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# Association between schizophrenia risk allele dosage of rs6994992 and whole-brain structural and functional characteristics

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ABSTRACT

The rs6994992 polymorphism has been reported as a candidate variant associated with schizophrenia (SZ). Neuroimaging studies have revealed that SZ is associated with widespread structural and functional alterations in brain. However, whether the allele dosage of rs6994992 is associated with brain structural or functional features is unclear. We aimed to investigate the association between the risk allele dosage of rs6994992 and whole-brain structural and functional characteristics and to further explore the relationship between these characteristics and cognition. Magnetic resonance images and the rs6994992 genotype were obtained from 53 healthy participants. A general linear model was used to determine the effects of risk allele dosage of rs6994992 on brain characteristics. Spearman correlation analysis was employed to calculate the correlation between altered brain characteristics and cognitive scores. Our results demonstrated that regions with significant differences in structural characteristics between groups with different dosages of rs6994992 were mainly located in the frontal and temporal lobes, hippocampus and angular gyrus. Moreover, significant regions of functional connectivity (FC) partly overlapped with the structural results. Measurements in those significant regions and FCs were correlated with the cognition scales. This association can inform our understanding of the mechanisms through which rs6994992 variants increase the risk for SZ.

## 1. Introduction

Schizophrenia (SZ) is a highly complex disease with a high heritability rate (Hilker et al., 2018; Law et al., 2006). Previous studies have identified neuregulin-1 (NRG1) as a plausible candidate susceptibility gene for SZ (Stefansson et al., 2002). The NRG1 gene is localized at chromosome 8p12–21 and encodes many structural and functional isoforms through the use of alternative promoters (type I-IV) (Law et al., 2006; Steinthorsdottir et al., 2004). These isoforms are implicated in neuronal-glial development and synaptic plasticity (Kwon et al., 2008; Mei and Xiong, 2008). Recently, there has been significant interest in a polymorphism, rs6994992, in the type IV promoter region of NRG1, which has been reported to be related to an increased risk for schizophrenic and psychotic symptoms, as well as for cognitive impairment in schizophrenic patients (Sprooten et al., 2009; Stefanis et al., 2007). Previous research has found greater transcript levels of type IV NRG1 in brains of both healthy and schizophrenic patients with the TT risk allele (Law et al., 2006). Several studies have provided supportive evidence for the role of NRG1 rs6994992 in SZ pathology (Munafò et al., 2006; Petryshen et al., 2005), though others have not (Crowley et al., 2008; Kim et al., 2012). Two studies detected negative associations between rs6994992 and SZ using phenotypes (age at onset and neuro-cognition) and association analyses; the possible explanation for these negative reports might stem from dissimilar phenotypes and populations with geographically distinct origins. But anyway, based on previous studies, variation at NRG1 rs6994992 may have a pivotal role in SZ and psychosis pathology (Douet et al., 2014).

Magnetic resonance imaging (MRI) studies have reported that NRG1 variations modulate SZ candidate endophenotypes related to brain structure and function (Gao et al., 2018; Mata et al., 2009). Several SZ endophenotypes, including those related to neuropsychological and neurophysiological effects, have been evaluated, and their relation with various candidate genes has been assessed. One of the most promising SZ endophenotypes is structural and functional abnormalities in the brain.

Numerous structural and functional MRI (fMRI) studies have demonstrated that SZ is related to alterations in brain structure and function (Friston and Frith, 1995; Pol et al., 2001; Thompson et al.,

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2001; Zhou et al., 2007). Previous reports have consistently confirmed that abnormal morphological features, either alone or in concert, might be involved in the pathophysiology of SZ (Breier et al., 1992; DR, 1987). In general, structural abnormalities, including enlargement of the lateral ventricles, reduced temporal lobe volume, widespread cortical thinning and decreased surface area, are consistently observed in patients with SZ (Crespo-Facorro et al., 2000; Goldman et al., 2009; Rimol et al., 2010). Structural MRI studies have reported that the frontal and temporal lobes, cingulate gyrus, thalamus (THA), hippocampus (HIP) and basal ganglia are key cortical and subcortical brain regions that show structural abnormalities in SZ (Kawasaki et al., 2007; Pol et al., 2001; Tanskanen et al., 2008). In line with the presence of altered brain structures in SZ patients, considerable evidence from fMRI studies indicates that SZ patients exhibit widespread functional abnormalities in their brain regions (Venkataraman et al., 2012; Wang et al., 2017). Specifically, functional alterations in SZ occur throughout the brain, such as in the frontal lobe, cingulate gyrus, HIP, THA and so on (He et al., 2013; Ikuta et al., 2014; Liu et al., 2016; Pettersson-Yeo et al., 2011). To the best of our knowledge, SZ is a highly heritable psychiatric disease linked to a large number of risk genes (Tee et al., 2017); thus, abnormalities in brain structure and function might be related with the SZ risk variant NRG1 rs6994992. Additionally, cognitive deficit is a core characteristic of SZ (Elvevag and Goldberg, 2000; Green and Nuechterlein, 2004) and is detrimental to functional outcomes in patients with SZ (Green and Nuechterlein, 2004). However, whether altered brain characteristics modulated by rs6994992 have an impact on cognitive performance remains unknown. Thus, it is necessary to further analyze the relationship between these brain alterations and cognition.

At present, few studies have directly investigated the relationship between the SZ risk variant of rs6994992 and whole-brain structural and functional characteristics in healthy individuals. Hence, the first aim of the current study was to evaluate the possible associations between the SZ risk allele dosage[1] effect of rs6994992 and alterations in brain structure and function in healthy individuals. Investigation of the intrinsic relationship between the SZ risk variant of rs6994992 and changes in brain structure and function in healthy individuals would further improve our understanding of the genetic effects of this single nucleotide polymorphism (SNP) on functional mechanisms within the human brain. It is important to investigate the genetic effects of rs6994992 on brain features at the whole-brain level rather than confining the study to specific brain regions. Additionally, cognitive impairment is known to be a core symptom of SZ (Elvevag and Goldberg, 2000). Therefore, the second aim of our study was to further determine whether these brain structural and functional alterations influenced by the risk allele dosage effects of rs6994992 affect cognitive performance. This assessment of the possible association between the SZ risk variant at NRG1 rs6994992 and whole-brain characteristics in healthy participants would be the first step to understanding how genetic background impacts brain structure and function in clinical SZ patients.

## 2. Methods

### 2.1. Ethics statement

We confirm that all experimental protocols were approved by the ethics committee of Shanghai Mental Health Center, and the ethical standards of the institutional and national research committee are in accordance with the 1964 Declaration of Helsinki and its later amendments. All subjects gave written informed consent after receiving a complete description of the study.

[1] Dosage corresponds to the number of carrying T risk allele.

### 2.2. Participants

Fifty-three healthy participants were recruited from the Shanghai Mental Health Center. All participants satisfied the following inclusion criteria: (1) no current or past history of neuropsychiatric illnesses, as determined by using the fourth edition of the Chinese Classification of Mental Disorders (CCMD-4), (2) completion of multidimensional cognitive neuropsychological assessment tests, and (3) age ranging from 16–40 years. The exclusion criteria were as follows: (1) claustrophobia; (2) existence of a neurological disorder; (3) visible macroscopic brain lesions on MRI scans; (4) alcohol, nicotine or drug abuse; (5) existence of metal dentures, pacemakers and other metals in body; or (6) pregnancy.

### 2.3. Cognitive scales measurement

Fifty-three healthy participants were assessed with the Chinese version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Shi et al., 2015). The MCCB was developed as a terminal point for clinical trials aiming to improve cognition in SZ patients (Kern et al., 2008). Internationally recognized cognitive tests for SZ in the MCCB include the trail making test (TMT), brief assessment of cognition in schizophrenia-symbol coding (BACS-SC), Hopkins verbal learning test-revised (HVLT-R), Wechsler memory scale-third edition-spatial span (WMS-III SS), neuropsychological assessment battery-mazes (NAB-M), brief visuospatial memory test-revised (BVMT-R), verbal fluency (VF), Mayer–Salovey–Caruso emotional intelligence test-managing emotions (MSCEIT-ME), and continuous performance test-identical pairs (CPT-IP). Three professional psychiatrists who underwent training for approximately one week confirmed all tests and objectively assessed all scores.

### 2.4. Genotyping

All participants underwent blood collection for genotype determination. The plasma samples were stored at −80 ℃. For each participant, genomic DNA was extracted using the Flexi Gene DNA Kit (Thermo Fisher Scientific™, Waltham, MA, USA). The DNA was stored at −80 ℃ prior to SNP analysis. Samples were genotyped at rs6994992 (CC = 10, CT = 21, and TT = 16) using SNaPshot with a 3730xl DNA Analyzer (Thermo Fisher Scientific™, Waltham, MA, USA). SNP analysis was performed using the Kompetitive Allele Specific PCR genotyping system.

### 2.5. Data acquisition

All MRI data were obtained using a 3.0-Tesla Siemens Trio scanner at the Shanghai Mental Health Center. The participants were instructed to keep their eyes closed, relax, and avoid falling asleep or thinking systematically during the scan.

For each participant, structural T1-weighted images were acquired with the following parameters: echo time (TE) = 2.56 ms; repetition time (TR) = 2530 ms; inversion time = 1100 ms; flip angle (FA) = 7°; field of view (FOV) = 256 mm × 256 mm; data matrix = 256 × 256; slice thickness = 1 mm; and number of coronal slices (without gap) = 192.

The parameters for the functional imaging were as follows: TE = 30 ms; TR = 3000 ms; FA = 90°; FOV = 216 mm × 216 mm; matrix size = 64 × 64; slice thickness = 3.0 mm; number of slices = 45; voxel size = 3 mm × 3 mm × 3 mm; and number of volumes = 170.

### 2.6. Structural MRI data preprocessing

Structural MRI data were analyzed in an automated manner with

the FreeSurfer software suite (http://surfer.nmr.mgh.harvard.edu. version 4.0.1) (Fischl, 2012; Fischl and Dale, 2000). The implemented processing steps included the removal of nonbrain tissue; transformation to a Talairach space; segmentation of the white matter, gray matter and cerebrospinal fluid; and smoothing the T1-weighted images with an isotropic Gaussian kernel (8 mm). White matter and gray matter boundaries were tessellated, and topological defects were automatically corrected. After normalizing the intensity, the transition of the white and gray matter-reconstructed pial boundary was indicated by determining the maximum shift in intensity through surface deformation. Then, the entire cerebral cortex of each subject was visually inspected, and any inaccuracies in the segmentation process were manually corrected. After creation of the cortical representations, parcellation of the cerebral cortex was conducted to classify each brain vertex as either sulcal or gyral, and these vertexes were then subparcellated into 148 cortical regions (74 per hemisphere) via the aparc.a2009s template (Destrieux et al., 2010). Seven common morphological characteristics were selected for further statistical analysis on the basis of this brain template, including the surface area, folding degree, volume, Gaussian curvature, thickness, curvature, and local gyrification index (LGI).

### 2.7. fMRI data preprocessing

Resting-state fMRI data preprocessing was performed in MATLAB 2012a using the Data Processing Assistant for Resting-State fMRI (DPARSF) and the resting-state fMRI data analysis toolkit (REST) (Yan and Zang, 2010). The preprocessing steps for resting-state fMRI data were as follows: (1) discarding the first ten image volumes to adapt to the scanning environment, (2) adjusting of slice timing, (3) realigning the volume to the first volume for correction, (4) spatial normalizing to the Montreal Neurological Institute (MNI) template (resampling with a voxel size of 3 mm × 3 mm × 3 mm), (5) smoothing with an isotropic 8-mm full width at half maximum Gaussian kernel, (6) detrending and filtering (0.01 − 0.1 Hz), and (7) calculating a multiple regression model using the Friston 24 model (Friston et al., 2015) with the white matter, cerebrospinal fluid signal, and head motion parameters as covariates. Data from 6 subjects were excluded for head motion exceeding 1.5 mm in any dimension (x, y and z) or 1.5° of angular motion.

### 2.8. Functional connectivity (FC) analysis

Resting-state FC is commonly used to effectively assess intrinsic connectivity or functional networks in the brain without external stimuli (Beckmann et al., 2005; De Luca et al., 2006) and reflects a one-to-one relationship between two voxels, areas or networks (Liu et al., 2015; Tomasi and Volkow, 2011; Zhuo et al., 2014). We constructed a whole-brain FC network for each participant using a human brain anatomical automatic labeling (AAL) template that included 90 cerebral cortical regions. For each participant, signals for the 90 brain regions were extracted from the AAL atlas, resulting in an FC symmetric matrix that was 90 × 90.

### 2.9. Statistical analysis

For the follow-up statistical analysis, we divided all participants into three groups according to genotype. Analysis of variance (ANOVA) was employed to assess differences in demographics (age and education time), MCCB scores, morphological characteristics (surface area, folding degree, volume, Gaussian curvature, thickness, curvature, and LGI), and FC among the three genotype groups. The $\chi^2$ test was implemented to examine differences in gender among the three groups. Subsequently, the post hoc *t*-test was employed to compare significant differences in regions and FCs between each pair in the three groups. Gender, age, and education time were considered as nuisance covariates in the statistical analysis. All statistical analyses were conducted in Statistical Product and Service Solutions (SPSS 23.0). The significance level for statistical tests was set at $p < 0.05$ (two-tailed) with the Bonferroni correction in SPSS 23.0.

**Table 1**
The distribution of the rs6994992 gene polymorphism.

| SNP | Alleles | Call rate (%) | Test for HWE (*p*-value) | MAF | MAF(1000G-CHB) |
|---|---|---|---|---|---|
| rs6994992 | C/T | 100 | 0.4975 | 0.449 | 0.42548 |

Abbreviations: SNP, single nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency.

### 2.10. Correlation analysis

All significant brain regions or FCs identified in the statistical tests were selected for further correlation analysis. Spearman correlation analysis implemented in SPSS 23.0 was used to detect correlations between significant regions or FCs and the cognition scale scores (MCCB scales). The statistical significance level for structural and functional data was set at $p < 0.05$ and $p < 0.01$, respectively.

## 3. Results

### 3.1. Demographic and genotypic characteristics and cognition scales

Forty-seven Han Chinese participants were finally included in our study. As seen in Table 1, the genotypic distribution of the SNP rs6994992 did not significantly deviate from that expected based on Hardy-Weinberg equilibrium (HWE) ($p = 0.4975$), and the minor allele frequency (MAF) did not differ significantly among the participants. There were no significant differences in gender, age, education time, TMT, BACS-SC, WMS-III SS, NAB-M, BVMT-R, VF, MSCEIT-ME, or CPT-IP among the three genotype groups ($p > 0.05$, Table 2), though there was a significant difference in HVLT-R scores ($p < 0.05$, Table 2).

### 3.2. Structural data analysis

ANOVA of the seven morphological characteristics suggested significant differences in cortical surface area of the left superior temporal pole (L.STP) and the right angular gyrus (R.ANG); the folding degree of the right opercular portion of the inferior frontal gyrus (R.pIFG) and the right fusiform gyrus (R.FG); the volume of the L.STP and the left inferior temporal gyrus (L.ITG); the Gaussian curvature of the right parahippocampal gyrus (R.PHG); the thickness of the left opercular portion of the inferior frontal gyrus (L.pIFG); the bilateral superior temporal gyrus (STG), right middle temporal gyrus (R.MTG), and right inferior temporal gyrus (R.ITG); the curvature of R.ANG; and the LGI of the right supramarginal gyrus (R.SMG) ($p < 0.05$, with Bonferroni correction; Figs. 1–3). The brain regions and its abbreviations corresponded in the AAL template were listed in Table 3.

### 3.3. FC analysis

For the whole-brain FC analysis, brain regions with significant FC among the three genotype groups were predominantly located in the caudate nucleus (CAU), ANG, HIP, ITG, olfactory cortex (OLF), and dorsolateral superior frontal gyrus (dSFG) ($p < 0.05$, with Bonferroni correction, Fig. 4A and Supplementary materials.xls). Subsequently, the post hoc *t*-tests for the CT and TT groups demonstrated that regions with significant FC were mainly located in the CAU, ANG, HIP, ITG, STG, and dSFG ($p < 0.05$, with Bonferroni correction, Fig. 4B and Supplementary materials.xls). The post hoc *t*-tests for the CC and CT groups showed that significant differences in FC were mainly concentrated in the ANG, OLF, HIP, amygdala (AMYG), ITG and THA ($p < 0.05$, with

**Table 2**
Demographic characteristics of healthy participants. .

| Information | rs6994992 CC($n$ = 10) (Mean ± SD) | CT($n$ = 21) (Mean ± SD) | TT($n$ = 16) (Mean ± SD) | $F$-value | $p$-value |
|---|---|---|---|---|---|
| Gender | 5 M/5F | 8 M/13F | 7 M/9F | 0.549 | 0.582[a] |
| Age | 24.00 ± 2.61 | 26.67 ± 1.24 | 25.82 ± 1.68 | 0.192 | 0.826 |
| Education time | 12.00 ± 0.86 | 13.57 ± 6.00 | 12.31 ± 0.72 | 1.458 | 0.244 |
| TMT | 22.90 ± 2.54 | 29.00 ± 2.07 | 32.38 ± 4.45 | 1.709 | 0.193 |
| BACS-SC | 68.90 ± 3.08 | 61.95 ± 2.56 | 61.57 ± 2.97 | 1.537 | 0.226 |
| HVLT-R | 27.50 ± 1.00 | 25.19 ± 0.94 | 22.63 ± 1.35 | 3.737 | 0.032 |
| WMS-III SS | 18.30 ± 0.94 | 16.29 ± 0.71 | 16.06 ± 0.83 | 1.709 | 0.193 |
| NAB-M | 21.00 ± 4.34 | 18.29 ± 1.16 | 16.38 ± 1.62 | 2.142 | 0.129 |
| BVMT-R | 28.60 ± 1.40 | 29.33 ± 0.88 | 26.56 ± 2.11 | 1.003 | 0.375 |
| VF | 24.20 ± 2.28 | 22.76 ± 1.35 | 22.13 ± 1.37 | 0.349 | 0.707 |
| MSCEIT-ME | 83.80 ± 2.11 | 82.86 ± 1.81 | 84.00 ± 1.41 | 0.131 | 0.877 |
| CPT-IP | 2.96 ± 0.17 | 2.76 ± 0.16 | 2.59 ± 0.24 | 0.690 | 0.507 |

Data are means (standard deviation) for age, education time and MCCB scores. Abbreviations: SD, standard deviation; M, male; F, female; TMT, trail making test; BACS-SC, brief assessment of cognition in schizophrenia-symbol coding; HVLT-R, Hopkins verbal learning test-revised; WMS-III SS, Wechsler memory scale-third edition-spatial span; NAB-M, neuropsychological assessment battery-mazes; BVMT-R, brief visuospatial memory test-revised; VF, verbal fluency; MSCEIT-ME, Mayer–Salovey–Caruso emotional intelligence test-managing emotions; CPT-IP, continuous performance test-identical pairs.

[a] The $p$-value was obtained from a two-tailed Pearson chi-square test.

Bonferroni correction, Fig. 4C and Supplementary materials.xls). For post hoc $t$-tests for the CC and TT groups, regions with significant FC differences were mainly located in the CAU, HIP, dSFG, middle frontal gyrus (MFG), STG, and medial superior frontal gyrus (mSFG) ($p < 0.05$, with Bonferroni correction, Fig. 4D and Supplementary materials.xls).

### 3.4. Correlations between altered brain characteristics and MCCB scales

In the correlations between altered morphological characteristics and MCCB scales, a significant negative correlation was detected between the curvature of the R.ANG and VF scores in the TT genotype group ($p = 0.038$, $r = -0.522$; Fig. 2C, Table 4). The R.ITG thickness was inversely correlated with HVLT-R scores for the TT genotype group ($p = 0.020$, $r = -0.575$; Fig. 2D, Table 4). In the CT genotype group, the R.SMG LGI was positively correlated with the BACS-SC, BVMT-R and CPT-IP scores ($p = 0.001$, $r = 0.668$; $p = 0.003$, $r = 0.615$; $p = 0.005$, $r = 0.592$; Fig. 3B–D, Table 4).

For correlations between the significant FCs and MCCB scales, we detected that FC values with significant differences were significantly correlated with the speed of processing (TMT, VF, and BACS-SC).

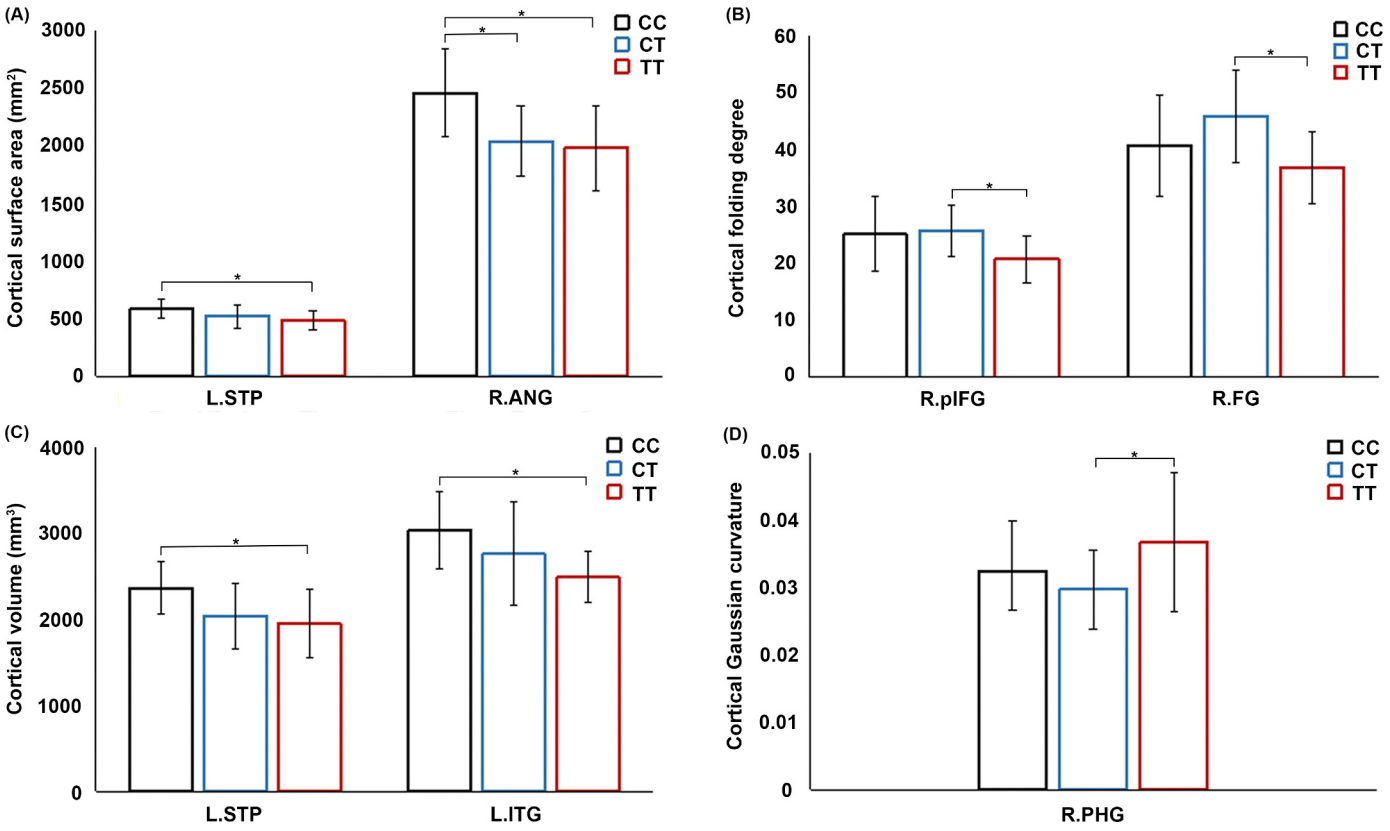


**Fig. 1.** Regions with significant differences in whole-brain structural characteristics ($p < 0.05$, two-tailed, Bonferroni correction). (A–D) Regions with significant differences in cortical surface area (L.STP and R.ANG), cortical folding degree (R.pIFG and R.FG), cortical volume (L.STP and L.ITG) and cortical Gaussian curvature (R.PHG). The error bars denote standard deviations. Abbreviations: L, left; R, right; STP, superior temporal pole; ANG, angular gyrus; pIFG, opercular part of inferior frontal gyrus; FG, fusiform gyrus; ITG, inferior temporal gyrus; PHG, parahippocampal gyrus.

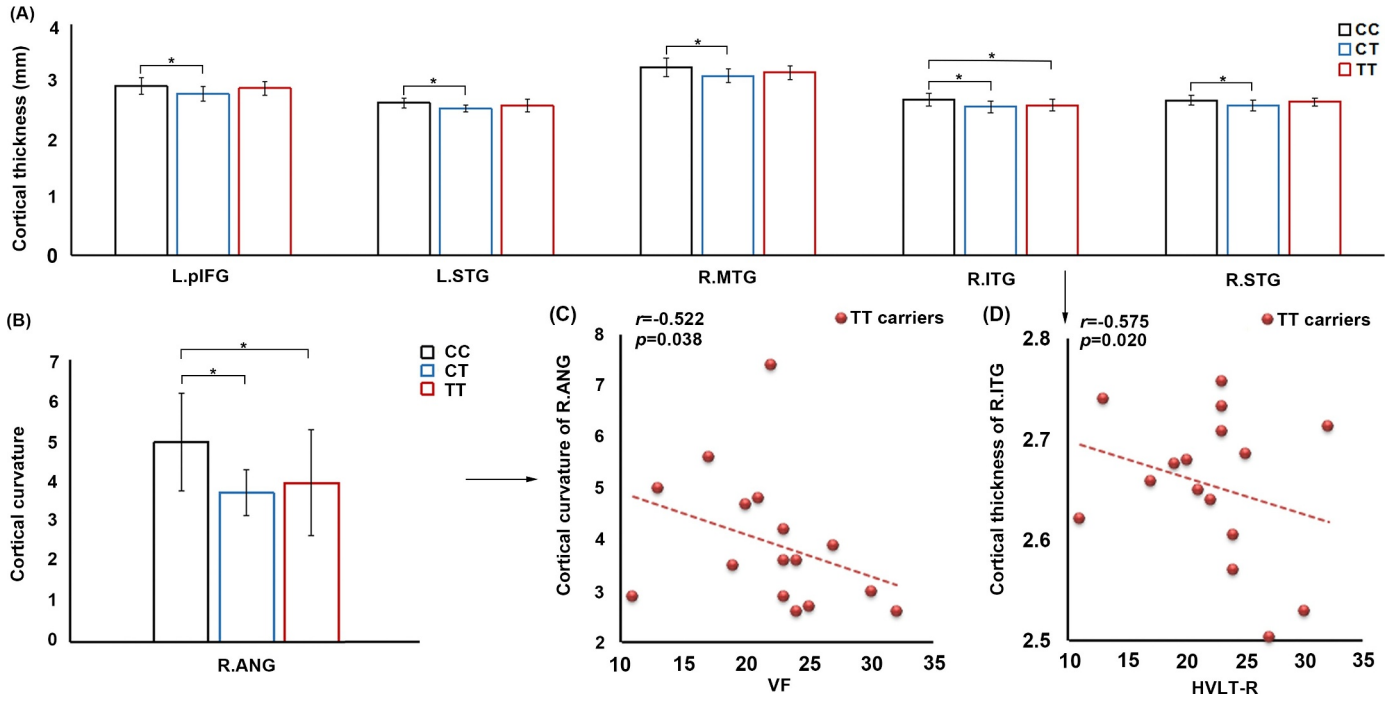


**Fig. 2.** Significant differences in cortical thickness and curvature and correlations with MCCB cognition scales. (A) Brain regions with significant differences in cortical thickness, including the L.pIFG, L.STG, R.MTG, R.ITG and R.STG ($p < 0.05$, two-tailed, Bonferroni correction). (B) The brain region (R.ANG) with significant differences in cortical curvature ($p < 0.05$, two-tailed, Bonferroni correction). (C) Correlation between the R.ANG curvature and VF in TT carriers. (D) Correlation between the cortical thickness of R.ITG and HVLT-R in TT carriers. The error bars denote standard deviations. Abbreviations: L, left; R, right; pIFG, opercular part of inferior frontal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; ANG, angular gyrus; VF, verbal fluency; HVLT-R, Hopkins verbal learning test-revised.

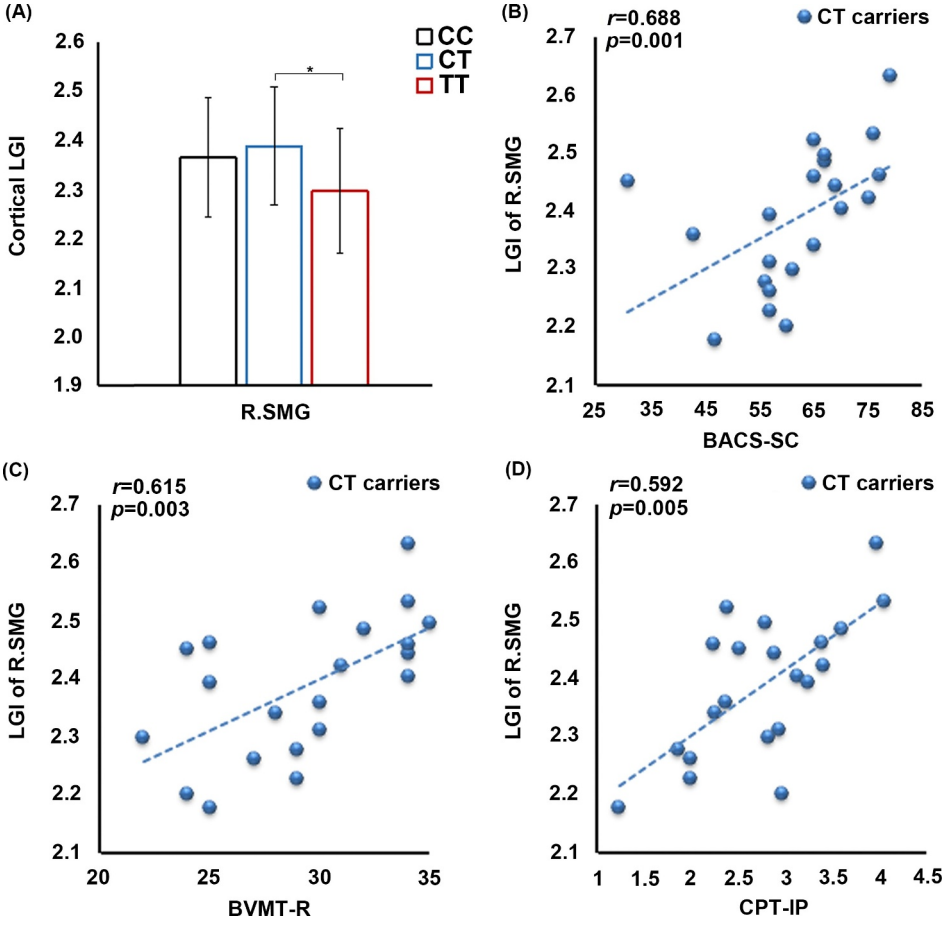


**Fig. 3.** Brain region with significant differences in LGI and correlations with MCCB cognition scales. (A) The R.SMG region showed significant differences in LGI ($p < 0.05$, two-tailed, Bonferroni correction). (B-D) Correlations between the R.SMG LGI and BACS-SC, BVMT-R, and CPT-IP scores in CT carriers. The error bars denote standard deviations. Abbreviations: R, right; SMG, supramarginal gyrus; LGI, local gyrification index; BACS-SC, brief assessment of cognition in schizophrenia-symbol coding; BVMT-R, brief visuospatial memory test-revised; CPT-IP, continuous performance test-identical pairs.

**Table 3**
The brain regions in the aparc.a2009s template correspond to the brain regions in the AAL template.

| Regions of aparc.a2009s template | Regions of AAL template | Abbreviations (AAL) |
|---|---|---|
| Fronto-marginal gyrus (of Wernicke) and sulcus | Supramarginal gyrus | SMG |
| Opercular part of the inferior frontal gyrus | Opercular part of inferior frontal gyrus | pIFG |
| Lateral occipito-temporal gyrus (fusiform gyrus, O4-T4) | Fusiform gyrus | FG |
| Parahippocampal gyrus, parahippocampal part of the medial occipito-temporal gyrus, (T5) | Parahippocampal gyrus | PHG |
| Angular gyrus | Angular gyrus | ANG |
| Planum polare of the superior temporal gyrus | Superior temporal pole | STP |
| Middle temporal gyrus (T2) | Middle temporal gyrus | MTG |
| Inferior temporal sulcus | Inferior temporal gyrus | ITG |
| Superior temporal sulcus (parallel sulcus) | Superior temporal gyrus | STG |

AAL: anatomical automatic labeling.

Specifically, Spearmen correlation showed a significant positive correlation between the FC of the left median cingulate and paracingulate gyri (L.DCG) and the L.ITG and TMT scores in the TT genotype group ($p = 0.002$, $r = 0.724$; Fig. 5A, Table 5). A significant positive correlation was also detected between the FC of the left MFG (L.MFG) and the L.ANG and VF scores in the TT genotype group ($p = 0.006$, $r = 0.654$; Fig. 5B, Table 5). The FCs of the left CAU (L.CAU) and right MFG (R.MFG), the right CAU (R.CAU) and R.MFG, the L.CAU and right inferior parietal lobe (R.IPL), and the R.CAU and left inferior parietal lobe (L.IPL) were inversely correlated with BACS-SC scores ($p = 0.002$, $r = -0.619$; $p = 0.010$, $r = -0.551$; $p = 0.009$, $r = -0.553$; $p = 0.008$, $r = -0.565$; Fig. 5C–F, Table 5) in the CT genotype group.

## 4. Discussion

The present study explored the association between the dosage of the SZ risk variant of rs6994992 and whole-brain structural and functional alterations in healthy individuals. We then further explored the relationship between these brain alterations and cognition. The four major findings are as follows: (1) significant differences among the three genotype groups in whole-brain structural characteristics were predominantly observed in the temporal lobe (correlated with HVLT-R), frontal lobe (correlated with BACS-SC, BVMT-R, and CPT-IP), ANG (correlated with VF), and HIP; (2) regions with significant FC differences among the three genotype groups were predominantly located in the CAU, ANG, HIP, and parts of the frontal and temporal lobes, which roughly overlapped with the significant differences in brain structure; (3) harboring one risk allele was associated with FC in cortical regions, while harboring two risk alleles was related with FC in subcortical regions; and (4) significant differences in the FC among the three groups were mainly attributable to differences between the CT and TT groups, and related FC values were significantly correlated with the speed of processing scores.

It is widely believed that SZ is characterized by gray matter abnormalities in multiple brain regions, especially within the frontal, temporal and parietal structures (Nenadic et al., 2015; Pina-Camacho

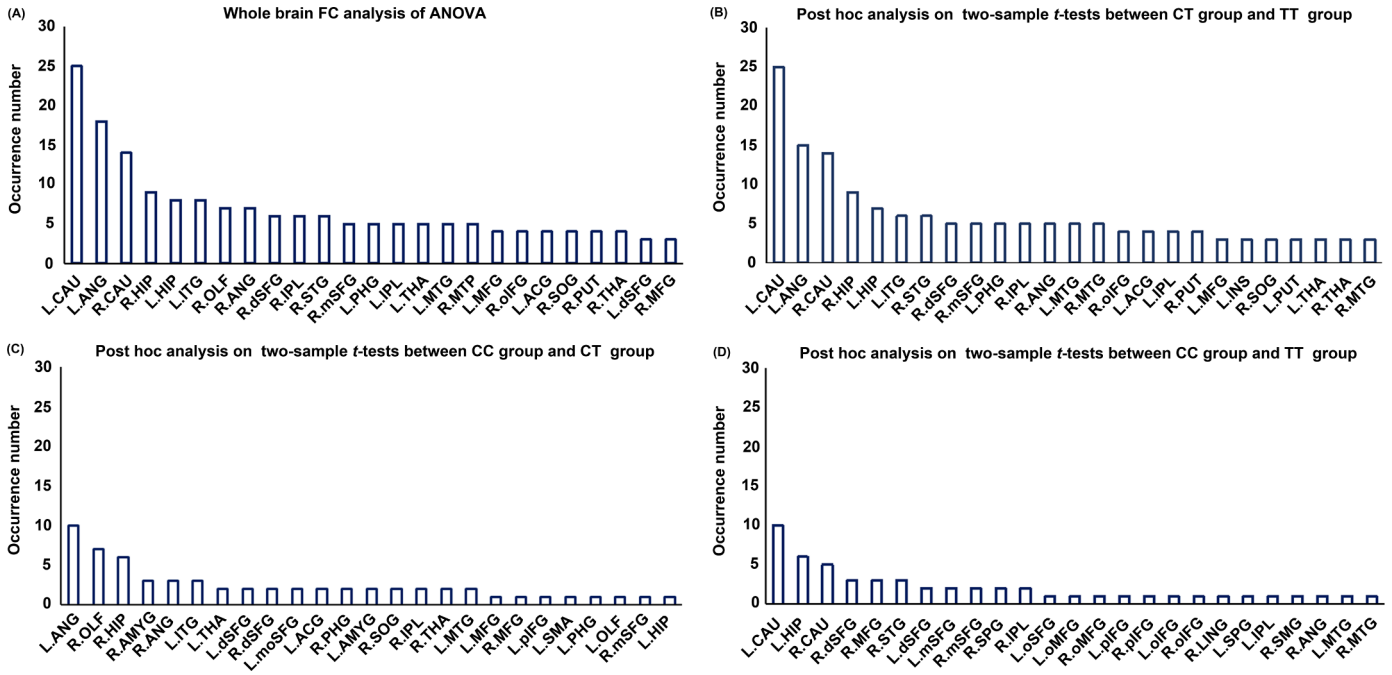


**Fig. 4.** Regions with significant differences in whole-brain FC ($p < 0.05$, two-tailed, Bonferroni correction). (A–D) Number of brain regions with a significant difference in FC based on ANOVA and post hoc *t*-tests. The *x*-axis is the brain region with significant differences and the *y*-axis represents the number of brain regions with significant differences. More detailed information on the significant FCs and number of significant regions is provided in the Supplementary materials. Abbreviations: L, left; R, right; FC, functional connectivity; CAU, caudate nucleus; ANG, angular gyrus; HIP, hippocampus; ITG, inferior temporal gyrus; OLF, olfactory cortex; dSFG, dorsolateral of superior frontal gyrus; IPL, inferior parietal lobe; STG, superior temporal gyrus; mSFG, medial superior frontal gyrus; PHG, parahippocampal gyrus; THA, thalamus; MTG, middle temporal gyrus; MTP, middle temporal pole; MFG, middle frontal gyrus; oIFG, orbital part of inferior frontal gyrus; ACG, anterior cingulate and paracingulate gyri; SOG, superior occipital gyrus; PUT, putamen; INS, insula; AMYG, amygdala; moSFG, superior frontal gyrus, medial orbital; pIFG, opercular part of inferior frontal gyrus; SMA, supplementary motor area; oSFG, orbital part of superior frontal gyrus; SPG, superior parietal gyrus; oMFG, orbital part of middle frontal gyrus; LING, lingual gyrus.

**Table 4**
The correlations between significant regions and MCCB cognitive scales.

| Characteristics of structure | Brain regions | Post hoc *t*-test | Genotype | MCCB Scales | *r* | *p*-value |
|---|---|---|---|---|---|---|
| Curvature | R.ANG | CC-TT | TT | VF | −0.522 | 0.038 |
| Thickness | R.ITG | CC-TT | TT | HVLT-R | −0.575 | 0.020 |
| LGI | R.SMG | CT-TT | CT | BACS-SC | 0.668 | 0.001 |
| LGI | R.SMG | CT-TT | CT | BVMT-R | 0.615 | 0.003 |
| LGI | R.SMG | CT-TT | CT | CPT-IP | 0.592 | 0.005 |

The *r* is the correlation coefficient which was obtained by Spearman correlation analysis in SPSS 23.0 and *p*-value is the significance of *r*. Abbreviations: R, right; LGI, local gyrification index; ANG, angular gyrus; ITG, inferior temporal gyrus; SMG, supramarginal gyrus; VF, verbal fluency; HVLT-R, Hopkins verbal learning test-revised; BACS-SC, brief assessment of cognition in schizophrenia-symbol coding; BVMT-R, brief visuospatial memory test-revised; CPT-IP, continuous performance test-identical pairs.

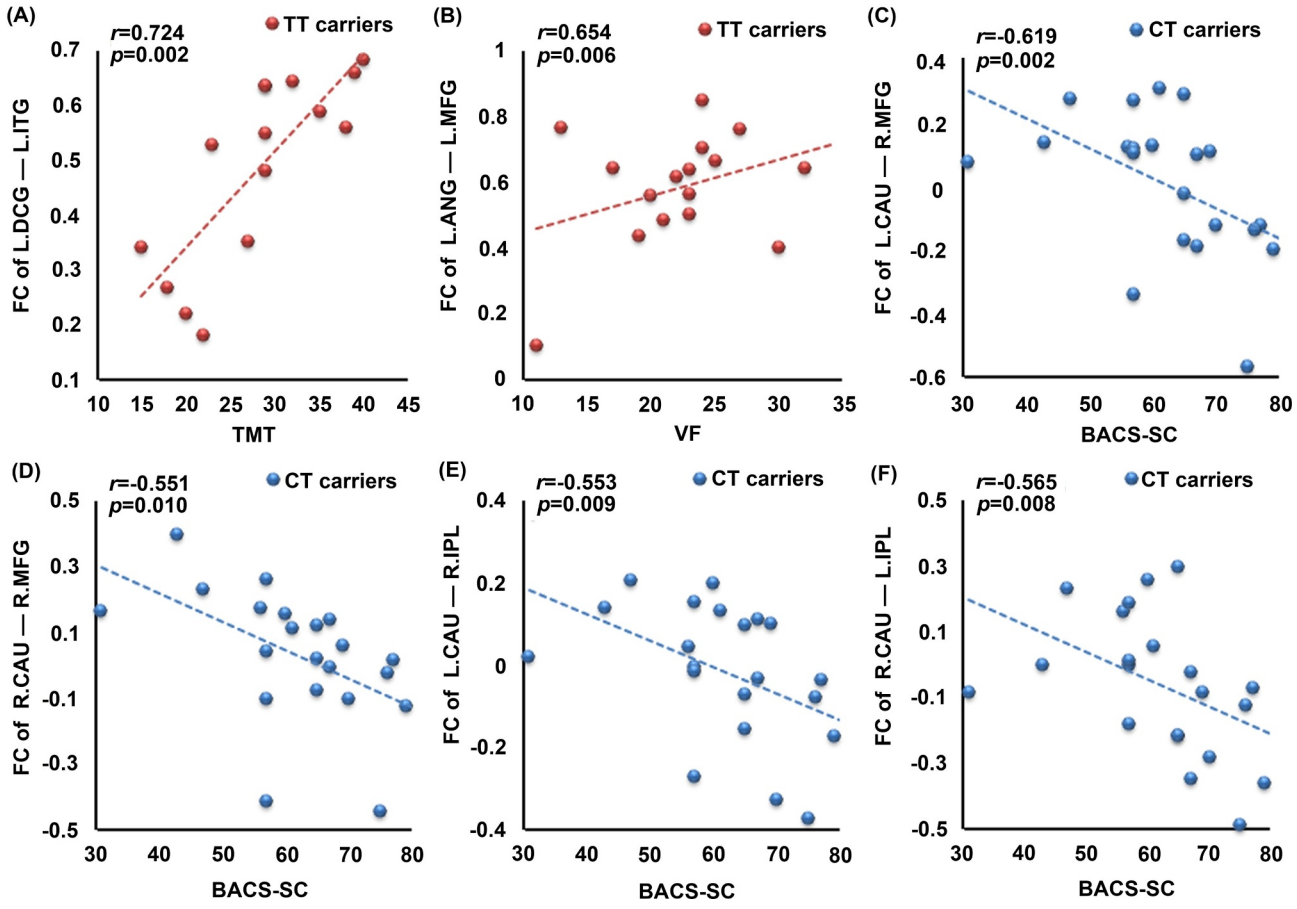


**Fig. 5.** Correlations between FCs with significant differences and MCCB cognition scales in post hoc *t*-tests for CT and TT groups. (A) The correlation between the L.DCG - L.ITG FC and the TMT scores in TT carriers. (B) The correlation between the L.ANG - L.MFG FC and the VF scores in TT carriers. (C-F) The correlations between FCs in L.CAU - R.MFG, R.CAU - R.MFG, L.CAU - R.IPL, and R.CAU - L.IPL and the BACS-SC scores in CT carriers. Abbreviations: L, left; R, right; FC, functional connectivity; TMT, trail making test; VF, verbal fluency; BACS-SC, brief assessment of cognition in schizophrenia-symbol coding; DCG, median cingulate and paracingulate gyri; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; ANG, angular gyrus; CAU, caudate nucleus; IPL, inferior parietal lobe.

et al., 2015). In the current study, we observed that regions with significant differences in seven morphological characteristics were mainly located in the frontal lobe, temporal lobe, ANG, and HIP. To the best of our knowledge, the frontal lobe is the prototypical center of higher order cognitive processing and plays an important role in the pathophysiology of SZ (Barch and Dowd, 2010; Meyer-Lindenberg et al., 2002). Temporal regions, especially the STG and ANG, are related to word fluency, word encoding and recognition (Ragland et al., 2005, 2003; Yurgeluntodd et al., 1996). Both the frontal and temporal lobes have been associated with a set of cognitive processes that are affected in schizophrenic patients (Antonova et al., 2004). The HIP plays a critical role in recollection (Lehn et al., 2009; Ragland et al., 2009). The significant differences in those regions may be caused by specific regulation of the SZ risk gene NRG1. Previous studies have reported that NRG1 is expressed throughout the human brain, including in the frontal cortex, temporal lobe and HIP (Law et al., 2004). More interestingly, the SNP rs6994992 has been reported to be associated with alterations in brain activation in the frontal/temporal lobes in SZ patients (Hall et al., 2006). Variations at rs6994992 have been found to influence the activity of the type IV promoter region of NRG1 (Wei et al., 2007). Previous reports suggest that individuals homozygous for this risk allele have the highest NRG1 type IV expression levels and provide evidence for an allele dose-dependent effect that is more pronounced in SZ patients (Law et al., 2006). Therefore, significant differences between different rs6994992 genotypes in the regions mentioned above are explicable and logical. Such alterations in

**Table 5**
The correlations between significant FCs and MCCB cognitive scales.

| Connections | Post hoc *t*-test | Genotype | MCCB Scales | *r* | *p*-value |
|---|---|---|---|---|---|
| L.DCG - L.ITG | CT - TT | TT | TMT | 0.724 | 0.002 |
| L.MFG - L.ANG | CT - TT | TT | VF | 0.654 | 0.006 |
| L.CAU - R.MFG | CT - TT | CT | BACS-SC | −0.619 | 0.003 |
| R.CAU - R.MFG | CT - TT | CT | BACS-SC | −0.551 | 0.010 |
| R.CAU - L.IPL | CT - TT | CT | BACS-SC | −0.565 | 0.008 |
| L.CAU - R.IPL | CT - TT | CT | BACS-SC | −0.553 | 0.009 |

The *r* is the correlation coefficient which was obtained by Spearman correlation analysis in SPSS 23.0 and *p*-value is the significance of *r*. Abbreviations: L, left; R, right; TMT, trail making test; VF, verbal fluency; BACS-SC, brief assessment of cognition in schizophrenia-symbol coding; DCG, median cingulate and paracingulate gyri; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; ANG, angular gyrus; CAU, caudate nucleus; IPL, inferior parietal, but supramarginal and angular gyri.

the brain may compromise cortical and subcortical function through the role of the NRG1 gene and reflect, at least in part, the contribution of this gene to the genetic risk of SZ.

In our study, correlation analysis between alterations in morphological structures and MCCB cognition scales revealed a significant negative correlation between the curvature of the R.ANG and VF scores. Specifically, greater R.ANG curvature corresponded to poorer VF scores. To our knowledge, ANG is relevant for complex language functioning (Niznikiewicz et al., 2000), and this correlation confirms this knowledge. We also found that the R.SMG LGI was positively correlated with BACS-SC, BVMT-R, and CPT-IP scores. Given the important findings of these correlation analyses, we further studied these regions, which correlated with the cognitive scales, and found that they were predominantly located in Wernicke's area. Our findings might demonstrate that genetic variation at rs6994992 is involved in alterations in brain structure and that these alterations could further impact the cognitive performance of Wernicke's area.

Regions with significant differences in whole-brain FC were mainly located in the CAU, ANG, HIP, and portions of the frontal and temporal lobes. The frontal and temporal cortex are cortical regions, while the CAU, HIP, and ANG are subcortical regions. These results observed in cortical and subcortical regions would indicate more pervasive alterations in brain connectivity under the genetic effects of the schizophrenic risk variant of rs6994992. A possible explanation for these results might relate to the widespread expression of NRG1 in the human brain (Law et al., 2004). Additionally, these significant regions were roughly consistent with the significant differences in brain structure, which have been frequently observed in the main areas of dissociation in SZ patients (Friston, 2002; Pettersson-Yeo et al., 2011; Volk and Lewis, 2010; Woodward et al., 2011). These functional results may improve our understanding of the underlying association between the schizophrenic risk variant of rs6994992 and brain functional activity.

As illustrated in Fig. 4, the top six brain areas with significant differences in FC, based on ANOVA, are the same as those identified using the post hoc analysis between the CT and TT groups. This finding indicates that the significant differences among the three groups were primarily attributable to the differences between the CT and TT groups. In the post hoc *t*-test analysis of the CC and CT groups, the first two brain regions with significant FC differences were the left ANG and right OLF, which may imply that carrying one risk allele (CT) is primarily associated with FCs in cortical regions. The post hoc *t*-test analysis of the CC and TT groups showed that the first two regions with the significant FC differences were the left CAU and left HIP, which might demonstrate that carrying two risk alleles (TT) is predominantly implicated in FC in subcortical regions. These two post hoc *t*-tests demonstrated that different allele dosage of the SZ risk variant of rs6994992 would have different effects on the distribution of FC in the human brain. These are interesting findings and fully reflect the allele dose effect of NRG1 rs6994992 on brain FC. As described by previous studies, NRG1 rs6994992 is the only functional Icelandic haplotype polymorphism that has been reported to be implicated in cognition (Buonanno, 2010). Our results of correlations between FCs and cognitive scales is consistent with previous findings. Specifically, the correlation analysis revealed that FC has a significant correlation with the speed of processing (TMT, VF, and BACS-SC). Particularly, the FC between ANG and MFG was correlated with VF, which is in line with the structural correlation analysis. These functional results may contribute to a more comprehensive understanding of the intrinsic relationship between aberrant FC affected by genetic variation at rs6994992 and the clinical cognitive symptoms in SZ patients.

There are three limitations of the present study. First, the genetic influences of the different genotypes on brain structure and function need to be replicated with a larger sample. Second, we analyzed the genetic effects of only one SNP; the effects of multiple SNPs or genes on the structure and function of the brain are more likely to be epistatic or additive. Third, further studies using different structural and functional characteristics are required to validate our findings.

## 5. Conclusions

In the current study, we investigated how a genetic variant in an SZ candidate SNP, rs6994992, affects whole-brain structural and functional characteristics in healthy individuals, as well as the relationship between the altered characteristics and cognition. We showed that structural and functional alterations in the entire brain largely overlapped, especially in the frontal lobe, temporal lobe, HIP, and ANG. The pattern of changes in brain structure and function may have significant implications for understanding the effects of genetic variation at NRG1 rs6994992 on brain alterations in the early stages of SZ. Additionally, these brain alterations were significantly correlated with cognition scales, implying that cognitive performance is generally influenced by brain structural and functional changes. The association between the rs6994992 risk allele dosage and brain structural and functional characteristics in healthy participants can provide further evidence for the characterization of rs6994992 as a candidate SNP implicated in SZ. More importantly, this association can inform our understanding of the mechanisms through which NRG1 rs6994992 increases the risk for SZ, which was the ultimate goal of the current study.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.05.005.

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