophrenia and found abnormal prefrontal activation patterns; a few focused on the PGRS for bipolar disorder. These studies may suggest that common genetic variants influence the main neurobiological phenotypes of these psychiatric disorders.

Previous studies indicated that abnormalities associated with different disorders may occur in common brain regions. The meta-analysis results from Neurosynth (Yarkoni et al., n.d.) (http://neurosynth.org/) showed that the bilateral anterior insula are related to all five major psychiatric disorders, so it is a reasonable ROI to find functional connectivity alterations related to cross-disorder PGRS. However, previous publications also indicated that abnormal insula functional connectivity patterns of different disorders may be different(Avery et al., 2014; Chai et al., 2011; Ebisch et al., 2011; Horn et al., 2010; Liang et al., 2006; Tian et al., 2006; Zhou et al., 2007). So this is an interesting ROI to identify cross-disorder and disorder-specific functional connectivity alterations. The anterior insula is a hub in the salience network. The insula is believed to be involved in diverse functions, including perception (Baliki et al., 2009), motor control (Anderson et al., 1994), cognitive functioning (Menon and Uddin, 2010), self-awareness (Craig, 2009), and emotions (Menon and Uddin, 2010; Phan et al., 2002). Many studies have indicated that the salience network, especially the anterior insula, plays an important role in psychiatric disorders and insula dysfunctions and that these abnormalities are associated with major psychiatric disorders(Caria and de Falco, 2015; Gerretsen et al., 2014; Menon and Uddin, 2010; Uddin and Menon, 2009; White et al., 2010).

The associations between the cross-disorder PGRS and functional connectivity observed in our study indicate that the cross-disorder PGRS is associated with the altered functional connectivity within the salience network and these functional connectivity alterations are associated with shared common genetic variants of these five disorders. The salience network abnormalities are found in all of these five major psychiatric disorders (Choi et al., 2013; Goodkind et al., 2015; Uddin et al., 2013). It is also found that symptom severity of autism and MDD is related to the salience network (Manoliu et al., 2014a; Uddin et al., 2013). Our results suggest that the salience network may play an important role in the neurobiological mechanisms of these five major psychiatric disorders.

To identify the genetic effects on functional connectivity alterations of each specific disorder, we analyzed the associations between PGRSs for each of these five disorders and whole brain functional connectivities. We did not find PGRSs for a specific disorder have significant associations with functional connectivities between the bilateral insula and the left supplementary motor area and the left superior temporal lobe, indicating cross-disorder impacts. However, we found disorder-specific functional connectivity alterations associated with PGRSs for specific disorders, indicating that these functional connectivity alterations were related to specific genetic variants.

We observed hyperconnectivity associated with the PGRS for autism between the left insula and the bilateral insula within the salience network, which is involved in affective processing, interoception, and identifying related internal and extrapersonal stimulation to guide behavior (Menon and Uddin, 2010). The altered functional connectivity with the bilateral insula may suggest the neuropathology of autism. The salience network acts to find salient endogenous events and initiates and mobilizes resources for suitable responses (Uddin et al., 2013). A study stated that hyperconnectivity in the salience network could be used to distinguish autism patients from healthy controls (Uddin et al., 2013). However, some studies (Caria and de Falco, 2015; Uddin and Menon, 2009) that identified reduced functional connectivities in the salience network in autism are incongruent with ours, so additional evidence is needed to confirm the functions of the anterior insula and the salience network in autism. We also found hyperconnectivity between the bilateral insula and the right middle temporal lobe and superior temporal lobe. These regions are involved in biological motion processing, play an important part in social and speech perception, and are implicated in the development of autism (Redcay, 2008). The altered functional

connectivity that correlated with the PGRS for autism supports some functions that are known to be impaired in autism. Thus, our findings may help to partially explain the functional impairment in autism (Clarke et al., 2016; Redcay, 2008).

We found that an increasing PGRS for bipolar disorder was associated with decreasing functional connectivities between the bilateral midbrains and the bilateral insula and with increasing functional connectivity patterns between the bilateral insula and the bilateral posterior cingulate cortex, cuneus, and precuneus. The brainstem regions may mediate the bodily changes that accompany emotional behaviors (Drevets, 2001). Many studies suggested that the brainstem may be involved in the pathophysiology of bipolar disorder (Lauterbach, 1996). Specifically, impairment in the brainstem has been implicated in manic symptoms (Lauterbach, 1996). Increasing functional connectivities with the insulae were found for the posterior cingulate cortex and precuneus, which are parts of default mode network. Previous studies have detected abnormalities in the default mode network associated with bipolar disorder (Calhoun et al., 2008; Ongur et al., 2010). The salience network plays an important role in switching between the default and the central-executive networks (Menon and Uddin, 2010; Sridharan et al., 2008). The increasing functional connectivities between the salience and default mode networks with increasing PGRS for bipolar disorder may indicate a disturbance in the switch function and be associated with cognitive and affective processing problems in bipolar disorder (Maddock et al., 2001).

We also found that the PGRS for schizophrenia was associated with functional connectivity positively between the bilateral insula and the left angular gyrus and negatively between the bilateral insula and the left DLPFC. The angular gyrus is a part of the default network and is involved in semantic processing, memory retrieval, attention, and social cognition (Seghier, 2013). The DLPFC is a hub of the central-executive network (Sridharan et al., 2008) and is involved in decision making, working memory, and cognitive functions (Elliott, 2003). A recent case-control study provided evidence for an aberrant dependence of the default mode network and central executive network interactions on salience network activity and associations between the impaired activity in these regions and psychosis in schizophrenia (Manoliu et al., 2014b). Our research indicates that these abnormal interactions are modulated by genetic factors and may be an aid in understanding the neurobiological mechanism of schizophrenia.

These five major psychiatric disorders are clinically and genetically heterogeneous disorders with high heritability. However, the specificity of the link between polygenetic risk and neural mechanisms remains elusive. By simultaneously analyzing the associations between the PGRSs for these five disorders and the functional connectivities associated with them, we identified disorder-specific functional connectivity patterns correlated with the PGRSs for these disorders in two independent general populations. From an imaging genetics perspective, our findings revealed disorder specificity at the genetic and neural connectivity level, shed light on the distinct pathophysiologies of these major psychiatric disorders, and supported their clinical and genetic heterogeneity. These results further support the contribution of genetic factors in the development of neural circuits and the risk for psychiatric disorders.

Using two independent datasets, we found shared functional connectivity alterations related to the cross-disorder PGRSs and specific functional connectivity patterns associated with the PGRSs for these disorders. However, some issues need to be considered in future studies. First, although we applied the same data processing procedures, differences existed in the raw data because they were acquired using different scanners from different sites. This may help explain why we did not find consistent specific functional patterns associated with the PGRS for ADHD and MDD. Next, we have conducted quality control, but there may be still some noise in the data. The different results across P-thresholds may reflect some noise in the data and the results should be viewed with caution until they are independently replicated. Additionally, more samples would increase the statistical power of our study. In our study, the voxel-wise statistical results were corrected for multiple comparisons using the "AlphaSim" implemented in REST, based on the Monte Carlo simulation in AFNI (Song et al., 2011). The AlphaSim algorithm implemented in REST is widely used to correct multiple comparisons in previous studies (Fan et al., 2017; Peng and Hsin, 2017). Since the subjects in our research were all healthy individuals, their differences may not have been significant enough to survive a more stringent correction. Although we chose a relatively liberal multiple correction method and threshold, our results are robust because we validated them using an independent dataset by conducting conjunction analysis. Conjunction analysis, which can reduce type I error, is a powerful tool to identify typical and generic aspects of the functional architecture of the human brain among contrasts (Friston et al., 1999) and is widely used to provide evidence of replication (Ivanoff et al., 2009; Liu et al., 2016; Narain, 2003). Conjunction analysis is a useful method in our exploratory study. Moreover, the PGRS model does not consider the interactions between SNPs; it is an aggregative model. Interactions between the SNPs should be considered in future studies. Furthermore, the subjects used in this study were Chinese and, if the training dataset for calculating the PGRS had been Chinese, the power would have been increased. Finally, multi-modal data could be included in future studies to find both structural and functional abnormalities.

In conclusion, the present study primarily examined the shared functional connectivity patterns associated with the cross-disorder PGRSs and specific functional connectivity patterns associated with the PGRSs for five major psychiatric disorders. We used 2 independent datasets to show that robust functional connectivity patterns were associated with the cross-disorder PGRSs and the PGRSs for autism, BD, and schizophrenia and that these relationships seem to be genetically modulated. Our results appear to support the validity of the PGRS model, the genetic imaging method, and the hypothesis that polygenic risk may contribute to the main neurobiological phenotypes of psychiatric diseases. Relating the specific functional connectivity with polygenic risks may help elucidate the neurobiological pathways for these diseases.

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Conflict of interest

The authors declare no conflict of interest.

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