Neurosci Bull February 1, 2015, 31(1): 31–42. http://www.neurosci.cn
DOI: 10.1007/s12264-014-1491-7

·Original Article·

Morphological changes in gray matter volume correlate with catechol-O-methyl transferase gene Val158Met polymorphism in first-episode treatment-naïve patients with schizophrenia

Ming-Li Li[1,2,*], Bo Xiang[2,*], Yin-Fei Li[1], Xun Hu[3], Qiang Wang[1], Wan-Jun Guo[1], Wei Lei[1], Chao-Hua Huang[1], Lian-Sheng Zhao[2], Na Li[1], Hong-Yan Ren[1], Hui-Yao Wang[1], Xiao-Hong Ma[1,2], Wei Deng[1], Tao Li[1,2]

[1]*The Mental Health Center and the Psychiatric Laboratory,* [2]*State Key Laboratory of Biotherapy,* [3]*Huaxi Biobank, West China Hospital, Sichuan University, Chengdu 610041, China*

*These authors contributed equally to this work.

Corresponding authors: Tao Li and Wei Deng. E-mail: litaohx@scu.edu.cn, mrdengwei@163.com

ABSTRACT

The catechol-O-methyltransferase (COMT) gene is a schizophrenia susceptibility gene. A common functional polymorphism of this gene, Val158/158Met, has been proposed to influence gray matter volume (GMV). However, the effects of this polymorphism on cortical thickness/surface area in schizophrenic patients are less clear. In this study, we explored the relationship between the Val158Met polymorphism of the COMT gene and the GMV/cortical thickness/cortical surface area in 150 first-episode treatment-naïve patients with schizophrenia and 100 healthy controls. Main effects of diagnosis were found for GMV in the cerebellum and the visual, medial temporal, parietal, and middle frontal cortex. Patients with schizophrenia showed reduced GMVs in these regions. And main effects of genotype were detected for GMV in the left superior frontal gyrus. Moreover, a diagnosis × genotype interaction was found for the GMV of the left precuneus, and the effect of the COMT gene on GMV was due mainly to cortical thickness rather than cortical surface area. In addition, a pattern of increased GMV in the precuneus with increasing Met dose found in healthy controls was lost in patients with schizophrenia. These findings suggest that the $COMT_{Met}$ variant is associated with the disruption of dopaminergic influence on gray matter in schizophrenia, and the effect of the COMT gene on GMV in schizophrenia is mainly due to changes in cortical thickness rather than in cortical surface area.

Keywords: schizophrenia; COMT; gray matter; imaging genetics

INTRODUCTION

Catechol-O-methyltransferase (COMT), which metabolizes the neurotransmitters dopamine (DA), epinephrine, and norepinephrine, has been reported to be related to schizophrenia[1-6]. Studies have also shown that alterations of DA signaling[7], as well as structural cortical maturation[8], are associated with a genetic susceptibility for schizophrenia. It has been suggested that DA plays an important role in the structural development of the cortex[9], and inherited disruptions of DA signaling can induce cortical dysmaturation, which has been found in patients with schizophrenia onset in adolescence and early adulthood[10, 11]. Furthermore, the catabolic action of COMT is important in regulating the levels of DA in the prefrontal cortex[12, 13], and the structure and function of this region have been confirmed to contribute to schizophrenia. These studies suggest that COMT plays a crucial role in the onset of schizophrenia and may act on the morphological changes of brain structure in this mental disorder.

The COMT gene is located on chromosome 22q11.22–23. A functional COMT polymorphism with a single nucleic acid change of guanine to adenine results in the replacement of valine (Val) by methionine (Met) (known as Val158Met, rs4680). This common polymorphism has been studied

extensively since the 1980s[14]. Compared with the Met158 allele, the Val158 allele is associated with greater COMT enzyme activity and greater DA degradation. The alleles are co-dominant as the heterozygotic genotype (Val158/Met158) and are associated with an intermediate level of the enzymatic activity of COMT[15, 16]. Met158 carriers with Val158/Met158 and Met158/Met158 have four- to five-fold lower COMT activity than carriers with Val158/Val158. Honea *et al*.[17] reported that the Val158 variant of rs4680 affects hippocampal and dorsolateral prefrontal gray matter volumes (GMVs) in healthy populations. Previous studies also identified an effect of the COMT Val158Met polymorphism on cortical activation or functional connectivity in schizophrenia[18-20]. In addition, as GMV is determined by cortical thickness and cortical surface area, alterations of GMV might be due to both of these measurements, or either one. However, few studies have probed the relationship between variants of the COMT gene and morphological changes, including GMV, cortical thickness, and cortical surface area in schizophrenia.

Therefore, this study was performed to explore the COMT Val158Met polymorphism underlying the abnormal gray matter morphological changes (GMV/cortical thickness/cortical surface area) in schizophrenia.

PARTICIPANTS AND METHODS

Participants

One hundred and fifty first-episode, treatment-naïve patients with schizophrenia and 100 healthy controls (HCs) were enrolled in this study. All patients were interviewed and assessed using the Structured Clinical Interview (SCID-I/P) of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition)[21], and fulfilled the diagnostic criteria for schizophrenia or schizophreniform disorder in DSM-IV. Forty-nine patients diagnosed with schizophreniform disorder when they first participated in this study were followed up for at least 6 months to confirm a diagnosis of schizophrenia. Psychiatric symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS)[22]. The HCs were recruited locally by advertisement and were screened for a lifetime absence of psychiatric illness using the Structured Clinical Interview (SCID-NP) in the DSM-IV Non-Patient Edition[23]. In addition, HCs were interviewed to ascertain that there was no psychiatric illness in their first-degree relatives. Participants with evidence of organic brain disorders, alcohol or drug abuse, or any other severe physical illness were excluded.

All participants were ethnic Han Chinese. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Review Board of West China Hospital, Sichuan University. All participants provided written informed consent to their participation.

Genotyping

DNA was obtained from whole blood using the standard phenol-chloroform isolation method[24]. The Val158Met polymorphism of the COMT gene was genotyped as a restriction fragment length polymorphism after polymerase chain reaction amplification and digestion with NlaIII. COMT val allele has a G at position 1947, generating a 114-bp fragment after digestion with NlaIII, while COMT met allele has an A at this position, which resulted in digestion of the 114-bp fragment into two products of 96 and 18 bp. The amplicons were separated by agarose gel (3%) electrophoresis.

T1-Weighted Magnetic Resonance Imaging (MRI) Data Acquisition

Two hundred and fifty participants underwent MRI scans in the Department of Radiology at West China Hospital with a 3T MR imaging system (EXCITE, General Electric, Milwaukee, WI) with an 8-channel phase-array head coil. High-resolution T1 images were obtained from all participants using a 3D spoiled gradient echo sequence. The sets used in this protocol were as follows: TR = 8.5 ms; TE = 3.93 ms; flip angle = 12°; slice thickness = 1 mm; single shot; field of view = 24 cm × 24 cm; matrix = 256 × 256; voxel size = 0.47 × 0.47 × 1 mm^3. In total, 156 axial slices were collected from each brain. All scans were inspected for motion artifacts, and a neuroradiologist confirmed the absence of gross pathology.

MRI Data Preprocessing

Voxel-Based Morphometry

The non-parametric, non-uniformity intensity normalization technique in the MINC software package (http://wiki. bic.mni.mcgill.ca/index.php/MINC) was used to rectify the non-uniformity of the high magnetic-field signal in all

images. Then, the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) toolbox in Statistical Parametric Mapping (SPM) 8 was used to process these images. The details are as follows: all structural MRI scans were realigned manually according to the anterior commissure-posterior commissure line and were segmented into probability maps of gray matter (GM), white matter (WM), and cerebrospinal fluid using the 'new-segment' routine implemented in SPM8. Flow fields and a series of template images were produced by running the 'DARTEL (create templates)' routine using imported versions of the GM and WM generated in the previous step. The flow fields as well as the final template images were used to generate smoothed (6 mm full-width at half-maximum isotropic Gaussian kernel), Jacobian modulated, and spatially normalized GM in Montreal Neurological Institute (MNI) space. Finally, GMVs were retained for subsequent statistical analysis.

Surface-Based Morphometry

FreeSurfer 5.1 (http://surfer.nmr.mgh.harvard.edu/fswiki) was used to reconstruct the cortical surface from the structural MRI scans[25]. After skull-stripping and intensity correlation, tissue intensity and neighborhood constraints were used to determine the GM-WM boundary for each hemisphere. Then, all the surfaces were checked following an automated topology-fixation procedure, and minor defects were manually corrected. The pial surface was created by GM-WM assessment as the starting point of a deformable surface algorithm. Spherical morphing and spherical registration were processed after that. Finally, cortical thickness and surface area were calculated using the methods developed by Fischl and Dale[26].

Statistical Analyses

Patients with schizophrenia and HCs were divided into the following subgroups according to the SNP genotypes: Val158/Val158, Val158/Met158, and Met158/Met158.

A full factorial model was used to obtain the main effects including the genotype effect and the diagnostic effect as well as diagnosis-by-genotype (D×G) interaction in the GMVs according to the genotype of the Val158Met polymorphism. Statistical significance was defined as $P < 0.001$ (uncorrected) with >200 linked voxels (cluster of voxels)[27].

Then, significant region-of-interest (ROI) masks of brain regions were obtained from the results of main effects or D×G interaction analysis of the GMVs. The masks were extracted using Xjview (http://www.alivelearn.net/xjview8/) and used to acquire their respective cortical surface area and cortical thickness in Freesurfer. The binary masks were registered onto an average image using 'bbregister' in Freesurfer, which is a boundary-based affine registration method that aligns images by maximizing the intensity gradient across tissue boundaries[28]. Then, the ROI labels were obtained from the masks and unwrapped back onto each participant's native image. Finally, the cortical surface area and thickness of each ROI were acquired by averaging the respective values from all the vertices included within the defined clusters for each participant.

RESULTS

Demographic Characteristics and Clinical Information

The demographic characteristics of participants are summarized in Table 1. All groups were of comparable age, gender, and years of education. No significant differences were found in PANSS scores among the three subgroups of patients.

The distribution of the COMT Val158Met polymorphism did not deviate from Hardy-Weinberg expectation in HCs ($P = 0.15$). The allelic and genotypic frequencies are presented in Table 2. There were no significant differences in the frequencies of genotypes and alleles between patients with schizophrenia and HCs.

Main Effects of Genotype and Diagnosis on GMV

Significant main effects of diagnosis were found for the bilateral cerebellar posterior lobe and vermis, right hippocampal-parahippocampal gyrus, lingual gyrus, bilateral calcarine, bilateral inferior and middle occipital gyri, bilateral superior temporal gyrus, right middle frontal gyrus, right supramarginal gyrus, bilateral precentral gyrus, left paracentral lobule, and bilateral supplementary motor area. Patients with schizophrenia showed reduced GMVs in these regions (Fig. 1). Moreover, a significant main effect of genotype was detected for the left superior frontal gyrus (MNI coordinates: x = −23, y = 66, z = 9; voxels = 1063). Compared with Met homozygotes, Val-allele carriers and Val homozygotes showed a decreased GMV in this gyrus.

Table 1. Demographics and clinical data

	Healthy Controls			Patients with Schizophrenia			Diagnosis	Genotype	Diagnosis × Genotype
	Met/Met	Met/Val	Val/Val	Met/Met	Met/Val	Val/Val	*F* (*P*)	*F* (*P*)	*F* (*P*)
Number	14	40	46		19	59		72	
Sex (M/F)	7/7	20/20	25/21		8/11	31/28		30/42	
Age (years)	27.07 (7.14)	25.13 (8.53)	25.54 (8.19)	24.84 (7.41)	24.20 (7.12)	24.29 (7.28)	1.65 (0.20)	0.35 (0.71)	0.09 (0.92)
Education (years)	12.86 (3.88)	12.01 (4.44)	12.97 (3.10)	11.68 (3.80)	11.83 (2.83)	12.68 (2.76)	1.22 (0.27)	1.95 (0.15)	0.29 (0.75)
Course (months)	-	-	-	6.89 (11.14)	9.12 (14.89)	10.41 (20.24)	-	0.33 (0.72)	-
PANSS_T	-	-	-	91.37 (12.29)	91.17 (21.47)	90.06 (17.50)	-	0.07 (0.93)	-
PANSS_P	-	-	-	22.95 (4.22)	26.53 (7.55)	26.17 (7.47)	-	2.06 (0.13)	-
PANSS_N	-	-	-	18.58 (6.07)	20.00 (8.49)	19.21 (11.06)	-	0.20 (0.82)	-
PANSS_G	-	-	-	49.84 (9.40)	47.90 (10.97)	45.39 (8.66)	-	2.05 (0.13)	-

Mean (SD). PANSS, Positive and Negative Syndrome Scale; PANSS_T, total score; PANSS_P, positive score; PANSS_N, negative score; PANSS_G, general psychopathology score.

Table 2. Genotype distributions and allelic frequencies of catechol-O-methyl transferase gene Val158Met polymorphism

	Genotype distributions			df	χ^2	*P*	Allele frequencies		df	χ^2	*P*
	Val/Val	Val/Met	Met/Met				Val	Met			
Patients	72	59	19	2	0.14	0.93	203	97	1	0.15	0.70
Controls	46	40	14				132	68			

However, no GMV difference was found between Val-allele carriers and Val homozygotes.

Diagnosis × Genotype Interaction in GMV

A significant D×G interaction in GMV was found. Our results showed that schizophrenic patients with the Met158/Met158 genotype had a decreased GMV in the left precuneus region compared to HCs (Fig. 2). Furthermore, the cortical thickness of the left cerebral parietal lobe in the precuneus region was reduced in schizophrenic patients with this genotype compared to HCs; however, there was no significant difference in the cortical surface area of this region between schizophrenic patients and HCs with this genotype (Fig. 3; Table 3).

Table 3. Differences in GMV, cortical thickness, and surface area of the left precuneus in patients with Met158 and controls with Met158

	Patients	Controls	*F*	*P* value
Volume	0.09 (0.02)	0.13 (0.04)	12.7	0.001
Thickness	2.94 (0.39)	3.23 (0.27)	5.66	0.02
Surface area	84.21 (26.38)	95.25 (24.16)	0.66	0.43

Mean (standard deviation); sex and age were included as covariates.

Effects of Val158Met Polymorphism on Brain Morphology in Healthy Controls and Patients with Schizophrenia

Since the D×G interaction effects occurred in the volume and cortical thickness in the precuneus, we estimated the effects of genotype on brain morphology in the HC and schizophrenic groups. In the HC group, we found a step-wise increase of GMV (P <0.01) and a trend of increasing cortical thickness (P = 0.06) in the precuneus,

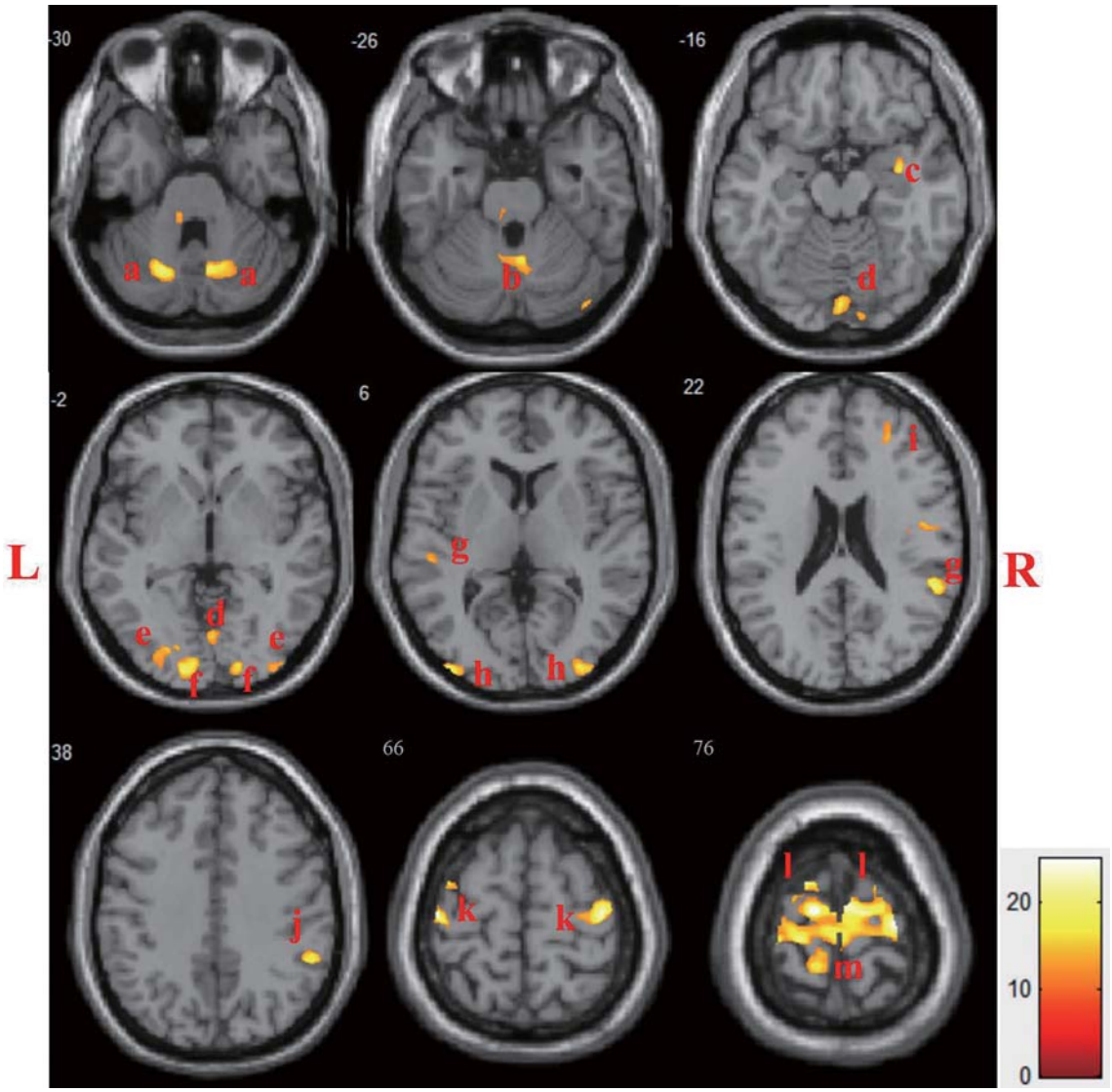

Fig. 1. Main effect of diagnosis on gray matter volume. Statistical inferences were made at *P* <0.001 (uncorrected) with >200 linked voxels. Patients with schizophrenia showed widespread reduced gray matter volume. a, posterior lobe of cerebellum; b, vermis; c, hippocampal-parahippocampal gyrus; d, lingual gyrus; e, inferior occipital gyrus; f, calcarine; g, superior temporal gyrus; h, middle occipital gyrus; i, middle frontal gyrus; j, supramarginal gyrus; k, precentral gyrus; l, supplementary motor area; m, paracentral lobule; L, left; R, right.

with increased dosage of the Met allele. However, contrary to the HC group, the schizophrenia group displayed no significant morphological differences in GMV (P = 0.27) and cortical thickness (P = 0.92) among patients with the Met158/Met158, Met158/Val158, and Val158/Val158 genotypes (Fig. 3). Thus, compared to HCs, patients with schizophrenia showed a loss of relationship between Met dose and GMV and thickness in the precuneus.

DISCUSSION

In the present study, the effect of the COMT Val158Met polymorphism on abnormal morphological changes (gray matter) in patients with schizophrenia was explored using the imaging genetic approach. We found a main effect of diagnosis on GMV, as GMV was decreased in the cerebellum and the visual, medial temporal, parietal,

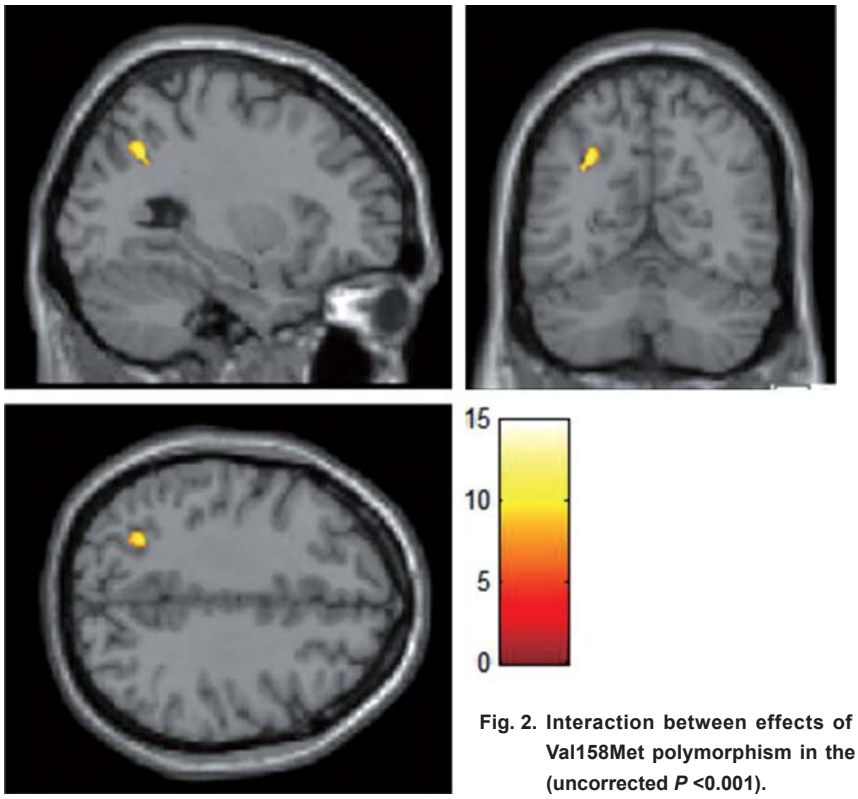

Fig. 2. Interaction between effects of diagnosis and COMT Val158Met polymorphism in the left precuneus region (uncorrected *P* <0.001).

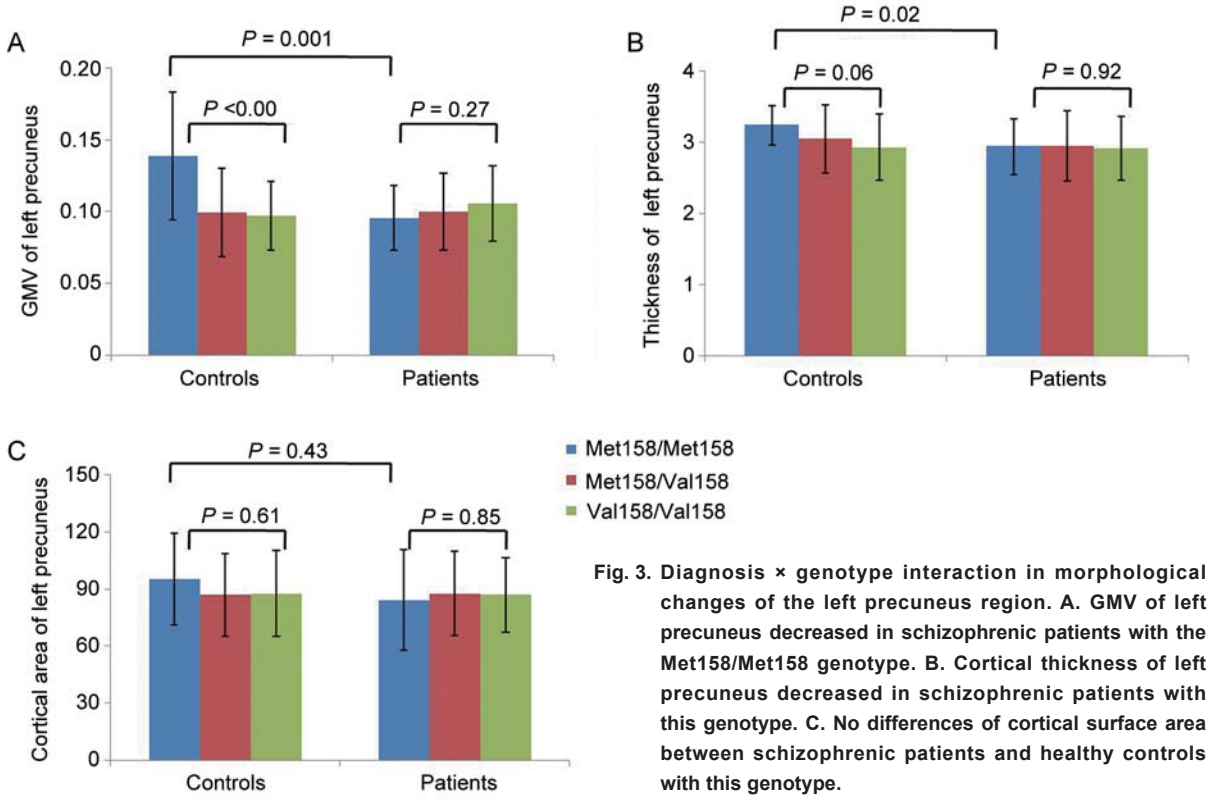

Fig. 3. Diagnosis × genotype interaction in morphological changes of the left precuneus region. A. GMV of left precuneus decreased in schizophrenic patients with the Met158/Met158 genotype. B. Cortical thickness of left precuneus decreased in schizophrenic patients with this genotype. C. No differences of cortical surface area between schizophrenic patients and healthy controls with this genotype.

and middle frontal cortex in schizophrenia. Furthermore, schizophrenic patients with the Met158/Met158 genotype had decreased GMV and reduced cortical thickness in the left precuneus compared with HCs of the same genotype.

We found that patients with first-episode schizophrenia showed widespread GMV reduction in the posterior lobe and vermis of the cerebellum, and the occipital cortex (inferior/middle occipital gyrus), lingual and calcarine gyrus, right hippocampal-parahippocampal gyrus, bilateral superior temporal gyrus, right middle frontal gyrus, and parietal lobe (supramarginal gyrus, precentral gyrus, paracentral lobule, and supplementary motor area). Two large meta-analysis studies[29, 30] highlighted deficits in the hippocampus-parahippocampus, superior temporal gyrus, and middle frontal gyrus in schizophrenia, and these abnormalities were further confirmed in MRI studies of first-episode schizophrenic patients[31-35]. GMV loss in the parietal cortex also occurs in schizophrenia. Abnormalities of the parietal lobe including the supramarginal gyri were reported in a meta-analysis carried out in the 2001[30]. Recent studies also found a decreased volume of the precentral gyrus in patients with first-episode schizophrenia[36]. In addition, among twin pairs discordant for schizophrenia, reduced GMV in the pre/postcentral gyrus was found in those with schizophrenia compared with their nonpsychotic twins, suggesting that the aberrant GMV in the pre/postcentral gyrus might be important in the development of schizophrenia[37]. Other than these regions, the cerebellum was traditionally supposed to be involved only in motor functions, but some studies have suggested its role in cognition and emotion[38] as well as in schizophrenia[39]. For example, abnormalities in the cerebellum and the occipital visual cortex have been detected in first-episode and/or drug-naïve patients[37, 40-43] using either the ROI approach or the voxel-based morphometry (VBM) method. In this study, the main effect of diagnosis on GMV suggested that the GM deficits in schizophrenia might involve widespread regions and circuits in the brain.

In line with previous studies[44], our results supported the idea that the COMT Val158Met variant might play an important role in the abnormal development of GM in schizophrenia. Moreover, our findings suggested that the effect of the COMT gene on GMV in schizophrenia is mainly due to cortical thickness rather than surface area. The radial-unit hypothesis of cortical development suggests that cortical thickness is different from surface area and both are characteristic features of human cortical development[45]. Cortical thickness and volume follow similar developmental patterns[46, 47]. Some studies have suggested that the deficit patterns of GMV and cortical thickness are similar in patients with schizophrenia[48], and that the aberrant cortical thickness might date back to adolescence in those patients[49]; although contradictory results have also been found. For example, Voets *et al*. found that differences in local surface area accounted for the GMV changes[50]. Moreover, although high heritability was detected in both the total cortical surface area and the average cortical thickness (0.89 and 0.81, respectively), no essential related genetics were found for them (genetic correlation = 0.08), which implied that GMV might be influenced by at least two distinct genetic sources[51]. These studies provided a newer and in-depth genetic view of the role of traditional GMV in pathological explanations.

In VBM method, regional GMVs are obtained by computing numbers of voxels, resulting in a mixture of thickness and cortical folding in the final measures, while in surface-based methods, GMVs are calculated based on cortical thicknesses and surface areas. However, compared with FreeSurfer, GMVs based on VBM provide more precise measures of subcortical structures such as the basal ganglia[52, 53] which may be one of the important etiological locations in schizophrenia. In addition, as suggested by Palaniyappan *et al.*[54], the differences in GMVs between two groups obtained using VBM are partially dependent on cortical thickness, surface area, and gyrification which are acquired using surface-based morphometric methods in Freesurfer software. Thus, in the present study, we first used VBM to explore the relationship between the Val158Met polymorphism and GMV, and then explored the anatomical properties of cortical thickness and surface area using part of the Freesurfer software. We found that compared with healthy carriers of the Met158/Met158 genotype, schizophrenic patients with this genotype had a decreased GMV and reduced cortical thickness in the left precuneus. The precuneus is located in the posteromedial parietal cortex and plays an important role in a wide spectrum of highly-integrated tasks, including visuo-spatial imagery, episodic memory retrieval, and self-processing operations[55]. These cognitive functions are widely impaired in schizophrenia[56-63]. Moreover, the precuneus has been

suggested to be the 'core node' of the default mode network[64], which has been hypothesized to be relevant to the pathological mechanism of schizophrenia[65-67]. Decreased volume and cortical thickness of the precuneus in schizophrenia have also been detected in previous studies[50, 54, 68-70], but are relatively rarely reported compared with the prefrontal and temporal lobes. A decreased volume of the precuneus has not been reported in drug-naive, first-episode schizophrenic patients[33, 35], but was found in patients with the Met158/Met158 genotype in this study. One explanation of this discrepancy might be high sample heterogeneity. Schizophrenia is a clinically and etiopathogenetically heterogeneous disorder, thus the association between abnormal morphology of the precuneus and schizophrenia might be concealed by the effects of population stratification[71]. So the significantly reduced volume in the precuneus might exist only within a particular genetic background, such as in the subtype of schizophrenic patients with the Met158/Met158 genotype.

As the D×G interaction had significant effects on GMV, we further evaluated the genotype effect on brain morphology between the different diagnostic groups. We found that the patterns of the Val158Met effect on the morphology of the precuneus differed in schizophrenic patients and HCs. HCs demonstrated a pattern of increased GMV and cortical thickness in the precuneus with dosage of the Met allele. Relative to Val homozygotes, a trend of increased brain volume, thickness, and density in Met-allele carriers and Met homozygotes has also been reported in the hippocampus, the parahippocampal gyrus, the medial temporal lobe and the anterior cingulate in HCs in previous studies[17, 71-74]. A possible explanation for these findings in HCs might be the DA effect on brain maturation. The expression of brain-derived neurotrophic factor in neurons can be regulated by DA[75]. Compared with the Val158 allele, the Met158 allele associated with lower COMT enzyme activity and reduced DA degradation would lead to relatively higher synaptic DA levels contributing to differential brain development.

But the pattern of increased GMV and cortical thickness in the precuneus with increasing Met dose did not occur in patients with schizophrenia, which suggested that the Met158 allele might lose its normal function in regulating the morphological development of the precuneus (especially GMV and cortical thickness) in schizophrenia. A disrupted gene-brain relationship (val158met polymorphism and adolescent cortical development) has also been reported in patients with childhood-onset schizophrenia and their non-psychotic siblings[76]. Otherwise, it is also possible that the COMT gene is just a genetic marker, while other genes linked to the COMT gene might contribute to abnormal brain morphology and function in schizophrenia. For example, the Val158Met polymorphism interacts with a P2 promoter region SNP (rs2097603) and an SNP in the 3' region (rs165599) in predicting an inefficient prefrontal working memory response[77]. Besides, other genetic variants, such as the DA D2 receptor[78], might also play an important role in regulating the DA systems.

There are strengths and limitations in the present study. We recruited first-episode, neuroleptic-naïve schizophrenic patients to explore the effect of the COMT Val158Met polymorphism on brain morphology, by which confounding factors such as illness chronicity and antipsychotic administration were excluded. Moreover, besides GMV, cortical thickness and cortical area were studied to clarify the effect of the COMT Val158Met polymorphism. However, several limitations must be borne in mind. First, only a modest proportion of the variance in GMV can be explained by surface-based morphometric methods[54], so GMV obtained by Freesurfer software might be more useful for exploring the relationship between GMV and surface anatomical properties. Second, considering the genotype effect on the structural maturation of the brain and that schizophrenia is a polygenetic disorder, a longitudinal neuroimaging genetic study exploring the relationship between genes and brain structural maturation could provide more information on the pathological mechanisms. Third, we explored only the effect of the COMT Val158Met polymorphism on morphological changes in schizophrenia. The effects on brain function need to be studied in future.

In summary, in a large sample, we found decreased GMV in the cerebellum and the visual, medial temporal, parietal, and middle frontal cortex in schizophrenia. In addition, our study is one of the largest imaging genetic studies to test the COMT effects on gray matter in schizophrenia in a Han Chinese population, and that the effect of the COMT gene on GMV in the precuneus in schizophrenia might be due mainly to changes in cortical thickness rather than changes in cortical surface area.

ACKNOWLEDGEMENTS

This work was supported by the National Nature Science Foundation of China (81130024, 30530300, and 30125014), the National Key Technology R & D Program of the Ministry of Science and Technology of China during the 12th Five-Year Plan (2012BAI01B06), the Ph.D. Program Foundation of the Ministry of Education of China (20110181110014) and the National Basic Research Development Program(973 Program) of China (2007CB512301).

Received date: 2014-07-10; Accepted date: 2014-11-20

REFERENCES

[1] Badner J, Gershon E. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 2002, 7: 405–411.

[2] Bassett AS, Chow EWC, Husted J, Weksberg R, Caluseriu O, Webb GD*, et al.* Clinical features of 78 adults with 22q11 deletion syndrome. Am J Med Genet A 2005, 138: 307–313.

[3] Karayiorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J*, et al.* Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc Natl Acad Sci U S A 1995, 92: 7612–7616.

[4] Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch Gen Psychiatry 1999, 56: 940.

[5] Li T, Sham P, Vallada H, Xie T, Tang X, Murray R*, et al.* Preferential transmission of the high activity allele of COMT in schizophrenia. Psychiatr Genet 1996, 6: 131–134.

[6] Li T, Ball D, Zhao J, Murray R, Liu X, Sham P*, et al.* Family-based linkage disequilibrium mapping using SNP marker haplotypes: application to a potential locus for schizophrenia at chromosome 22q11. Mol Psychiatry 2000, 5: 77–84.

[7] Hirvonen J, van Erp T, Huttunen J, Aalto S, Någren K, Huttunen M*, et al.* Brain dopamine d1 receptors in twins discordant for schizophrenia. Am J Psychiatry 2006, 163: 1747–1753.

[8] Brans RGH, van Haren NEM, van Baal GCM, Schnack HG, Kahn RS, Pol HEH. Heritability of changes in brain volume over time in twin pairs discordant for schizophrenia. Arch Gen Psychiatry 2008, 65: 1259.

[9] Bhide PG. Dopamine, cocaine and the development of cerebral cortical cytoarchitecture: a review of current concepts. Semin Cell Dev Biol 2009, 20: 395–402.

[10] Greenstein D, Lerch J, Shaw P, Clasen L, Giedd J, Gochman P*, et al.* Childhood onset schizophrenia: cortical brain abnormalities as young adults. J Child Psychol Psychiatry 2006, 47: 1003–1012.

[11] Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R*, et al.* Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proc Natl Acad Sci U S A 2001, 98: 11650.

[12] Lewis DA, Melchitzky DS, Sesack SR, Whitehead RE, Auh S, Sampson A. Dopamine transporter immunoreactivity in monkey cerebral cortex: regional, laminar, and ultrastructural localization. J Comp Neurol 2001, 432: 119–136.

[13] Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. Biol Psychiatry 2006, 60: 141–151.

[14] Scanlon PD, Raymond FA, Weinshilboum RM. Catechol-O-methyltransferase: thermolabile enzyme in erythrocytes of subjects homozygous for allele for low activity. Science 1979, 203: 63–65.

[15] Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S*, et al.* Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet 2004, 75: 807–821.

[16] Papaleo F, Crawley JN, Song J, Lipska BK, Pickel J, Weinberger DR*, et al.* Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice. J Neurosci 2008, 28: 8709–8723.

[17] Honea R, Verchinski BA, Pezawas L, Kolachana BS, Callicott JH, Mattay VS*, et al.* Impact of interacting functional variants in COMT on regional gray matter volume in human brain. Neuroimage 2009, 45: 44–51.

[18] Prata DP, Mechelli A, Fu CH, Picchioni M, Kane F, Kalidindi S, *et al.* Opposite effects of catechol-O-methyltransferase Val158Met on cortical function in healthy subjects andpatients with schizophrenia. Biol Psychiatry 2009, 65: 473–480.

[19] Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, *et al.* Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A 2001, 98: 6917–6922.

[20] Eisenberg DP, Sarpal D, Kohn PD, Meyer-Lindenberg A, Wint D, Kolachana B*, et al.* Catechol-o-methyltransferase valine(158)methionine genotype and resting regional cerebral blood flow in medication-free patients with schizophrenia. Biol Psychiatry 2010, 67: 287–290.

[21] First MB. User's guide for the Structured clinical interview for DSM-IV axis I disorders SCID-I: clinician version. Amer Psychiatric Pub Inc, 1997.

[22] Kay SR, Flszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987, 13: 261.

[23] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. American

Psychiatric Publishing, Inc., 2000.

[24] Ciulla TA, Sklar RM, Hauser SL. A simple method for DNA purification from peripheral blood. Anal Biochem 1988, 174: 485–488.

[25] Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000, 97: 11050.

[26] Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 1999, 9: 179–194.

[27] Adler CM, DelBello MP, Jarvis K, Levine A, Adams J, Strakowski SM. Voxel-based study of structural changes in first-episode patients with bipolar disorder. Biol Psychiatry 2007, 61: 776–781.

[28] Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. Neuroimage 2009, 48: 63–72.

[29] Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 2005, 162: 2233–2245.

[30] Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res 2001, 49: 1–52.

[31] Mane A, Falcon C, Mateos JJ, Fernandez-Egea E, Horga G, Lomena F*, et al.* Progressive gray matter changes in first episode schizophrenia: a 4-year longitudinal magnetic resonance study using VBM. Schizophr Res 2009, 114: 136–143.

[32] Sheng J, Zhu Y, Lu Z, Liu N, Huang N, Zhang Z*, et al.* Altered volume and lateralization of language-related regions in first-episode schizophrenia. Schizophr Res 2013, 148: 168–174.

[33] Chen Z, Deng W, Gong Q, Huang C, Jiang L, Li M*, et al.* Extensive brain structural network abnormality in first-episode treatment-naive patients with schizophrenia: morphometrical and covariation study. Psychol Med 2014, 44: 2489–2501.

[34] Lui S, Deng W, Huang X, Jiang L, Ma X, Chen H*, et al.* Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. Am J Psychiatry 2009, 166: 196–205.

[35] Hu M, Li J, Eyler L, Guo X, Wei Q, Tang J*, et al.* Decreased left middle temporal gyrus volume in antipsychotic drug-naive, first-episode schizophrenia patients and their healthy unaffected siblings. Schizophr Res 2013, 144: 37–42.

[36] Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM. Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. Neuroimage 2002, 17: 880–889.

[37] Borgwardt SJ, Picchioni MM, Ettinger U, Toulopoulou T, Murray R, McGuire PK. Regional gray matter volume in monozygotic twins concordant and discordant for schizophrenia. Biol Psychiatry2010, 67: 956–964.

[38] Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 2010, 46: 831–844.

[39] Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biol Psychiatry1999, 46: 908–920.

[40] Wang Q, Xiang B, Deng W, Wu J, Li M, Ma X*, et al.* Genome-wide association analysis with gray matter volume as a quantitative phenotype in first-episode treatment-naive patients with schizophrenia. PLoS One 2013, 8: e75083.

[41] Bottmer C, Bachmann S, Pantel J, Essig M, Amann M, Schad LR*, et al.* Reduced cerebellar volume and neurological soft signs in first-episode schizophrenia. Psychiatry Res 2005, 140: 239–250.

[42] Nopoulos PC, Ceilley JW, Gailis EA, Andreasen NC. An MRI study of cerebellar vermis morphology in patients with schizophrenia: evidence in support of the cognitive dysmetria concept. Biol Psychiatry1999, 46: 703–711.

[43] Okugawa G, Nobuhara K, Takase K, Kinoshita T. Cerebellar posterior superior vermis and cognitive cluster scores in drug-naive patients with first-episode schizophrenia. Neuropsychobiology 2008, 56: 216–219.

[44] Raznahan A, Greenstein D, Lee Y, Long R, Clasen L, Gochman P*, et al.* Catechol-o-methyl transferase (COMT) val< sup> 158</sup> met polymorphism and adolescent cortical development in patients with childhood-onset schizophrenia, their non-psychotic siblings, and healthy controls. Neuroimage 2011, 57: 1517–1523.

[45] Rakic P. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci 1995, 18: 383–388.

[46] Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci 2004, 1021: 77–85.

[47] Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N*, et al.* Neurodevelopmental trajectories of the human cerebral cortex. J Neurosci 2008, 28: 3586–3594.

[48] Narr KL, Bilder RM, Toga AW, Woods RP, Rex DE, Szeszko PR*, et al.* Mapping cortical thickness and gray matter concentration in first episode schizophrenia. Cereb Cortex 2005, 15: 708–719.

[49] Thormodsen R, Rimol LM, Tamnes CK, Juuhl-Langseth M, Holmen A, Emblem KE*, et al.* Age-related cortical thickness differences in adolescents with early-onset schizophrenia compared with healthy adolescents. Psychiatry Res 2013, 214: 190–196.

[50] Voets NL, Hough MG, Douaud G, Matthews PM, James A, Winmill L, *et al.* Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. Neuroimage 2008, 43: 665–675.

[51] Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, *et al.* Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex 2009, 19: 2728–2735.

[52] Jiao Y, Chen R, Ke XY, Chu KK, Lu ZH, Herskovits EH. Predictive models of autism spectrum disorder based on brain regional cortical thickness. Neuroimage 2010, 50: 589–599.

[53] Hyde KL, Samson F, Evans AC, Mottron L. Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. Hum Brain Mapp 2010, 31: 556–566.

[54] Palaniyappan L, Liddle PF. Differential effects of surface area, gyrification and cortical thickness on voxel based morphometric deficits in schizophrenia. Neuroimage 2012, 60: 693–699.

[55] Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006, 129: 564–583.

[56] Whittaker JF, Deakin JF, Tomenson B. Face processing in schizophrenia: defining the deficit. Psychol Med 2001, 31: 499–507.

[57] Lakis N, Jimenez JA, Mancini-Marie A, Stip E, Lavoie ME, Mendrek A. Neural correlates of emotional recognition memory in schizophrenia: effects of valence and arousal. Psychiatry Res 2011, 194: 245–256.

[58] Lepage M, Pelletier M, Achim A, Montoya A, Menear M, Lal S. Parietal cortex and episodic memory retrieval in schizophrenia. Psychiatry Res 2010, 182: 191–199.

[59] Ranganath C, Minzenberg MJ, Ragland JD. The cognitive neuroscience of memory function and dysfunction in schizophrenia. Biol Psychiatry 2008, 64: 18–25.

[60] Danion JM, Huron C, Vidailhet P, Berna F. Functional mechanisms of episodic memory impairment in schizophrenia. Can J Psychiatry 2007, 52: 693–701.

[61] Brent BK, Seidman LJ, Thermenos HW, Holt DJ, Keshavan MS. Self-disturbances as a possible premorbid indicator of schizophrenia risk: a neurodevelopmental perspective. Schizophr Res 2014, 152: 73–80.

[62] Guo S, Kendrick KM, Yu R, Wang HL, Feng J. Key functional circuitry altered in schizophrenia involves parietal regions associated with sense of self. Hum Brain Mapp 2014, 35: 123–139.

[63] Vercammen A, Knegtering H, den Boer JA, Liemburg EJ, Aleman A. Auditory hallucinations in schizophrenia are associated with reduced functional connectivity of the temporo-parietal area. Biol Psychiatry 2010, 67: 912–918.

[64] Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. Neuroimage 2008, 42: 1178–1184.

[65] Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, *et al.* Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci U S A 2009, 106: 1279–1284.

[66] Holt DJ, Cassidy BS, Andrews-Hanna JR, Lee SM, Coombs G, Goff DC, *et al.* An anterior-to-posterior shift in midline cortical activity in schizophrenia during self-reflection. Biol Psychiatry 2011, 69: 415–423.

[67] Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 2009, 33: 279–296.

[68] Narr KL, Toga AW, Szeszko P, Thompson PM, Woods RP, Robinson D, *et al.* Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry 2005, 58: 32–40.

[69] Schultz CC, Koch K, Wagner G, Roebel M, Nenadic I, Schachtzabel C, *et al.* Complex pattern of cortical thinning in schizophrenia: results from an automated surface based analysis of cortical thickness. Psychiatry Res 2010, 182: 134–140.

[70] Rimol LM, Nesvåg R, Hagler Jr DJ, Bergmann Ø, Fennema-Notestine C, Hartberg CB, *et al.* Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. Biol Psychiatry 2012, 71: 552–560.

[71] McIntosh AM, Baig BJ, Hall J, Job D, Whalley HC, Lymer GKS, *et al.* Relationship of catechol-O-methyltransferase variants to brain structure and function in a population at high risk of psychosis. Biol Psychiatry 2007, 61: 1127–1134.

[72] Mechelli A, Tognin S, McGuire PK, Prata D, Sartori G, Fusar-Poli P, *et al*. Genetic vulnerability to affective psychopathology in childhood: a combined voxel-based morphometry and functional magnetic resonance imaging study. Biol Psychiatry 2009, 66: 231–237.

[73] Taylor WD, Züchner S, Payne ME, Messer DF, Doty TJ, MacFall JR, *et al.* The COMT Val158Met polymorphism and temporal lobe morphometry in healthy adults. Psychiatry Res 2007, 155: 173–177.

[74] Cerasa A, Gioia MC, Labate A, Liguori M, Lanza P, Quattrone A. Impact of catechol-O-methyltransferase Val108/158 Met genotype on hippocampal and prefrontal gray matter volume. Neuroreport 2008, 19: 405–408.

[75] Küppers E, Beyer C. Dopamine regulates brain-derived

neurotrophic factor (BDNF) expression in cultured embryonic mouse striatal cells. Neuroreport 2001, 12: 1175–1179.

[76] Raznahan A, Greenstein D, Lee Y, Long R, Clasen L, Gochman P*, et al*. Catechol-o-methyl transferase (COMT) val158met polymorphism and adolescent cortical development in patients with childhood-onset schizophrenia, their non-psychotic siblings, and healthy controls. Neuroimage 2011, 57: 1517–1523.

[77] Meyer–Lindenberg A, Nichols T, Callicott JH, Ding J, Kolachana B, Buckholtz J*, et al.* Impact of complex genetic variation in COMT on human brain function. Mol Psychiatry 2006, 11: 867–877.

[78] Fazio L, Blasi G, Taurisano P, Papazacharias A, Romano R, Gelao B*, et al.* D2 receptor genotype and striatal dopamine signaling predict motor cortical activity and behavior in humans. Neuroimage 2011, 54: 2915–2921.