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MIR137 polygenic risk is associated with schizophrenia and affects functional connectivity of the dorsolateral prefrontal cortex

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Abstract

Background. Genome-wide association studies (GWAS) have consistently revealed that a variant of microRNA 137 (*MIR137*) shows a quite significant association with schizophrenia. Identifying the network of genes regulated by *MIR137* could provide insights into the biological processes underlying schizophrenia. In addition, DLPFC functional connectivity, a robust correlate of *MIR137,* may provide plausible endophenotypes. However, the regulatory role of the *MIR137* gene network in the disrupted functional connectivity remains unclear. Here, we tested the effects of the *MIR137* regulated genes on the risk for schizophrenia and DLPFC functional connectivity.

Methods. To evaluate the additive effects of the *MIR137* regulated genes ($N = 1274$), we calculated a *MIR137* polygenic risk score (PRS) for schizophrenia and tested its association with the risk for schizophrenia in the genomic data of a Han Chinese population that included schizophrenia patients ($N = 589$) and normal controls ($N = 575$). We then investigated the association between *MIR137* PRS and DLPFC functional connectivity in two independent young healthy cohorts ($N = 356$ and $N = 314$).

Results. We found that the *MIR137* PRS successfully captured the differences in genetic structure between the patients and controls, but the single gene *MIR137* did not. We then consistently found that a higher *MIR137* PRS was correlated with lower functional connectivities between the DLPFC and both the superior parietal cortex and the inferior temporal cortex in two independent cohorts.

Conclusion. The findings suggested that these two functional connectivities of the DLPFC could be important endophenotypes linking the *MIR137*-regulated genetic structure to schizophrenia.

Introduction

Many previous studies reported that the microRNA-137 (*MIR137*) gene is a schizophrenia risk gene (Schizophrenia Psychiatric Genome-Wide Association Study, 2011; Ripke *et al*., 2013, 2014). A schizophrenia genome-wide association study (GWAS) (Psychiatric Genomics Consortium, PGC) based on a European ancestry population reported that the single nucleotide polymorphism (SNP) rs1625579 within an intron of a putative primary transcript for *MIR137* showed the most significant association with schizophrenia (Schizophrenia Psychiatric Genome-Wide Association Study, 2011). Later, a landmark schizophrenia GWAS PGC2 was conducted using more cases and revealed that another SNP rs1702294 within *MIR137* was the second highest genetic variant among 108 loci that achieved genome-wide significance level (Ripke *et al*., 2014). However, a recent genome-wide meta-analysis that combined Chinese and PGC2 samples found that rs1625579 and rs1702294 had no significant association with schizophrenia, but the SNP rs1198589 in high linkage disequilibrium (LD) with *MIR137* variant rs1702294 ($r^2 = 0.629$) met a genome-wide significance level (Li *et al*., 2017). Moreover, previous studies provided evidence that *MIR137* plays a critical regulatory role in embryonic neural stem cell (NSC) proliferation and differentiation (Sun *et al*., 2011), adult NSC neurogenesis (Szulwach *et al*., 2010), neuronal maturation (Smrt *et al*., 2010), and presynaptic plasticity (Siegert *et al*., 2015), findings which are in line with the neurodevelopmental hypothesis of schizophrenia. These findings converge to suggest that *MIR137* has

been implicated in the etiology of schizophrenia. In fact, *MIR137* is one of many microRNAs that regulate a variety of biological processes (Mahmoudi and Cairns, 2017). Specifically, *MIR137* can modulate the expression of other genes through the degradation of mRNA or suppression of protein synthesis (Filipowicz *et al.*, 2008). Schizophrenia GWAS have indicated that the genes with bioinformatically predicted *MIR137* target sites, such as *TCF4*, *CACNA1C*, *CSMD1*, *ZNF804A*, and *C10orf26* showed significant association with schizophrenia (Schizophrenia Psychiatric Genome-Wide Association Study, 2011; Williams *et al.*, 2011). Another study performed a genome-wide assessment of transcriptional changes in human neural progenitor cells after *MIR137* over-expression and inhibition and found a large set of genes affected by the up- and down-regulation of *MIR137* (Hill *et al.*, 2014). These studies suggest that a gene network of interacting *MIR137* targets may provide some insight into the biological processes underlying schizophrenia (Wright *et al.*, 2013; Vallès *et al.*, 2014). Therefore, relative to the SNPs located in the *MIR137* gene, the *MIR137* PRS, a score that measures the additive effects of schizophrenia-related genetic variants within *MIR137*-regulated genes, may better reflect the case-controlled difference in the genetic structure and may identify the association of this difference with phenotypes.

Cosgrove and his colleages have extensively investigated the association between the *MIR137* PRS and cognitive performance, brain volume, and cortical measures (Cosgrove *et al.*, 2017, 2018), but the functional phenotypes underlying the *MIR137*-regulated genetic structure are still largely unknown. Resting-state functional magnetic resonance imaging (rs-fMRI) has become an increasingly important technique for mapping the functional networks of the brain (Shirer *et al.*, 2015). Therefore, it has been widely used to identify the abnormal resting-state functional connectivity (FC) related to many psychiatric disorders, including schizophrenia. FC reflects the temporal dependence of neuronal activity patterns of anatomically separated brain regions (Aertsen *et al.*, 1989) and can provide new insights into large-scale neuronal communication in the human brain. Previous functional imaging studies revealed that *MIR137* influenced the FC of many brain regions, especially the dorsolateral prefrontal cortex (DLPFC), involved in the pathogenesis of schizophrenia (Liu *et al.*, 2014; Mothersill *et al.*, 2014; Zhang *et al.*, 2018). Several studies also reported a consistently meaningful finding that *MIR137* target genes are significantly enriched for association with functional activation of the DLPFC (Potkin *et al.*, 2010; Guella *et al.*, 2013). Moreover, a specific *MIR137* SNP, rs1625579, has been reported to be associated with functional activation of the left DLPFC rather than the right DLPFC (Potkin *et al.*, 2014). The DLPFC has been shown to play a critical modulatory and integrative role in executive functions (Su *et al.*, 2013), especially working memory (Barch *et al.*, 2012). Intriguingly, both schizophrenia patients and normal controls showed greater left than right DLPFC activation in working memory conditions (Potkin *et al.*, 2009). These studies suggested that the left DLPFC might be an important region involved with the *MIR137* gene and working memory. However, whether and how the left DLPFC functional connectivity is related to the gene network of interacting *MIR137* targets remain unclear.

Here, we hypothesized that the FCs between the left DLPFC and some specific regions may be related to the *MIR137* PRS. To test this hypothesis, we first examined whether the *MIR137* PRS could capture the genetic difference between the schizophrenia patients and the normal controls in a Han Chinese population better than the SNPs located in the *MIR137* gene (rs1625579, rs1702294, and rs1198589). Then we investigated the association of the *MIR137* PRS with DLPFC functional connectivity in two independent, general-population samples. The *MIR137* PRS was calculated based on a recent meta-analysis of Chinese GWAS samples and PGC2 GWAS samples (Li *et al.*, 2017). A DLPFC functional connectivity map for each individual was obtained by taking the left DLPFC as a region of interest (ROI) to calculate the voxel-wise map. Consistent findings in two independent samples were desired to confirm the relationship between the *MIR137* PRS and DLPFC functional connectivity.

Methods

Participants

The genomic data of 1164 subjects of Chinese Han ancestry (575 schizophrenia patients, SZ, and 589 normal controls, NC) were included in this study (Table 1). The diagnostic assessments of all the schizophrenia patients were made consistently by two board-certified psychiatrists according to the criteria for schizophrenia from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The included schizophrenia patients had no history of other psychiatric disorders, severe physical diseases, epilepsy, drug or alcohol abuse, electroconvulsive therapy, or suicide attempt. The normal controls were also clinically determined to be free of psychiatric disorders or family history of such disorders (including first-, second- and third-degree relatives). After receiving a complete description of the study, all the participants provided written informed consent. The project was approved by the Medical Research Ethics Committees of the local hospitals and institutes.

Two other independent datasets with both high-quality genomic and neuroimaging data were included in this study. Target dataset 1 included 360 healthy young Chinese subjects (186 males; mean age = 19.4±1.1 years; age range = 18–24), and target dataset 2 had a total of 323 healthy young Chinese participants (157 males; mean age = 22.7±2.5 years; age range = 18–31) (see Table 1 for demographic details). None of the participants or their first-, second-, and third-degree relatives in either dataset had any history of psychiatric disorders. We also screened all of the participants to ensure that none of them had a history of psychiatric treatment, drug or alcohol abuse, traumatic brain injury, or visible brain lesions on conventional MRI. They all provided written informed consent for this study, which was also approved by the Ethics Committee of the School of Life Science and Technology at the University of Electronic Science and Technology of China and the Ethics Committee of Tianjin Medical University. Four of the target dataset 1 and nine of the target dataset 2 participants were excluded from further analysis due to genotyping quality control failure or a lack of rs-fMRI data.

Genotype processing

We collected whole blood samples and used the EZgene Blood Gdna Miniprep Kit to extract genomic DNA. Whole-genome genotyping was then performed on Illumina Human OmniZhongHua-8 BeadChips. Subsequently, we carried out genotype quality control using PLINK version 1.07 (Purcell *et al.*, 2007). First, we excluded the subjects if their missing genotype rates were greater than 0.05. Then, we estimated the pairwise identity-by-descent (IBD) to remove the possibly related

Table 1. Demographic characteristics of the participants

	SZ	NC	Target dataset 1	Target dataset 2
Number	589	575	356	314
Male (%)	53.14%	49.91%	51.40%	48.57%
Age (y)	28.10 ± 7.24	28.44 ± 7.00	19.39 ± 1.09	22.70 ± 2.44
Age range	16.42–54.00	17.08–45.75	17.00–24.00	18.00–29.00
Education(y)	10.63 ± 3.81	13.42 ± 3.40	12.34 ± 0.81	15.49 ± 2.65

individuals. Specifically, we removed the one with the greater missing rate from each pair who had more similar genotypes than we would have expected by chance in a random sample. Next, we filtered the SNPs with missing genotype rates >0.05, a minor allele frequency <0.01, or a significant departure from Hardy – Weinberg equilibrium ($p < 0.001$). To control for population stratification, we performed a principal component analysis (PCA) using EIGENSTART 5.0.2 (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 ($r^2 < 0.05$) and removed 5 long-range LD regions with the HapMap phase 3 reference data set (Thorisson *et al.*, 2005). After obtaining 10 principal components, we excluded the outliers of the samples >6 S.D. Ungenotyped SNPs were imputed using SHAPEIT v2 (r790) (Delaneau *et al.*, 2012) and IMPUTE2 (Howie *et al.*, 2009) with the 1000 Genomes Phase 1 reference dataset. Further analyses focused on autosomal SNPs with imputation quality scores greater than 0.8.

MIR137 *PRS calculation*

Hill and his colleagues investigated the effects of *MIR137* overexpression and inhibition on global RNA expression in human neural progenitor cells (Hill *et al.*, 2014). They found a set of 1033 genes affected by the up-regulation of *MIR137* and a set of 958 genes affected by the down-regulation of *MIR137*. Of these, 166 genes were detected in both situations. In total, 1825 different genes were found to be regulated by *MIR137*, of which 1274 genes were unambiguously mapped to autosomes (online Supplementary Data S1). Then, we used the 'score' utility in PLINK to calculate the *MIR137* PRS. The score for each subject was computed by summing the number of risk alleles located in these 1274 genes weighted by the strength of the association of each SNP with schizophrenia. The strength of the association was obtained using a recent meta-analysis that combined Chinese GWAS samples and PGC2 GWAS samples (Li *et al.*, 2017). Ten PRSs for each subject were obtained by different SNP inclusion thresholds: $p < 0.5$; $p < 0.4$; $p < 0.3$; $p < 0.2$; $p < 0.1$; $p < 0.05$; $p < 0.01$; $p < 0.001$; $p < 0.0001$; $p < 1 \times 10^{-5}$. Using these results, we could choose a PRS with an appropriate threshold for subsequent analysis. Many studies chose the threshold based on experience. However, we conducted a preliminary test that compared the PRSs between normal controls and schizophrenia cases at different thresholds to find a score that could best explain the difference in the *MIR137*-regulated genetic structure.

fMRI image acquisition

Resting-state functional imaging data from target dataset 1 was acquired with a 3.0 T MR750 GE Scanner using a gradient-echo echo-planar-imaging (GRE-EPI) sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 240 × 240 mm^2, matrix = 64 × 64, voxel size = 3.75 × 3.75 × 4 mm^3, 39 slices and 255 volumes. The resting-state functional images from target dataset 2 were, however, acquired with a 3.0 T Signa HDx GE scanner using a single-shot-gradient-echo echo-planar-imaging (SS-GRE-EPI) sequence with the following parameters: TR = 2000 ms, TE = 30 ms, FA = 90°, FOV = 240 × 240 mm^2, matrix = 64 × 64, resolution of axial slice = 3.75 × 3.75, slice thickness = 4 mm, 40 slices, and 180 volumes. All the resting-state fMRI image acquisition for the two datasets was accomplished within 6 months. During the scanning, the same sequence and protocols were applied to each subject, and the hardware and systems were not upgraded. All the subjects were told to close their eyes, avoid movement, and stay awake during the scanning.

Image preprocessing

The same preprocessing steps were used for the EPI images in both datasets using the MATLAB-based pipeline toolbox BRANT (https://github.com/kbxu/brant). Specifically, eight steps were followed successively: (1) discarding the first 10 timepoints; (2) slice timing; (3) head motion correction; (4) rigid-body registration of the T1 image to the EPI mean image; (5) normalization of the EPI images to MNI standard space using the T1 image and subsequent resampling to 3 × 3 × 3 mm^3; (6) removing noise from the whole brain signals, head motions, and linear trends; (7) temporal band-pass filtration (0.01–0.08 Hz); and (8) smoothing with a 6 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel.

DLPFC functional connectivity analyses

Based on the results from a meta-analysis study (Rottschy *et al.*, 2012), we extracted a spherical region with a radius of 6 mm at the center of the MNI coordinate (−42, 33, 33) and defined this mask of the left DLPFC as a ROI. For each subject in target dataset 1 and target dataset 2, the voxel-wise left DLPFC functional connectivity map of the whole brain was calculated using the BRANT toolbox. These functional maps were obtained by computing the Pearson's correlation coefficient between the average BOLD time series in the ROI and the time series from all the voxels. The resulting correlations were then transformed to approximate a Gaussian distribution using Fisher's z transformation. Here, we obtained individual DLPFC functional connectivity maps for each subject.

Statistical analysis

To assess whether the *MIR137* PRS could capture a greater genetic difference between the schizophrenia patients and the normal

controls than the single *MIR137* SNP, we conducted a two-sample *t* test to compare the *MIR137* PRS between the schizophrenia patients and the normal controls in the genomic data of a Han Chinese population. As a contrast test, we investigated the odds ratios (ORs) with 95% confidence intervals (95% CIs) for three significant loci in *MIR137* (rs1625579, rs1702294, and rs1198589) by case-control studies. Then, we formed a second-level multiple regression model using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) to investigate the association between the *MIR137* PRS and the DLPFC FCs in two independent cohorts with healthy individuals. Age and sex were added as covariates, and the multiple comparisons were corrected by the AlphaSim method using the Resting-State fMRI Data Analysis Toolkit (REST) (http://restfmri.net/forum). Finally, we obtained the common DLPFC FCs that were significantly associated with *MIR137* PRS in two independent cohorts and estimated the Pearson's correlations between the common DLPFC FCs and *MIR137* PRS. Moreover, we calculated coefficient of determination (R^2) by the linear regression model to estimate the amount of variance in FCs that could be explained by *MIR137* PRS.

Results

In total, 1164 Han Chinese subjects with GWAS data were included in the genetic analysis (Table 1). We first compared the *MIR137* PRS between the schizophrenia patients ($n = 589$) and the normal controls ($n = 575$) under each threshold. We found that the *MIR137* PRS in the schizophrenia patients was significantly higher than that in the normal controls when the threshold was larger than 0.001 (Table 2). The lowest p value was obtained for the PRS with a threshold of 0.05, which suggested that this PRS could best explain the difference in the *MIR137*-regulated genetic structure (the details of the SNPs with a threshold of 0.05 are included in online Supplementary Data S2). Therefore, the SNP inclusion threshold of *MIR137* PRS for the individuals in target dataset 1 and target dataset 2 was selected to be 0.05. Previous GWAS studies have reported that rs1625579 (Schizophrenia Psychiatric Genome-Wide Association Study, 2011), rs1702294 (Ripke *et al.*, 2014), and rs1198589 (Li *et al.*, 2017) located in *MIR137* were the three loci that showed the most significant association with schizophrenia. Comparing the allele and genotyping frequency of the three loci between schizophrenia patients and normal controls, we found that none of them reached significance (online Supplementary Table S1). These results suggested that only genetic information from the *MIR137* gene network could capture a significant genetic case-controlled difference in our Han Chinese dataset. These findings confirmed the genetic effects of *MIR137* polygenic risk on schizophrenia in the Han Chinese population.

With respect to the imaging genetic analyses, the 356 samples in target dataset 1 and 314 samples in target dataset 2 that had sufficient genomic and resting-state fMRI data were included (Table 1). Similar DLPFC FC patterns in target dataset 1 and in target dataset 2 were found by comparing the mean voxel-wise FC maps (Fig. 1*a*, *c*). Specifically, the positive FCs of the DLPFC were primarily in regions of the frontoparietal network, such as the dorsolateral frontal cortex, superior parietal cortex, and inferior temporal cortex, whereas the negative FCs were in the orbitofrontal cortex, precentral/postcentral gyrus, temporal pole cortex, and occipital cortex. Further multiple regression analyses found that a higher *MIR137* PRS was significantly associated with lower FC between the left DLPFC and the right superior parietal cortex (peak voxel MNI coordinate = 36, −69, 57; peak intensity = −2.986; cluster size = 32) and the left inferior temporal cortex (peak voxel MNI coordinate = −66, −54, −15, peak intensity = −3.819, cluster size = 213) in target dataset 1 (Fig. 1*b*). The same analyses in the independent target dataset 2 also found that lower FCs between the left DLPFC and the right superior parietal cortex (peak voxel MNI coordinate = 36, −63, 51; peak intensity = −2.804; cluster size = 31) and the left inferior temporal cortex (peak voxel MNI coordinate = −57, −63, −15, peak intensity = −2.933, cluster size = 54) were significantly associated with a higher *MIR137* PRS, a finding which replicated those from target dataset 1 (Fig. 1*d*). We also made scatter plots to illustrate the association of the *MIR137* PRS with the FCs between the left DLPFC and the two overlapping significant regions in the two independent cohorts (Fig. 2). Moreover, in both independent cohorts, the coefficients of determination (R^2) from linear regression analysis were more than 0.022, which indicated that the *MIR137* PRS could explain more than 2.2% of the variance in these two FCs (Fig. 2).

Discussion

In this study, we assessed the association between the *MIR137* PRS and the risk of schizophrenia in our Han Chinese dataset and found that the *MIR137* PRS, not the single gene *MIR137*, greatly captured the difference in the *MIR137*-regulated genetic structure. Then, we revealed a consistent effect of *MIR137*-regulated genes on the FCs between the DLPFC and the superior parietal cortex and inferior temporal cortex in two independent general population samples. A higher *MIR137* PRS was significantly associated with lower FCs between the DLPFC and the superior parietal cortex and inferior temporal cortex. These results supported our hypothesis that the *MIR137* PRS, as a measure of *MIR137*-related cumulative genetic effects, correlates with the DLPFC functional connectivity, which has been widely reported to be disrupted in schizophrenia patients. These findings could provide clues for understanding the underlying neural mechanisms of the schizophrenia risk gene, *MIR137*.

One of the major findings of the present study was the significantly higher *MIR137* PRS of the schizophrenia patients than that of the normal controls in a Han Chinese population. Based on a large set of genes that are reported to be affected by the up- and down-regulation of *MIR137* (Hill *et al.*, 2014), the *MIR137* PRS for each subject was calculated by summing the additive effects of the schizophrenia-related genetic variants within the *MIR137*-regulated genes using a recent meta-analysis that combined Chinese GWAS samples and PGC2 GWAS samples (Li *et al.*, 2017). We also found that the *MIR137* PRSs were significantly higher in the schizophrenia patients than in the normal controls when the threshold was larger than 0.001 and that the most significant case-controlled difference was obtained when the threshold was equal to 0.05. This finding suggested that the *MIR137* PRS ($P < 0.05$) best explained the difference in the *MIR137*-regulated genetic structure. This finding was in line with a previous GWAS study that reported that a threshold of 0.05 could maximally capture the heritability of schizophrenia (Schizophrenia Psychiatric Genome-Wide Association Study, 2011). For the three loci in *MIR*137, rs16255791, rs17022943, and rs1198589, that were reported as showing a greatly significant association with schizophrenia in a European GWAS (Schizophrenia Psychiatric Genome-Wide Association Study,

Table 2. Two sample *t* test of the *MIR137* PRS

		PRS (NC)		PRS (SZ)		*t* test: NC *v.* SZ	
Threshold	Number of SNPs	Mean(10^{-2})	S.D.(10^{-4})	Mean(10^{-2})	S.D.(10^{-4})	*T*	*p*
0.5	56 075	1.256	2.872	1.260	2.761	−2.4320	0.0152
0.4	47 909	1.314	3.240	1.319	3.157	−2.5110	0.0122
0.3	39 737	1.414	3.748	1.420	3.707	−2.4395	0.0149
0.2	31 043	1.527	4.538	1.533	4.522	−2.5939	0.0096
0.1	20 728	1.700	5.805	1.709	5.760	−2.5959	0.0096
0.05	14 208	1.838	7.476	1.850	7.657	**−2.6671**	**0.0078**
0.01	6256	2.129	13.630	2.150	13.823	−2.6073	0.0092
0.001	2535	2.568	29.075	2.605	29.705	−2.2192	0.0267
0.0001	1417	3.054	43.123	3.094	44.872	−1.5482	0.1218
1×10^{-5}	888	3.293	56.374	3.340	60.941	−1.3736	0.1698

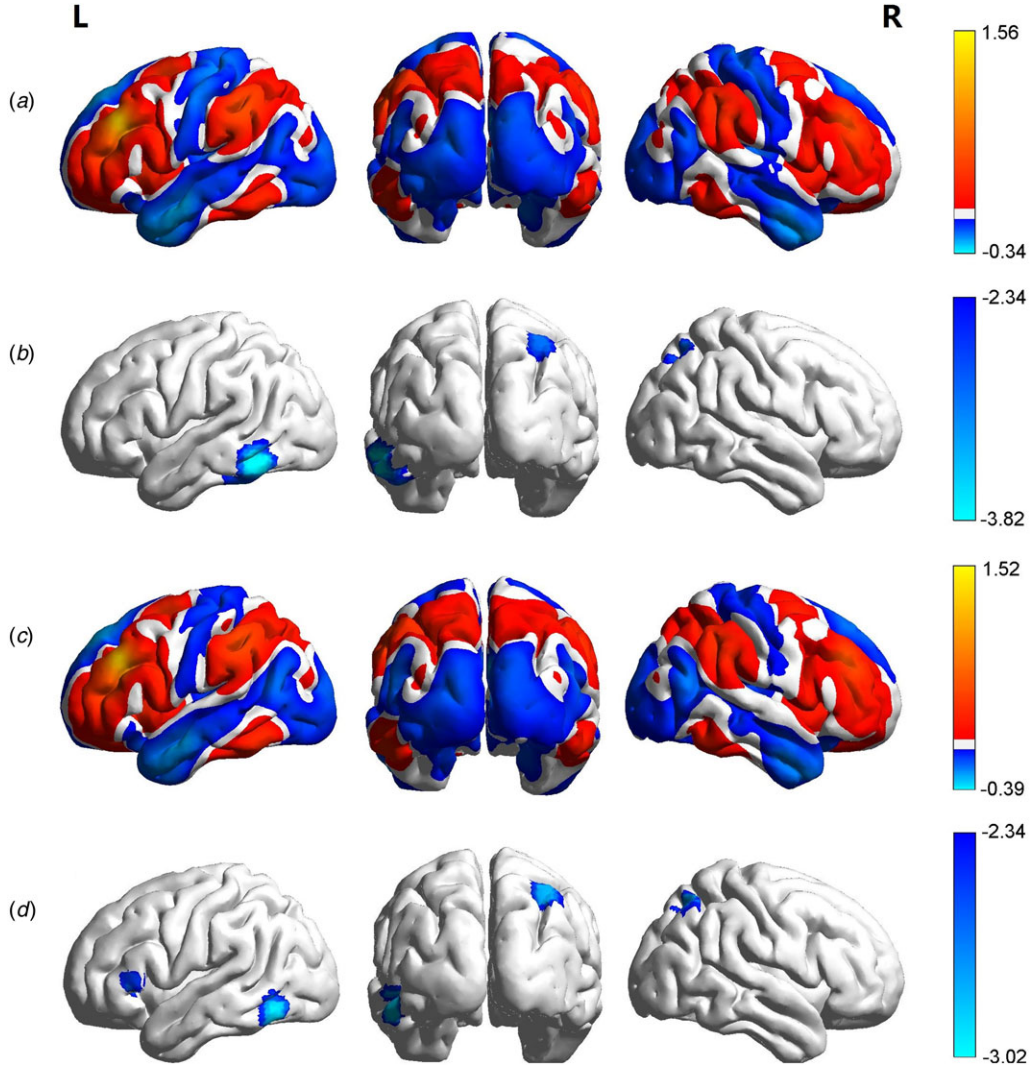

Fig. 1 - Colour online, Colour in print

Fig. 1. Association between the *MIR137* PRS ($p < 0.05$) and the FC of the DLPFC. (*a*) Mean pattern map of the FC in target dataset 1; (*b*) multiple regression testing the association between the *MIR137* PRS and the FC of the left DLPFC in target dataset 1 with AlphaSim correction (single voxel $p < 0.01$, corrected threshold $p < 0.05$ and cluster size threshold CS > 31 voxels); (*c*) mean pattern map of the FC in the target dataset 2; (*d*) multiple regression testing the association between the *MIR137* PRS and the FC of the left DLPFC in target dataset 2 with AlphaSim correction (single voxel $p < 0.01$, corrected threshold $p < 0.05$ and cluster size threshold CS > 31 voxels).

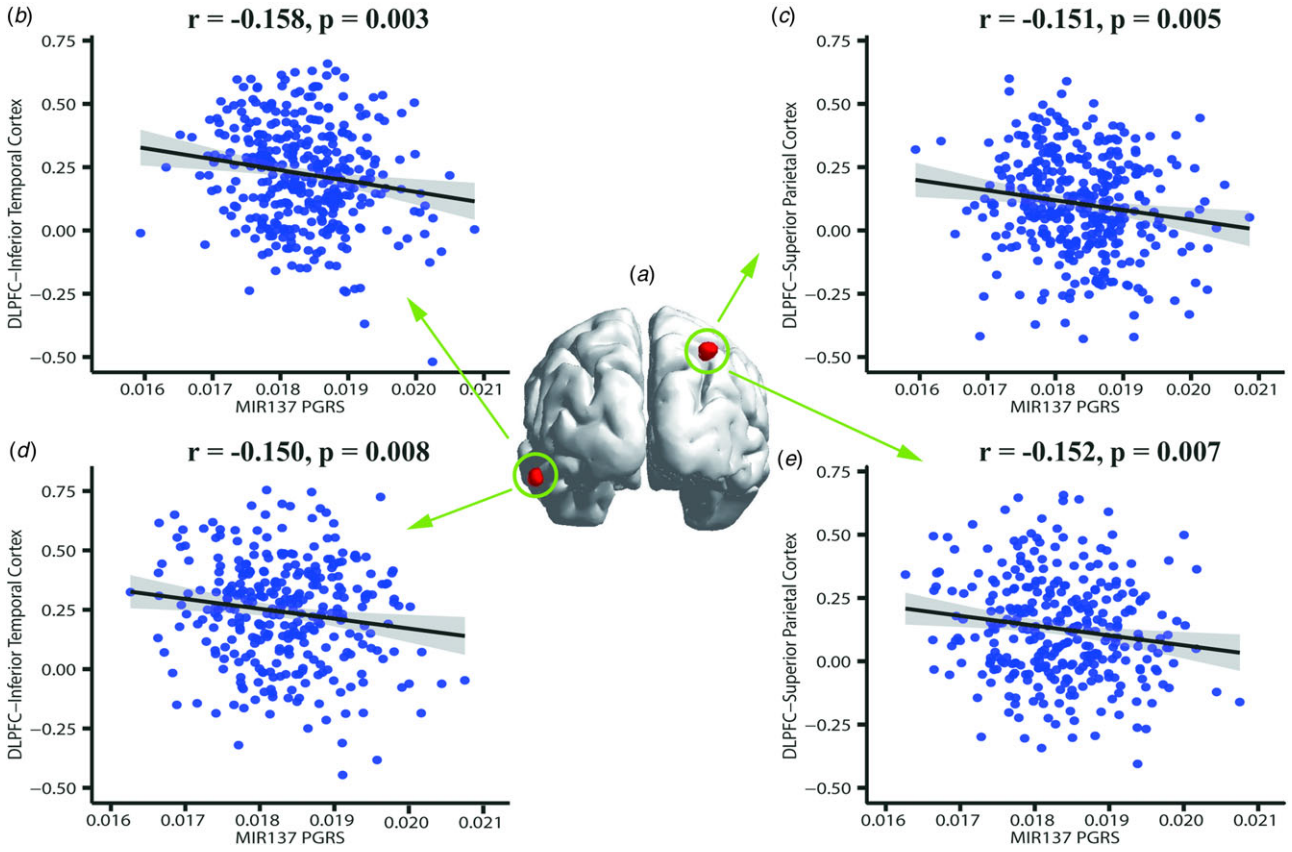

Fig. 2 - Colour online, Colour in print

Fig. 2. Overlapping regions in the association analysis of two independent cohorts with healthy subjects. (*a*) Two overlapping regions whose FCs with the DLPFC were significantly associated with the *MIR137* PRS ($p < 0.05$) in target dataset 1 and target dataset 2; (*b*) scatter plots illustrating the association between the *MIR137* PRS and the FC between the left DLPFC and the overlapping regions in the left inferior temporal cortex in target dataset 1 ($R^2 = 0.0248$); (*c*) scatter plots illustrating the association between the *MIR137* PRS and the FC between the left DLPFC and overlapping regions in the right superior parietal cortex in target dataset 1 ($R^2 = 0.0227$); (*d*) scatter plots illustrating the association between the *MIR137* PRS and the FC between the left DLPFC and overlapping regions in the left inferior temporal cortex in target dataset 2 ($R^2 = 0.0226$); (*e*) scatter plots illustrating the association between the *MIR137* PRS and the FC between the left DLPFC and overlapping regions in the right superior parietal cortex in target dataset 2 ($R^2 = 0.0231$).

2011; Ripke *et al.*, 2014) or a Chinese GWAS (Li *et al.*, 2017), we did not find that they were associated with the risk of schizophrenia in our Han Chinese samples when we compared the patients with the controls. In fact, many studies have investigated whether the *MIR*137 contributes to the susceptibility to schizophrenia in samples from the Han Chinese population. Some studies also observed a significant association between *MIR137* loci and schizophrenia in the Chinese population (Ma *et al.*, 2014; Zhang *et al.*, 2016), but others did not (Guan *et al.*, 2014; Yuan *et al.*, 2014; Sun *et al.*, 2015). The reasons for these inconsistent results may be that Chinese subjects from different geographical areas may exhibit genetic heterogeneity with respect to schizophrenia. In addition, the quite small size of our samples may lower the statistical power in our study (Hong *et al.*, 2012). Overall, our results further confirmed that *MIR137* PRS may better reflect the case-controlled difference in the genetic structure than the singe genetic variant in the Chinese population.

Another major finding of the present study was the consistently significant association of a higher *MIR137* PRS with lower FCs between the DLPFC and the superior parietal cortex and inferior temporal cortex in two independent cohorts with healthy individuals. Previous studies reported that the FC between the DLPFC and the superior parietal region was related to goal-relevant information in target processing (Fellrath *et al.*, 2016) as well as to the organization and maintenance of information (Wendelken *et al.*, 2008). The resting-state activities of the left DLPFC were also found to be strongly correlated with the resting-state activities of the bilateral superior parietal cortex in healthy individuals (Li *et al.*, 2014). In addition, reduced FC between the DLPFC and the inferior temporal cortex was observed in schizophrenia patients under a low spatial working memory load (Kang *et al.*, 2011). Moreover, both the DLPFC (D'Esposito *et al.*, 2000) and the inferior temporal cortex (Woloszyn and Sheinberg, 2009) were found to be activated during working memory or controlled visual processing. These studies, to some extent, indicated that the FCs between the DLPFC and the superior parietal cortex and inferior temporal cortex might be important neuroimaging phenotypes of schizophrenia and may affect the cognitive performance of patients. Intriguingly, the two significant FCs of the DLPFC belonged to the frontoparietal control network. This functionally defined network spans certain portions of the DLPFC, the dorsomedial prefrontal cortex, lateral parietal cortex, and posterior temporal cortex. In addition, the intra-network functional connectivity was found to be disrupted in individuals with a psychotic illness (Baker *et al.*, 2014). Moreover, schizophrenia-related studies have found that the frontoparietal network correlated with performance in episodic memory, verbal memory, processing speed,

goal maintenance, and visual integration (Sheffield *et al.*, 2015; Poppe *et al.*, 2016). The frontoparietal control network is located between the default and dorsal attention networks (Vincent *et al.*, 2008; Spreng *et al.*, 2013) and is thought to play a critical role in mediating the dynamic balance between the default and dorsal attention networks (Spreng *et al.*, 2013). Therefore, as an important bridge, disruption of the frontoparietal control network may lead to abnormities in cortical information processing reflected across multiple brain networks. Previously, several genes, such as *CPLX2* (Hass *et al.*, 2015), *NPSR1* (Neufang *et al.*, 2015), and *COMT val*^{158} *met* (Williams-Gray *et al.*, 2007) were reported to be associated with neural activity in the frontoparietal network. These studies indicated that functional activities and connectivity in the frontoparietal network are genetically influenced. As a gene that showed a quite significant association with schizophrenia, the *MIR137*-regulated genetic structure might influence the neural activity in the frontoparietal network and thus increase schizophrenia vulnerability.

In addition, Mothersill and his colleagues also found that *MIR137* gene influenced the FCs between the right amygdala and frontal regions (Mothersill *et al.*, 2014). Moreover, previous studies consistently reported that the FCs of the right amygdala could be impaired in schizophrenia patients (Bjorkquist *et al.*, 2016; Park *et al.*, 2018; Yue *et al.*, 2018). Therefore, we further explored the relationship between the right amygdala FCs and *MIR137* PRS in our two independent cohorts with healthy individuals. Specifically, we defined the right amygdala as the ROI using the automated anatomical labelling atlas within the Wake Forest University Pickatlas as the previous study did (Mothersill *et al.*, 2014) and calculated the FC map of the ROI to the whole brain using the BRANT toolbox. The same statistical model and multiple comparison correction method with the analysis of the DLPFC were then used to investigate the association between the right amygdala FCs and *MIR137* PRS. Although we found some significantly associated FCs in each independent dataset, however, no any overlapping in two independent cohorts was identified (online Supplementary Fig. S1). This finding might suggest that the effects of *MIR137* polygenic risk on DLPFC FC could not extend to right amygdala, which is another important brain region that has impaired FC in schizophrenia and have previously been reported to be associated with *MIR137*.

Our study reported a consistent finding that the *MIR137* PRS was correlated with the FCs between the DLPFC and the superior parietal cortex and inferior temporal cortex. However, the findings of our study should be interpreted in light of some potential limitations. First, our findings still need to be replicated in a considerably larger sample to improve the statistical power. Second, a relatively weak multiple comparison correction method was used after our imaging genetic analyses. However, the consistency in the results of the two independent cohorts further confirmed the robustness of our findings. Third, our findings were obtained using individuals of Han Chinese ancestry, so our results may need to be further compared with those derived from other ethnic populations. Finally, the participants included in the two healthy cohorts were young (means of 19.4 and 22.7 years old). Although they were clinically determined to be free of psychiatric disorders or family history of such disorders, we could not fully exclude subjects that might develop schizophrenia in the future.

In conclusion, the *MIR137* PRS was significantly higher in the schizophrenia patients than in the normal controls, and a higher *MIR137* PRS was found to be associated with lower FCs between the DLPFC and the superior parietal cortex and inferior temporal cortex in two independent datasets with healthy Han Chinese. These findings may help to identify one of the biological mechanisms modulated by *MIR137* by studying the effects of the *MIR137*-regulated genetic structure on DLPFC functional connectivity. Our findings may provide important clues for understanding the specific contribution of *MIR137*-related genetic variants to the complex phenotypes of schizophrenia.

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Conflict of interest. All of the authors declare no competing interests.

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