Common variant of NOTCH4 gene modulate functional connectivity of occipital cortex and its relationship with schizotypal traits

CURRENT STATUS: UNDER REVISION

xiaohui xie (Former Corresponding Author)
First Affiliated Hospital of Anhui Medical University
ORCiD: https://orcid.org/0000-0002-6324-2731

Meidan Zu
First Affiliated Hospital of Anhui Medical University

Long Zhang
First Affiliated Hospital of Anhui Medical University

Tongjian Bai
First Affiliated Hospital of Anhui Medical University

Ling Wei
First Affiliated Hospital of Anhui Medical University

Wanling Huang
First Affiliated Hospital of Anhui Medical University

Gong-Jun Ji
Anhui Medical College

Bensheng Qiu
China University of Science and Technology

Panpan Hu
First Affiliated Hospital of Anhui Medical University

Yanghua Tian
First Affiliated Hospital of Anhui Medical University

Kai Wang (New Corresponding Author)
wangkai1964@126.com Corresponding Author
DOI: 10.21203/rs.3.rs-15827/v1

SUBJECT AREAS
Psychiatry

KEYWORDS
NOTCH4, rs204993, functional connectivity strength, occipital cortex, schizotypal traits
Abstract
Background Schizotypal traits are considered as heritable traits and the endophenotype for schizophrenia. A common variant in NOTCH4 gene, rs204993, has been linked with schizophrenia, but the neural underpinnings are largely unknown.

Methods In present study, we compared the difference of brain function between different genotype of rs204993 and its relationship with schizotypal traits among 402 Chinese Han healthy volunteers. The brain function was evaluated with functional connectivity strength (FCS) using resting-state functional magnetic resonance image (rs-fMRI). The schizotypal traits were measured by the schizotypal personality questionnaire (SPQ).

Results Our results suggested that the carriers with AA genotype showed reduced FCS in left occipital cortex than the carriers with AG and GG genotype and the carriers with AG genotype showed reduced FCS in left occipital cortex than the carriers with GG genotype. The FCS values in the left occipital lobe were negatively associated with the SPQ scores and its subscale scores within the carriers with GG genotype, but not within the carriers with AA or AG genotype.

Conclusions Our results suggested that the common variant in NOTCH4 gene, rs204993, modulate the function of occipital cortex, which may contribute to the schizotypal traits. These findings provided insight for genetic effect on schizotypal traits and its potential neural substrate.

Background
Schizophrenia is a chronic, severe mental disorder, affecting approximately 1% of the population worldwide (Andreasen, 1995). Besides, some individuals present preclinical performance of schizophrenia called schizotypal traits (Rado, 1953). Schizotypal traits refer to a set of traits, continually distributed in the general population, that resemble some of the symptoms of schizophrenia. Schizotypal traits provide important insight to understand the origins of schizophrenia (Gottesman and Gould, 2003). Adrian Raine et al. concluded that structural and functional alteration in brain induced by genetic and early environmental influences contribute to the development of schizotypy (Raine, 2006). Indeed, schizotypal traits are more frequent in first-degree relatives of patients with schizophrenia, suggesting a genetic link between schizotypal traits and schizophrenia (Vollema and
Postma, 2002). The schizophrenia-risk gene also contributes to the presence of schizotypal traits (Baker and Skuse, 2005; Stefanis et al., 2004). Hence, schizophrenia-risk gene may have potential modulatory effect on schizotypal traits.

Although previous studies have found that some genes are susceptibility for schizophrenia (Ikeda et al., 2011; Ripke, 2011), only a small percentage of the genes have been consistently studied among different racial populations. The NOTCH4 (neurogenic locus notch homolog protein4) gene, located in the major histocompatibility complex (MHC) region of 6p21.3 in human, was highly associated with schizophrenia among different racial populations (Aberg et al., 2013; Luo et al., 2004; Wei and Hemmings, 2000). Wei and Hemmings found that the NOTCH4 locus was involved in susceptibility to schizophrenia in a British population (Wei and Hemmings, 2000). Subsequent studies also confirmed the relationship between schizophrenia and NOTCH4 polymorphisms, including microsatellite (Glatt et al., 2005) and single nucleotide polymorphisms (SNPs) (e.g., rs520692, rs3131296, and rs2071287) (Ikeda et al., 2013; Tochigi et al., 2007; Wang et al., 2006). Recently, study among 218 Taiwanese families has found another SNP, rs204993 with significant relationship with schizophrenia through testing the association of the entire genomic region of NOTCH4 (Liu et al., 2007). Specially, the AA genotype of rs204993 was associated with a higher risk for schizophrenia in the Chinese Han population (Zhang et al., 2015a). As the intermediary role of brain function for the genetic effect on schizophrenia, there may be significant differences of brain function in schizophrenia-related region between distinct genotypes of rs204993.

Imaging genetics may provide a neural basis to explain how the gene affects the occurrence and development of diseases via grafting the link between gene and brain diseases (Chen et al., 2013). Resting-state functional magnetic resonance imaging (rsfMRI), as a task-free and noninvasive measurement tool, has been applied in several mental disorders (Raichle et al., 2001). Functional connectivity strength (FCS), which identifies functional hubs of human brain networks based on the graph theory method (Buckner et al., 2009), is a developed method to test the connectivity of each voxel with all other voxels in the brain (Zhu et al., 2017). The FCS analysis has been used to explore neural mechanism in various psychiatric disorders (Wang et al., 2015), including schizophrenia and
schizotypal traits (Chen et al., 2018; Zhang et al., 2014). For example, decreased FCS in the bilateral occipital cortex and the right sensorimotor cortex as well as increased FCS in the bilateral temporal cortex, hippocampus and the left prefrontal cortex were observed in schizophrenia (Zhu et al., 2017). Besides, schizotypal traits presented the abnormal connectivity in the default mode network compared with healthy controls (Zhang et al., 2014).

In present study, we aimed at investigating the genetic effect of schizophrenia-related gene (NOTCH4 rs204993 genotype) on brain function and its relationship with schizotypal traits among healthy volunteers. Based on the above findings, we proposed that the schizophrenia-risk rs204993 genotype (AA genotype) may be linked with attenuated function in schizophrenia-related brain regions, which contribute to the schizotypal traits.

**Methods**

**Participants**

We totally recruited 641 eligible healthy Chinese Han participants from the Anhui Medical University in Hefei, Anhui province. All subjects were accepted with the Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Angell, 1996), in order to exclude any psychiatric disorder. Besides, other exclusion criteria included: neurological diseases, alcohol or drug abuse, brain injury, or visible brain structure abnormity, excessive motion during MRI scanning (> 2.0 mm, 2.0°). Participants with a first-degree relative with a neurological or psychiatric disorder were also excluded. Of these participants, a total of 239 participants with were excluded because of missing NOTCH4 genotype data or poor MRI data. Finally, a total of 402 participants were included in the data analysis of the current study. The study was approved by the Anhui Medical University Ethics Committee, and all participants signed informed consent forms after giving a thorough description of the study.

**SNP Genotyping**

Blood samples were collected to obtain DNA with standard procedures. The genotyping of all participants was determined in comparison with control DNA confirmed by sequencing in the SNP pattern. The NOTCH4 rs204993 were then genotyped by the SNP scan technique (Genesky Biotechnologies Inc., Shanghai, China) according to a previous study (Zhang et al., 2015b). Finally, the
genotype of NOTCH4 rs204993 was divided into the AA, GA and GG.

Schizotypal Traits Evaluation
The schizotypal traits was evaluated with the schizotypal personality questionnaire (SPQ) (Raine, 1991). The SPQ include 74-item with a “yes/no” response to assess schizotypal traits in the general population. Besides, the questionnaire subscale scores reflect different schizotypal dimensional features, including interpersonal, cognitive-perceptual and disorganized factors (Raine et al., 1994). In present study, we used the Chinese version SPQ, which has good internal consistency (0.95) and the reliability value (0.86) for Chinese population (Chen et al., 1997).

Neuroimaging Data Acquisition
We acquired rsfMRI images of participants at the University of Science and Technology of China, Hefei, Anhui Province. During scanning, all participants were instructed to keep their eyes closed without moving the body and not to think of anything in particular. Functional images were conducted with a 3.0 T MRI scanner (Signa HDxt 3.0 T; GE Healthcare, Buckinghamshire, UK) composed of 217 echo-planar imaging volumes with the following parameters: TR = 2400 ms; TE = 30 ms; flip angle = 90°; matrix size = 64 × 64; field of view = 192 × 192 mm²; slice thickness = 3 mm; 46 continuous slices (voxel size = 3 × 3 × 3 mm³). T1-weighted anatomic images with 188 slices were also acquired in sagittal orientation (TR = 8.16 ms; TE = 3.18 ms; flip angle = 12°; field of view = 256 × 256 mm²; slice thickness = 1 mm; voxel size = 1 × 1 × 1 mm³).

Functional Image Preprocessing
Data Processing Assistant for Resting-State Functional MRI imaging toolkit (DPARSF) was used for the functional image preprocessing, which based on software that Resting State Functional MR Imaging Toolkit (REST) and statistical parametric mapping software package (SPM8) (Chao-Gan and Yu-Feng, 2010; Song et al., 2011).

We discarded the first 5 volumes of data to ensure stable longitudinal magnetization and the rest volumes were corrected for slice timing and head motion. Next, we normalized the structural T1 image to the Montreal Neurological Institute (MNI) space based on T1 image unified segmentation with a 12-parameter non-linear transformation. Finally, the data were nuisance regressed with 24
Friston motion parameters, white matter high signal, cerebrospinal fluid signal and global signals as regressors, and filtered with a temporal band-pass of 0.01–0.1 Hz.

Whole-brain FCS Analysis
A voxel-wise whole-brain functional connectivity analysis was performed on the preprocessed rsfMRI data as same as our previous study (Wei et al., 2018). Firstly, the Pearson’s correlations between the residual time series of all pairs of brain voxels were computed and a whole-brain connectivity matrix for each participant was constructed. Then, the individual correlation matrices were transformed to a z-score matrix using a Fisher r-to-z transformation. For a given voxel, FCS was computed as the sum of the z-values between the given voxel and all the other voxels. We restricted our analysis to correlations above a threshold of \( r = 0.1 \) to eliminate weak correlations possibly arising from noises. These FCS maps were smoothed with a 4 mm full-width at half-maximum (FWHM) Gaussian kernel (Buckner et al., 2009; Liang et al., 2013).

Statistical Analysis
The \( \chi^2 \) test was applied to compare the gender differences and a one-way ANOVA were applied to check for differences in age, education years among the three genotype groups (AA, AG and GG). A one-way ANOVA was performed to determine the changed regions of FCS for healthy participants among the three genotype groups. This test was constrained in a gray matter mask, and multiple comparison corrections were based on Gaussian random field theory (voxel-level \( p < 0.001 \); cluster-level \( p < 0.05 \)). The FCS value of the changed regions was extracted and compared with a one-way ANOVA among the three genotype groups and Post hoc analysis was conducted with LSD method. Spearman correlation analyses were performed to assess the correlation between the values of FCS and the behavior scores (total SPQ scores and its sub-domains) for each NOTCH4 genotype group (the significance level: \( p < 0.05 \), two-tail).

Results
Demographic information
Table 1 presented the demographic, genetic, and behavioral data for participants included in the final analysis. The genotype distribution of NOTCH4 rs204993 in current study (AA = 142, AG = 188, and GG = 72) was consistent with the previous report of variation of this gene in healthy Chinese Han
population (Zhang et al., 2015a). There were no significant differences in gender, educational years and age between genotype groups. There was also no significant difference of SPQ between genotype groups.

**Genetic effect of rs204993 on FCS**

To explore the effects of genotype on FCS, a one-way ANOVA was performed among the FCS maps in the three genotype groups within the gray matter mask, correcting with Gaussian random field theory (voxel-level $p < 0.001$; cluster-level $p < 0.05$). The result showed that FCS was significantly abnormal in the left occipital cortex among the NOTCH4 genotype (See in Fig. 1). Then, the FCS values of the above cluster were extracted in the three genotype groups. We found a main effect of the genotype on FCS values ($F = 15.220$, $p < 0.001$). Post hoc analysis showed that AA individual shaving reduced values than AG and GG participants ($p < 0.001$ for both) and AG individual shaving reduced values than GG participants ($p = 0.043$) (See in Fig. 1 and Table 1).

Table 1 Demographic and behavioral-neuroimaging information for participants grouped by rs204993 genotype (mean ± SD).

|                | AA     | AG     | GG     | Statistics | $P$ value |
|----------------|--------|--------|--------|------------|-----------|
| Number of participants | 142    | 188    | 72     | /          | /         |
| Gender (male/female)   | 68/74  | 88/100 | 41/31  | 2.250      | 0.325     |
| Age (years)            | 20.761 ± 1.104 | 20.942 ± 1.061 | 21.097 ± 1.115 | 2.490 | 0.084 |
| SPQ                  | 26.930 ± 13.853 | 26.553 ± 14.038 | 31.167 ± 14.470 | 2.955 | 0.051 |
| FCS in occipital cortex | 0.379 ± 0.461 | 0.612 ± 0.531 | 0.755 ± 0.542 | 15.220 | < 0.001 |

Note: SPQ, schizotypal personality questionnaire; FCS, functional connectivity strength; SD, standard deviation.

The Correlation analyses between SPQ and FCS

The FCS values in the left occipital cortex was negatively associated with the total SPQ scores ($r = -0.389$, $p = 0.001$), cognitive-perceptual scores ($r = -0.409$, $p < 0.001$) and interpersonal scores ($r = -0.342$, $p = 0.003$) among GG participants (See in Fig. 2). No significant relationship was found between the values of FCS and the behavior scores (total SPQ scores and its sub-domains) for AA or AG group (See in Fig. 3).

**Discussion**

In the current study, we aimed at investigating the genetic effect of schizophrenia-related gene (NOTCH4 rs204993 genotype) on brain function and its relationship with schizotypal traits among healthy volunteers. With large sample size, we found that functional connectivity in occipital cortex is
the highest on GG individuals and decreases from GG individuals and AG individuals to AA individuals. Intriguingly, the values of FCS in the left occipital cortex were negatively correlated with total SPQ scores and its subset scores (cognitive-perceptual and interpersonal scores) in GG individuals. Previous studies have shown that the NOTCH4 polymorphism rs204993 was closely related to schizophrenia (Luo et al., 2004; Wei and Hemmings, 2000). However, as a candidate gene for schizophrenia, we didn’t find the direct effect of the NOTCH4 rs204993 on the schizotypal traits among healthy volunteers in present study. Even so, it was notable that we found the modulatory effect of the NOTCH4 rs204993 on brain function (the functional connectivity of occipital cortex), which was associated with schizotypal traits. The impact of NOTHC4 gene on central nervous system has been consistently reported (Justice and Jan, 2002). The NOTHC4 gene is one member of the NOTCH family, which may code notch protein, discovered as a Drosophila neurogenic protein during embryogenesis (Fortini and Artavanis-Tsakonas, 1993). Functionally, the NOTCH family mainly controls cell fate in the process of the neurodevelopment that promotes proliferative signaling (Fiuza and Arias, 2007; Sestan et al., 1999). Therefore, the NOTCH4 gene variants may potentially affect the function or expression level of Notch4 protein, which in turn influences the neurodevelopment of certain psychiatric disorders, such as schizophrenia and schizotypal traits. In the study, we found aberrant functional connectivity in the left occipital cortex among carriers with the NOTCH4 rs204993 schizophrenia-risk genotypes.

The occipital cortex plays an important role in the neural circuits of perceptual processing, such as visual and auditory processing (Benetti et al., 2018; Cappadocia et al., 2017). Considerable studies have confirmed that schizophrenia patients and their unaffected siblings presented impaired perceptual performance, which was associated with impaired structural and functional connectivity in occipital cortex (Oestreich et al., 2016; van de Ven et al., 2017; Zalesky et al., 2015). Besides, the occipital lobe is also gradually recognized as the neural basis for perceiving personal communication and social interactions (Che et al., 2014; Lingnau and Downing, 2015; Quadflieg et al., 2015). Of course, some studies have shown that negative symptoms in patients with schizophrenia are associated with abnormal change in occipital cortex (Giordano et al., 2018; Rigucci et al., 2013; Taylor
et al., 2011). For example, abnormal connectivity between occipital cortex and ventral tegmental area is related to the negative symptoms in schizophrenia (Giordano et al., 2018). In general, the occipital cortex may be a common neural pathway for the processing of positive and negative symptoms in schizophrenia. Consistent with these notions, our study revealed that the occipital-cortex functional connectivity was related with cognitive-perceptual and interpersonal sub-scores, which represented the positive and negative symptoms in schizotypal traits. Therefore, we speculate that the NOTCH4 gene may induce the occurrence and development of diseases by affecting the neurodevelopment of occipital cortex.

It is worth noting that we found that the FCS of occipital cortex is degressive in sequence of GG, AG and AA genotype group. This is not completely accordant with previous results that the AA genotype of rs204993 was associated with a higher risk for schizophrenia in the Chinese Han population (Zhang et al., 2015a). The difference between schizophrenia and schizotypal traits may contribute to this discrepancy. As our results suggested, individuals with AG genotype also present lower FCS in occipital cortex than the GG genotype carriers, which may indicate the risk of schizotypal traits in the AG genotype carriers, but not the risk of schizophrenia.

Several potential limitations of our study need to be considered. First, we did not find direct modulatory effect of the NOTCH4 gene on the schizotypal traits (no significant difference between NOTCH4 genotype groups). The gross feature of schizotypal-traits assessment (SPQ) may partly explain this defect. Second, the absence of long scanning durations reduced the reliability of measuring functional connectivity. Third, our study did not reveal the cognitive mental mechanism of NOTCH4 gene modulating occipital cortex and its relationship with schizotypal traits. Finally, we did not explore the modulatory effect of NOTCH4 gene on local and long-range functional connectivity respectively, which may represent distinct biological significance.

Conclusion
The results of this current study suggest that the lower functional connectivity of the occipital cortex in the AA genotype carriers, which consistent with previous results among schizophrenia patients. Our findings may provide insight for neural substrate underling the genetic effect on schizotypal
symptoms.

Abbreviations
FCS, functional connectivity strength; SPQ, Schizotypal Personality Questionnaire; rs-fMRI, resting-state functional magnetic resonance image; NOTCH4, neurogenic locus notch homolog protein4; MHC, major histocompatibility complex; SNPs, single nucleotide polymorphisms; FCS, functional connectivity strength; DPARSF, Data Processing Assistant for Resting-State Functional; SPM8, statistical parametric mapping software package; REST, Resting State Functional MR Imaging Toolkit; FWHM, full-width at half-maximum.

Declarations
Acknowledgements
We thank all the participants from the Anhui Medical University and operators of the Center for Biomedical Engineering, University of Science and Technology of China for their supports to this study.

Funding
This study was supported by the Natural Science Foundation of China (91432301, 31571149, 81171273, 31970979 and 91232717 to K.W., 81671354, 91732303 to Y.T., 31800909 to L.Z.). The funding agency had no role in the study design, data collection and analysis, or preparation of the manuscript.

Availability of data and materials
Data in the manuscript will not be shared. This was inconsistent with participant's written informed consent.

Author’s Contributors
XHX, MDZ, LZ and KW designed the study. LZ, TJB, WLH and PPH acquired behavior and imaging data. LW and GJJ collected and analyzed genetic data. TJB, GJJ, BSQ and YHT analyzed imaging data, XHX,
MDZ, LZ and KW wrote this article, which all authors have reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

**Competing interests**

All authors declare no competing interests.

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

All participants signed the informed consent. The study was executed in agreement with the declaration of Helsinki and was approved by Biomedical ethics committee of anhui medical university.

**Author’ information**

1Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230022, China; 2Collaborative Innovation Center for Neuropsychiatric Disorders and Mental Health, Anhui Medical University, Hefei, 230022, China; 3Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders, Hefei, 230022, China; 4Department of Medical Psychology, Chaohu Clinical Medical College, Anhui Medical University, Hefei, China; 5Center for Biomedical Engineering, University of Science and Technology of China, Hefei, Anhui, China.

**References**

Aberg, K.A., Liu, Y., Bukszar, J., McClay, J.L., Khachane, A.N., Andreassen, O.A., Blackwood, D., Corvin, A., Djurovic, S., Gurling, H., Ophoff, R., Pato, C.N., Pato, M.T., Riley, B., Webb, T., Kendler, K., O'Donovan, M., Craddock, N., Kirov, G., Owen, M., Rujescu, D., St Clair, D., Werge, T., Hultman, C.M., Delisi, L.E., Sullivan, P., van den Oord, E.J., 2013. A comprehensive family-based replication study of
schizophrenia genes. JAMA psychiatry 70(6), 573-581.
Andreasen, N.C., 1995. Symptoms, signs, and diagnosis of schizophrenia. Lancet 346(8973), 477-481.
Angell, M., 1996. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Alzheimer Disease & Associated Disorders 10(2), 20-22.
Baker, K.D., Skuse, D.H., 2005. Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. The British journal of psychiatry : the journal of mental science 186, 115-120.
Benetti, S., Novello, L., Maffei, C., Rabini, G., Jovicich, J., Collignon, O., 2018. White matter connectivity between occipital and temporal regions involved in face and voice processing in hearing and early deaf individuals. NeuroImage 179, 263-274.
Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R.A., Johnson, K.A., 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 29(6), 1860-1873.
Cappadocia, D.C., Monaco, S., Chen, Y., Blohm, G., Crawford, J.D., 2017. Temporal Evolution of Target Representation, Movement Direction Planning, and Reach Execution in Occipital-Parietal-Frontal Cortex: An fMRI Study. Cerebral cortex (New York, N.Y. : 1991) 27(11), 5242-5260.
Chao-Gan, Y., Yu-Feng, Z., 2010. DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI. Front. Syst. Neurosci. 4, 13.
Che, X., Wei, D., Li, W., Li, H., Qiao, L., Qiu, J., Zhang, Q., Liu, Y., 2014. The correlation between gray matter volume and perceived social support: a voxel-based morphometry study. Social neuroscience 9(2), 152-159.
Chen, J., Xu, Y., Zhang, J., Liu, Z., Xu, C., Zhang, K., Shen, Y., Xu, Q., 2013. A combined study of genetic association and brain imaging on the DAOA gene in schizophrenia. American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 162B(2), 191-200.
Chen, W.J., Hsiao, C.K., Lin, C.C., 1997. Schizotypy in community samples: the three-factor structure
and correlation with sustained attention. Journal of abnormal psychology 106(4), 649-654.

Chen, X., Ji, G.J., Zhu, C., Bai, X., Wang, L., He, K., Gao, Y., Tao, L., Yu, F., Tian, Y., Wang, K., 2018. Neural Correlates of Auditory Verbal Hallucinations in Schizophrenia and the Therapeutic Response to Theta-Burst Transcranial Magnetic Stimulation. Schizophrenia bulletin.

Fiuza, U.M., Arias, A.M., 2007. Cell and molecular biology of Notch. The Journal of endocrinology 194(3), 459-474.

Fortini, M.E., Artavanis-Tsakonas, S., 1993. Notch: neurogenesis is only part of the picture. Cell 75(7), 1245-1247.

Giordano, G.M., Stanziano, M., Papa, M., Mucci, A., Prinster, A., Soricelli, A., Galderisi, S., 2018. Functional connectivity of the ventral tegmental area and avolition in subjects with schizophrenia: a resting state functional MRI study. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 28(5), 589-602.

Glatt, S.J., Wang, R.S., Yeh, Y.C., Tsuang, M.T., Faraone, S.V., 2005. Five NOTCH4 polymorphisms show weak evidence for association with schizophrenia: evidence from meta-analyses. Schizophrenia research 73(2-3), 281-290.

Gottesman, II, Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. The American journal of psychiatry 160(4), 636-645.

Ikeda, M., Aleksic, B., Kinoshita, Y., Okochi, T., Kawashima, K., Kushner, I., Ito, Y., Nakamura, Y., Kishi, T., Okumura, T., Fukuo, Y., Williams, H.J., Hamshere, M.L., Ivanov, D., Inada, T., Suzuki, M., Hashimoto, R., Ujike, H., Takeda, M., Craddock, N., Kaibuchi, K., Owen, M.J., Ozaki, N., O'Donovan, M.C., Iwata, N., 2011. Genome-wide association study of schizophrenia in a Japanese population. Biological psychiatry 69(5), 472-478.

Ikeda, M., Aleksic, B., Yamada, K., Iwayama-Shigeno, Y., Matsuo, K., Numata, S., Watanabe, Y., Ohnuma, T., Kaneko, T., Fukuo, Y., Okochi, T., Toyota, T., Hattori, E., Shimodera, S., Itakura, M., Nunokawa, A., Shibata, N., Tanaka, H., Yoneda, H., Arai, H., Someya, T., Ohmori, T., Yoshikawa, T., Ozaki, N., Iwata, N., 2013. Genetic evidence for association between NOTCH4 and schizophrenia supported by a GWAS follow-up study in a Japanese population. Molecular psychiatry 18(6), 636-638.
Justice, N.J., Jan, Y.N., 2002. Variations on the Notch pathway in neural development. Current opinion in neurobiology 12(1), 64-70.

Lingnau, A., Downing, P.E., 2015. The lateral occipitotemporal cortex in action. Trends in cognitive sciences 19(5), 268-277.

Liu, C.M., Liu, Y.L., Fann, C.S., Chen, W.J., Yang, W.C., Ouyang, W.C., Chen, C.Y., Jou, Y.S., Hsieh, M.H., Liu, S.K., Hwang, T.J., Faraone, S.V., Tsuang, M.T., Hwu, H.G., 2007. Association evidence of schizophrenia with distal genomic region of NOTCH4 in Taiwanese families. Genes, brain, and behavior 6(6), 497-502.

Luo, X., Klempan, T.A., Lappalainen, J., Rosenheck, R.A., Charney, D.S., Erdos, J., van Kammen, D.P., Kranzler, H.R., Kennedy, J.L., Gelernter, J., 2004. NOTCH4 gene haplotype is associated with schizophrenia in African Americans. Biological psychiatry 55(2), 112-117.

Oestreich, L.K., McCarthy-Jones, S., Whitford, T.J., 2016. Decreased integrity of the fronto-temporal fibers of the left inferior occipito-frontal fasciculus associated with auditory verbal hallucinations in schizophrenia. Brain imaging and behavior 10(2), 445-454.

Quadflieg, S., Gentile, F., Rossion, B., 2015. The neural basis of perceiving person interactions. Cortex; a journal devoted to the study of the nervous system and behavior 70, 5-20.

Rado, S., 1953. Dynamics and classification of disordered behavior. Am. J. Psychiatry 110(6), 406-416.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc Natl Acad Sci U S A 98(2), 676-682.

Raine, A., 1991. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophrenia bulletin 17(4), 555-564.

Raine, A., 2006. Schizotypal personality: neurodevelopmental and psychosocial trajectories. Annu. Rev. Clin. Psychol. 2, 291-326.

Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Triphon, N., Kim, D., 1994. Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. Schizophrenia bulletin 20(1), 191-201.

Rigucci, S., Rossi-Espagnet, C., Ferracuti, S., De Carolis, A., Corigliano, V., Carducci, F., Mancinelli, I.,
Cicone, F., Tatarelli, R., Bozzao, A., Girardi, P., Comparelli, A., 2013. Anatomical substrates of cognitive and clinical dimensions in first episode schizophrenia. Acta psychiatrica Scandinavica 128(4), 261-270.

Ripke, S., 2011. Genome-wide association study identifies five new schizophrenia loci. Nature genetics 43(10), 969-976.

Sestan, N., Artavanis-Tsakonas, S., Rakic, P., 1999. Contact-dependent inhibition of cortical neurite growth mediated by notch signaling. Science 286(5440), 741-746.

Song, X.W., Dong, Z.Y., Long, X.Y., Li, S.F., Zuo, X.N., Zhu, C.Z., He, Y., Yan, C.G., Zang, Y.F., 2011. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 6(9), e25031.

Stefanis, N.C., Van Os, J., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Hantoumi, I., Stefanis, C.N., 2004. Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. Biological psychiatry 56(7), 510-515.

Taylor, S.F., Chen, A.C., Tso, I.F., Liberzon, I., Welsh, R.C., 2011. Social appraisal in chronic psychosis: role of medial frontal and occipital networks. Journal of psychiatric research 45(4), 526-538.

Tochigi, M., Zhang, X., Ohashi, J., Hibino, H., Otowa, T., Rogers, M., Kato, T., Okazaki, Y., Kato, N., Tokunaga, K., Sasaki, T., 2007. Association study between the TNXB locus and schizophrenia in a Japanese population. American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 144b(3), 305-309.

van de Ven, V., Rotarska Jagiela, A., Oertel-Knochel, V., Linden, D.E.J., 2017. Reduced intrinsic visual cortical connectivity is associated with impaired perceptual closure in schizophrenia. Neurolmage. Clinical 15, 45-52.

Vollema, M.G., Postma, B., 2002. Neurocognitive correlates of schizotypy in first degree relatives of schizophrenia patients. Schizophr. Bull. 28(3), 367-377.

Wang, L., Xia, M., Li, K., Zeng, Y., Su, Y., Dai, W., Zhang, Q., Jin, Z., Mitchell, P.B., Yu, X., He, Y., Si, T., 2015. The effects of antidepressant treatment on resting-state functional brain networks in patients with major depressive disorder. Human brain mapping 36(2), 768-778.
Wang, Z., Wei, J., Zhang, X., Guo, Y., Xu, Q., Liu, S., Shi, J., Yu, Y., Ju, G., Li, Y., Shen, Y., 2006. A review and re-evaluation of an association between the NOTCH4 locus and schizophrenia. American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 141b(8), 902-906.

Wei, J., Hemmings, G.P., 2000. The NOTCH4 locus is associated with susceptibility to schizophrenia. Nature genetics 25(4), 376-377.

Wei, Q., Bai, T., Chen, Y., Ji, G., Hu, X., Xie, W., Xiong, Z., Zhu, D., Wei, L., Hu, P., Yu, Y., Wang, K., Tian, Y., 2018. The Changes of Functional Connectivity Strength in Electroconvulsive Therapy for Depression: A Longitudinal Study. Front Neurosci 12, 661.

Zalesky, A., Pantelis, C., Cropley, V., Fornito, A., Cocchi, L., McAdams, H., Clasen, L., Greenstein, D., Rapoport, J.L., Gogtay, N., 2015. Delayed Development of Brain Connectivity in Adolescents With Schizophrenia and Their Unaffected Siblings. JAMA psychiatry 72(9), 900-908.

Zhang, B., Fan, Q.R., Li, W.H., Lu, N., Fu, D.K., Kang, Y.J., Wang, N., Li, T., Wen, X.P., Li, D.X., 2015a. Association of the NOTCH4 Gene Polymorphism rs204993 with Schizophrenia in the Chinese Han Population. BioMed research international 2015, 408096.

Zhang, B., Li, D.X., Lu, N., Fan, Q.R., Li, W.H., Feng, Z.F., 2015b. Lack of Association between the TSPAN18 Gene and Schizophrenia Based on New Data from Han Chinese and a Meta-Analysis. International journal of molecular sciences 16(6), 11864-11872.

Zhang, Q., Shen, J., Wu, J., Yu, X., Lou, W., Fan, H., Shi, L., Wang, D., 2014. Altered default mode network functional connectivity in schizotypal personality disorder. Schizophrenia research 160(1-3), 51-56.

Zhu, J., Zhuo, C., Xu, L., Liu, F., Qin, W., Yu, C., 2017. Altered Coupling Between Resting-State Cerebral Blood Flow and Functional Connectivity in Schizophrenia. Schizophrenia bulletin 43(6), 1363-1374.

Figures
Modulatory effect of rs204993 on the functional strength (FCS). Groups comparison revealed that the FCS in occipital cortex is the highest on GG individuals and decreases from GG individuals and AG individuals to AA individuals. All threshold for comparisons were set as whole brain Gaussian random field (GRF) correction (voxel $P < 0.001$, cluster $P < 0.05$).
Relationship between the FCS in occipital cortex and schizotypal traits among the GG genotype carriers. The FCS in occipital cortex is negatively correlated with the score of schizotypal personality questionnaire (SPQ) and its subscale scores (cognitive perceptual and interpersonal) among the GG genotype carriers. Note: *** p < 0.001, * p < 0.05.
Relationship between the FCS in occipital cortex and schizotypal traits among the AA and AG genotype carriers. No significant correlation was found between the FCS in occipital cortex and the score of SPQ or its subscale scores.

Figure 3