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ORIGINAL ARTICLE

Spontaneous Regional Brain Activity in Healthy Individuals is Nonlinearly Modulated by the Interaction of *ZNF804A* rs1344706 and *COMT* rs4680 Polymorphisms

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Abstract *ZNF804A* rs1344706 has been identified as one of the risk genes for schizophrenia. However, the neural mechanisms underlying this association are unknown. Given that *ZNF804A* upregulates the expression of *COMT*, we hypothesized that *ZNF804A* may influence brain activity by interacting with *COMT*. Here, we genotyped *ZNF804A* rs1344706 and *COMT* rs4680 in 218 healthy Chinese participants. Amplitudes of low-frequency fluctuations (ALFFs) were applied to analyze the main and interaction effects of *ZNF804A* rs1344706 and *COMT* rs4680. The ALFFs of the bilateral dorsolateral prefrontal cortex showed a significant *ZNF804A* rs1344706 × *COMT* rs4680 interaction, manifesting as a U-shaped modulation, presumably by dopamine signaling. Significant main effects were also found. These findings suggest that *ZNF804A* affects the resting-state functional activation by interacting with *COMT*, and may improve our understanding of the neurobiological effects of *ZNF804A* and its association with schizophrenia.

Keywords Zinc finger protein 804A · Catechol-O-methyltransferase · Amplitudes of low-frequency fluctuations · fMRI

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Introduction

Schizophrenia (SZ) is a severe and complex psychiatric disorder with high polygenic heredity [1–3]. Many studies have shown that the dopamine (DA) system is of fundamental importance to the etiology of SZ, and its dysfunction may lead to the neurobiological abnormalities in SZ [4]. Catechol-O-methyltransferase (COMT) is thought to be the most important modulator of synaptic DA concentration in the brain [5, 6]. COMT participates in DA degradation at the biochemical level, as well as complex cognitive functions such as cognitive control and working memory at the psychological level [7]. DA is vital for neuronal development and an appropriate DA level promotes neuronal growth and differentiation [8]. Compared with Val/Val homozygotes, *COMT* rs4680 Met-allele carriers have decreased enzymatic activity and increased synaptic DA concentration [2, 6]. The modulation of cognitive function and imaging phenotypes by extracellular DA is nonlinear. That is to say, both the lowest and highest DA levels may have an unfavorable effect [5, 9–11].

Zinc finger protein 804A (*ZNF804A*) is one of the candidate genes for schizophrenia and some association studies have been conducted for *ZNF804A* rs1344706 [12–14]. Overexpression of *ZNF804A* mRNA has been suggested to regulate the expression of schizophrenia-associated genes, including *COMT* [15]. Expressed *ZNF804A* can interact with the promoter region of *COMT* and increase the transcript level of *COMT* [15], suggesting that a potential genotypic interaction causes different phenotypes.

The resting-state spontaneous brain activity was selected because of the functional properties of the DA system, which has a complex release pattern, dynamically influencing the neuronal activity [16–18]. Based on the upregulating effect of *ZNF804A* on *COMT* [15] and the modulatory effect of *COMT* on DA signaling [5, 6, 19], we can roughly estimate the extracellular DA levels in the human brain. For instance, the *COMT* Met-allele-*ZNF804A* CC carriers would have the highest DA level, while the *COMT* Val/Val-*ZNF804A* CA carriers would have the lowest DA level.

The amplitude of low-frequency fluctuations (ALFF) is considered a reliable and sensitive measure in both healthy and clinical populations [20–22]. The spontaneous LFFs of blood oxygenation level-dependent (BOLD) signals at rest have been identified as a biological measure of baseline spontaneous activity in the brain [21, 23–26]. An abnormal ALFF can reflect a pathophysiological state in a brain area and help locate specific impaired brain regions during the resting state [21]. As an additional advantage, ALFF can be used to assess neuronal activity within the entire brain [21]. Most recent studies have suggested that ALFF might be a measure of the spontaneous neuronal activity in brain regions [21] associated with the low-frequency BOLD fluctuations obtained by resting fMRI [27]. In particular, using rs-fMRI, many previous studies have reported the dysfunctional regulation in schizophrenia patients [28–30].

In this study, we measured resting-state spontaneous activity in the brains of healthy participants to test the hypothesis that *ZNF804A* affects brain function by indirectly modulating the expression level of *COMT*.

Materials and Methods

A total of 218 right-handed Chinese participants (18–60 years, mean 29.0 years; 85 males and 133 females) were recruited from the community. There was no personal history of a DSM-IV Axis I Disorder (SCID) [31] in these individuals or their first-degree family members, as assessed by the Family History Screen for Epidemiologic Studies [32]. None had a history of medical or neurological disorders or took medications with a potential effect on the central nervous system or had a loss of consciousness for $\geq$ 5 min. The participants did not use substances the week prior to scanning, and all had negative results for urine toxicology screens on the day of scanning and had no contraindications for MRI examination. After a full explanation of the study, all participants provided written informed consent. This research was approved by the Medical Research Ethics Committee of China Medical University and were in accord with the Declaration of Helsinki.

Genotyping

Genomic DNA was extracted from peripheral blood samples using the Qiagen QIAamp DNA Mini Kit (Hilden, Germany). The *ZNF804A* rs1344706 (C/A) and *COMT* rs4680 (Val158Met) genotypes were determined using the Sanger sequencing method. The participants were divided into six genotypic subgroups: Val/Val/AA, Val/Val/CA, Val/Val/CC, Met-allele/AA, Met-allele/CA, and Met-allele/CC according to the *COMT* rs4680 and *ZNF804A* rs1344706 genotypes.

MRI Data Acquisition

MRI scans were performed on a 3-Tesla GE Signa HDX MR scanner (General Electric, Boston, MA) in the Department of Radiology of the First Hospital of China Medical University. Three-dimensional T1-weighted images were obtained using a fast spoiled gradient echo sequence: repetition time (TR) = 7.1 ms, echo time (TE) = 3.2 ms, field of view (FOV) = 24 cm $\times$ 24 cm, matrix = 240 $\times$ 240, flip angle = 15°, slice thickness = 1 mm, no gap. Functional imaging data were acquired using gradient echo planar imaging: TR = 2000 ms, TE = 30 ms, FOV = 24 cm $\times$ 24 cm, matrix = 64 $\times$ 64, flip angle = 90°, 35 3-mm slices without gap. Earplugs and soft pads were used during scanning to reduce scanner noise and restrict head motion. Participants were instructed to relax with their eyes closed but remain awake and think of nothing in particular throughout the resting-state scan.

MRI Data Preprocessing

Data preprocessing was conducted using the Data Processing & Analysis of Brain Imaging software package (http://rfmri.org/dpabi) [33], running on MatLab. The first 10 time points were discarded to allow adaptation to the scanning noise and spin saturation. Slice timing and realignment for head motion correction were performed. Participants with head motion > 3.0 mm of maximum displacement in any dimension (x, y, or z) or 3° of maximum angular motion were excluded. The images were normalized into standard

Montreal Neurological Institute (MNI) space, and re-sampled to 3 mm × 3 mm × 3 mm voxels. Then, spatial smoothing was conducted with a 6-mm full-width at half-maximum Gaussian kernel. Removal of linear trends and bandpass filtering (0.01–0.08 Hz) were performed to reduce very low-frequency drift and high-frequency noise [34]. Nuisance covariates (head motion parameters, cerebrospinal fluid signal, white matter signal, and global mean signal) generated in the above steps were regressed out.

ALFF Calculation

ALFF calculations were performed as described in previous studies [35]. The filtered time series were first converted to the frequency domain using a Fast Fourier transform, and the power spectrum was then determined. The square root was calculated at each frequency of the power spectrum and averaged between 0.01 and 0.08 Hz. This averaged square root was termed the ALFF [22]. For standardization, the ALFF of each voxel was divided by the global mean ALFF value. The global mean ALFF was calculated only within the brain, excluding the background and tissues outside of the brain.

Statistical Analysis

A two-way (*COMT* and *ZNF804A*) analysis of variance (ANOVA) was used to compare demographic data (age and education) with SPSS 13.0 software (SPSS Inc., Chicago, IL). Chi-square tests were used to compare gender between subgroups ($P < 0.05$). Two schemes were used to determine the order of the six genotypic groups based on DA signaling from low to high under different hypotheses for the effects of *ZNF804A* rs1344706 and *COMT* rs4680. If the *COMT* rs4680 has a stronger effect than *ZNF804A* rs1344706, the presumed order would be: Val/Val/CA < Val/Val/AA < Val/Val/CC < Met-allele/CA < Met-allele/AA < Met-allele/CC. Conversely, if the *ZNF804A* rs1344706 has a stronger effect, the presumed order would be: Val/Val/CA < Met-allele/CA < Val/Val/AA < Met-allele/AA < Val/Val/CC < Met-allele/CC. We used curve fitting analysis to determine which scheme was more plausible, based on the U-shaped modulation of DA.

Two-way ANOVA was performed in Statistical Parametric Mapping (SPM) software (SPM8; Wellcome Department of Cognitive Neurology, London, UK) with *ZNF804A* rs1344706 (AA, CA, and CC) and *COMT* rs4680 (Val/Val, Met-allele) as two independent variables. The main and interaction effects between genotype groups were modeled. Age, gender, and education were considered to be covariates. Significant genotype interactions were interpreted using graphic displays and by performing *post-hoc* exploratory analyses separately.

Voxels with a P value < 0.01 and cluster size > 837 mm^3 (31 voxels) were considered indicative of significant differences; this was equal to a corrected threshold of $P < 0.05$ as determined by the Monte Carlo simulation (AlphaSim by B.D. Ward in AFNI software, http://afni.nimh.nih.gov/ [36]).

Results

Demographics and genotypic results

There was no significant difference in age ($P = 0.317$), gender ($P = 0.738$) or education ($P = 0.714$) among the six genotypic subgroups (Table 1). The genotype frequencies of both *COMT* rs4680 and *ZNF804A* rs1344706 were consistent with Hardy-Weinberg equilibrium (*COMT*: $\chi^2 = 0.41$, $P = 0.52$; *ZNF804A*: $\chi^2 = 2.22$, $P = 0.13$).

ALFF Results

Interactions Involving COMT and ZNF804A Genotypes

The significant interaction and main effects between the two SNPs are listed in Table 2. We found a significant *COMT* rs4680 × *ZNF804A* rs1344706 interaction (Right: $= 23.583$, $P < 0.001$, corrected; Left: $F = 9.689$, $P < 0.001$, corrected) in the ALFF values for the bilateral dorsolateral prefrontal cortex (DLPFC) (Left: Peak MNI coordinates: x = − 21, y = 21, z = 54; cluster size = 31 voxels; peak $F = 9.2002$; Right: Peak MNI coordinates: x = 30, y = 33, z = 33; cluster size = 116 voxels; peak $F = 11.028$; Fig. 1A). The ALFF values with a significant *COMT* rs4680 × *ZNF804A* rs1344706 interaction were extracted from the data of each participant. The distributions of ALFFs of the two clusters in the genotypic subgroups (which reflected the presumed DA signaling) displayed a U-shape (Fig. 1B). By sorting according to *COMT*, the quadratic regression was significant (Right: $r^2 = 0.068$, $P = 0.001$; Left: $r^2 = 0.115$, $P < 0.001$) (Fig. S1).

Effect of COMT Genotype on ALFF

After performing a two-way ANOVA on the ALFF maps, significant main effects of *COMT* were found (all $P < 0.001$, corrected). *COMT* Met carriers showed increased ALFF in the left DLPFC and right orbitofrontal cortex (OFC), as well as decreased ALFF in the right parietal cortex, left paracentral lobule, and middle cingulate gyrus (Fig. 2).

Table 1 Demographics of different genotypic groups

Genotypic groups	n = 218	Age (years)	Education (years)	Gender (male/female)
COMT Met-allele/*ZNF804A* AA	18	27.28 (9.492)	12.11 (3.984)	8/10
COMT Met-allele/*ZNF804A* CA	58	28.43 (13.462)	12.11 (3.663)	26/32
COMT Met-allele/*ZNF804A* CC	22	26.50 (11.999)	12.05 (3.798)	8/14
COMT Val/Val/*ZNF804A* AA	31	27.65 (11.803)	12.16 (3.417)	10/21
COMT Val/Val/*ZNF804A* CA	62	29.05 (12.768)	11.81 (3.625)	25/37
COMT Val/Val/*ZNF804A* CC	27	34.07 (14.301)	13.27 (4.153)	8/19
Statistics	218	F = 1.186	F = 0.581	χ^2 = 2.751
P		0.317	0.714	0.738

Data are shown as the mean (SD)

Table 2 Clusters exhibiting the influence of *COMT* and *ZNF804A* polymorphism on ALFF

Brain areas	BA	Cluster size (Voxel)	Peak MNI coordinates			Peak F value
			X	Y	Z	
Main effect of *COMT* polymorphism						
Right orbitofrontal cortex	11	33	12	51	− 24	22.761
Left paracentral lobule/middle cingulate gyrus	6/31	47	0	− 15	45	22.554
Left dorsolateral prefrontal cortex	8	69	− 21	21	54	23.802
Right parietal cortex	7/5/40	352	6	− 51	69	40.151
Main effect of *ZNF804A* polymorphism						
Left calcarine gyrus/posterior cingulate gyrus/cuneus	18	42	− 18	− 69	12	11.550
Interaction effect of *COMT* × *ZNF804A*						
Right dorsolateral prefrontal cortex	8/9	116	30	33	33	23.583
Left dorsolateral prefrontal cortex	8	31	− 21	21	54	9.689

These findings correspond to a corrected $P < 0.01$ by AlphaSim correction.

BA Brodmann's area.

Effect of ZNF804A Genotype on ALFF

There was also a significant main effect of *ZNF804A* (F = 11.550, $P < 0.001$, corrected). *ZNF804A* CC homozygotes exhibited decreased ALFF in the left calcarine gyrus, posterior cingulate gyrus, and cuneus than the CA ($P < 0.001$, corrected) and AA genotypes ($P < 0.001$, corrected). There was no significant difference in ALFF between CA and AA carriers (P = 0.534, corrected) (Fig. 3).

Discussion

In the present study, we have demonstrated for the first time that two SNPs (*COMT* rs4680 and *ZNF804A* rs1344706) influence spontaneous regional brain activity in healthy individuals. We found a significant *COMT* rs4680 × *ZNF804A* rs1344706 interaction in the ALFF in the bilateral DLPFC, suggesting a U-shaped modulation by presumed DA signaling. These measurable alterations in brain activity may serve as useful hallmarks to help reflect different expression levels of DA.

It is well known that brain DA may closely affect neurobiological and behavioral phenotypes such as working memory, emotional response, and cognitive control, especially in prefrontal cortex (PFC) [37]. DA modulates the structural and functional properties of the brain in a nonlinear manner [38]. As a result, both lower and higher extracellular DA levels may impair neuronal integrity and survival. An optimal extracellular DA level may induce the generation of brain-derived neurotropic factor (BDNF) and facilitate neuronal growth. An excessive DA level can reduce *BDNF* gene expression [39]. In contrast, reduced DA signaling can impair the expression of DA-mediated behavioral responses by affecting the neurochemical architecture of the striatum [40]. This neural mechanism may be explained by the DA level-dependent neurotrophic and neurotoxic effects [5, 41–43]. Val-allele carriers have relatively high *COMT* activity and presumably low

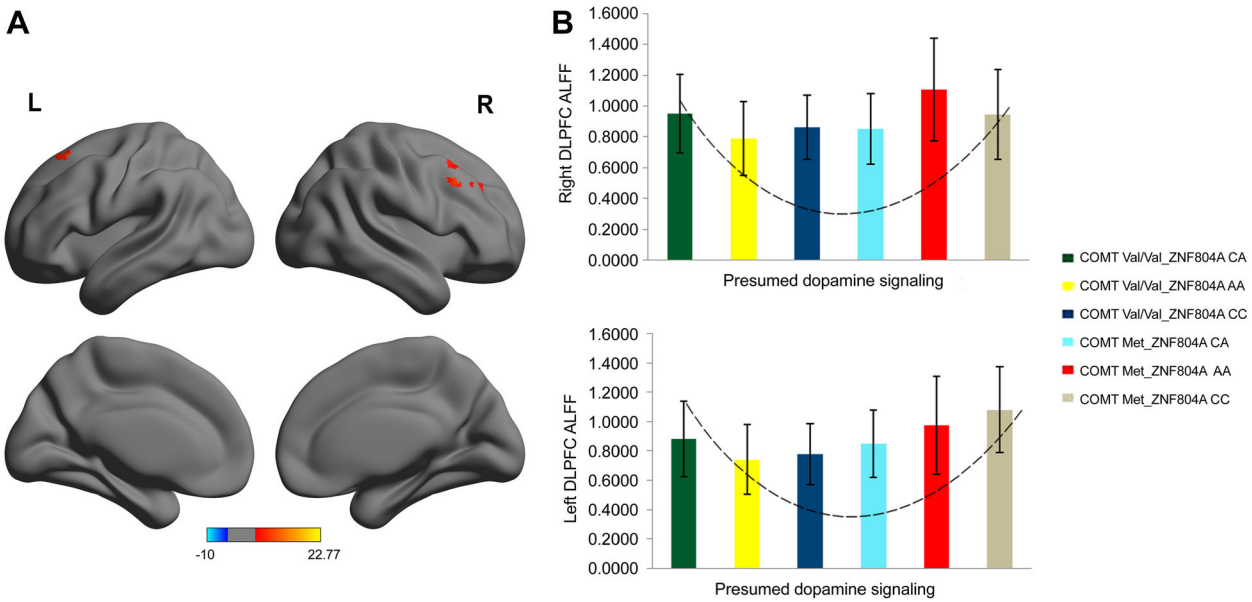

Fig. 1 The significant *COMT* rs4680 × *ZNF804A* rs1344706 interaction. **A** Clusters with significance for the interaction effect in the bilateral DLPFC (< 0.001 by AlphaSim correction, and 31 voxels minimum). Color bar represents the range of values. **B** Interaction graph showing the distribution of ALFFs of the two clusters in these genotypic subgroups (which reflected presumed DA signaling) displayed as a U-shape.

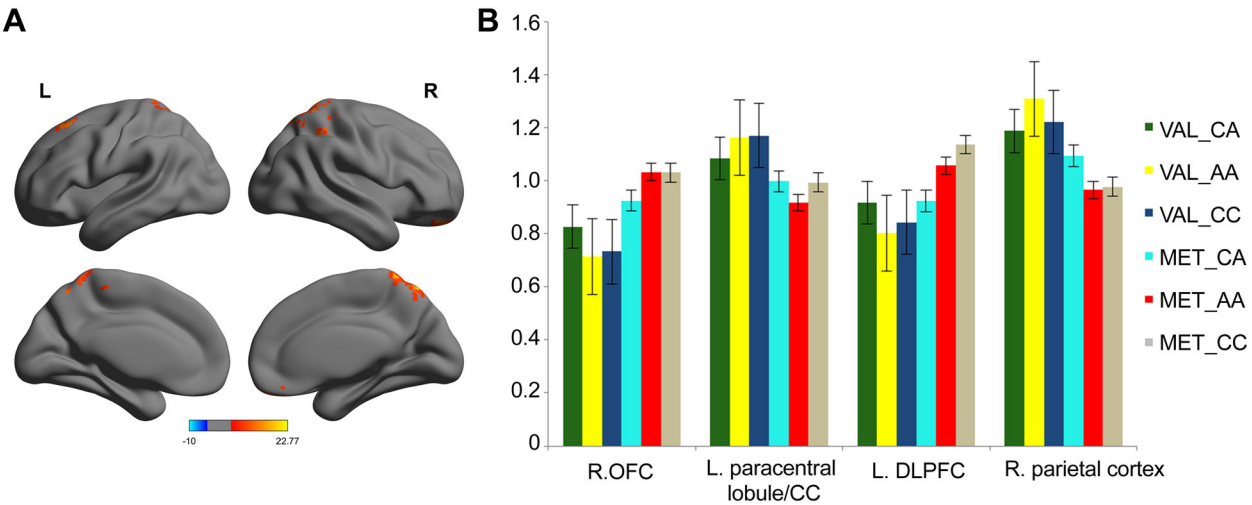

Fig. 2 The main effect of *COMT* genotype on ALFF. **A** Clusters with a significant main effect of *COMT* genotype in the left DLPFC, right OFC, right parietal cortex, left paracentral lobule, and middle cingulated gyrus. Color bar represents the range of values. **B** *COMT* Met carriers showed increased ALFF in the left DLPFC and right OFC, and decreased ALFF in the right parietal cortex, left paracentral lobule, and middle cingulated gyrus compared to *COMT* Val/Val carriers at rest (all $P < 0.001$, corrected).

baseline DA; conversely, Met-allele carriers have relatively low *COMT* activity and presumably high baseline DA.

Although it is known that *COMT* rs4680 affects brain function by modulating the DA concentration in brain regions especially the PFC, the effect of *ZNF804A* rs1344706 on DA signaling is rather complex [12, 44, 45]. A-allele carriers may have a higher expression of *ZNF804A* than CC homozygotes [46, 47]. The *ZNF804A* CA heterozygote in the other SNP (rs12476147) can further result in the over-expression of *ZNF804A* in the human brain [48, 49]. Consequently, this presumably results in a significant increase in the transcript levels of *COMT* [15]. Different genotypic combinations of *ZNF804A* rs1344706 and *COMT* rs4680 can generate multiple subgroups with different levels of DA. We proposed two sorting schemes according to the two genotypes. Based on the inverted U-shape hypothesis of DA signaling on the PFC [9], quadratic curve-fitting analysis suggested that a more

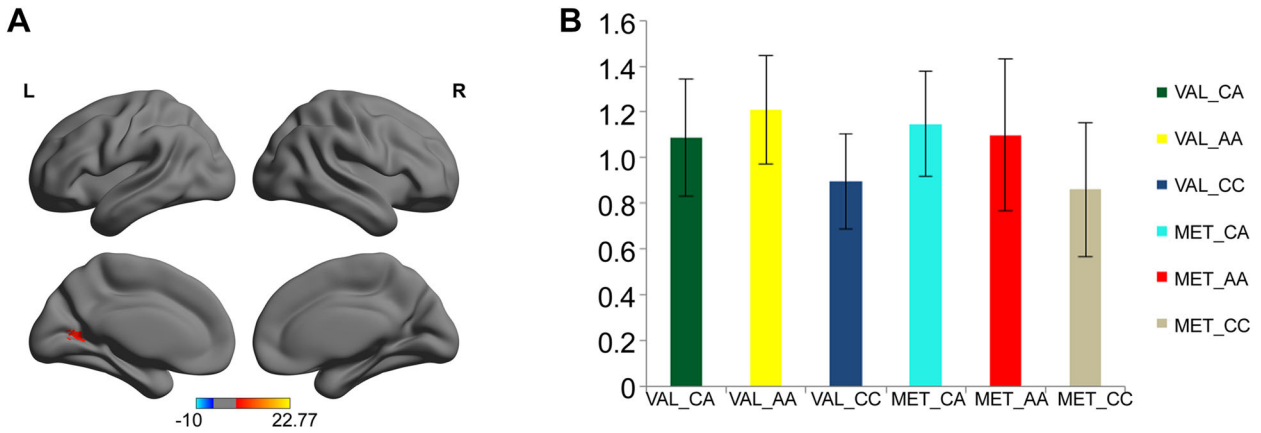

Fig. 3 The main effect of *ZNF804A* genotype on ALFF. **A** A cluster (red) with significant main effect of *ZNF804A* genotype, including the left calcarine gyrus, posterior cingulate gyrus, and cuneus. Color bar represents the range of values. **B** *ZNF804A* CC homozygotes exhibited decreased ALFF in the cluster containing the left calcarine gyrus, posterior cingulate gyrus, and cuneus than CA ($P < 0.001$, corrected) and AA genotypes ($P < 0.001$, corrected).

reasonable sorting scheme is Val/Val/ CA < Val/Val/AA < Val/Val/CC < Met-allele/CA < Met-allele/AA < Met-allele/CC in the presumed DA signaling from low to high. In addition, our presumed sorting scheme is consistent with other findings of rs-fMRI studies examining prefrontal volume [50].

Here, we found U-shaped modulation of the presumed DA signaling in the ALFF of the bilateral DLPFC, which can be well explained by DA-dependent neurotrophic and neurotoxic effects. The PFC contains a large number of DA receptors and is highly sensitive to its dopaminergic environment. The DLPFC is the major component of heteromodal cortex [51]. Human and non-human primate studies indicate that heteromodal cortex contains interconnected higher-order neural circuits mediating complex cognitive tasks, such as language, focused attention, and working memory. More evidence indicates that SZ patients have deficits in cognitive function, especially for functions subserved by heteromodal cortex. DLPFC involvement in SZ is well documented [52]. Increased ALFF values in the bilateral DLPFC indicated abnormities in brain activity [53, 54]. Individuals with the *COMT* Val/Val_*ZNF804A* CC or the *COMT* Met-allele_*ZNF804A* CA genotype have optimal DA levels, which correspond with a normal ALFF on the bilateral DLPFC. In contrast, individuals with the *COMT* Val/Val_*ZNF804A* CA or the *COMT* Met-allele_*ZNF804A* CC genotype have a DA level that is either too high or too low, which may impair neuronal survival and show an increased ALFF [50]. The U-shaped modulation of function may indicate a compensatory mechanism through which healthy young adults could maintain normal behavioral.

Although we focused on the significant interaction effect between the two SNPs, there were also significant main effects of *COMT* and *ZNF804A* on the ALFF. It is possible that variation in *COMT* and *ZNF804A* may contribute to the abnormal ALFF values in different brain regions separately in individuals. Both *COMT* and *ZNF804A* have their respective effects on brain activities, and our results are consistent with the previous findings of rs-fMRI studies [55, 56].

A number of limitations of this study should be discussed. First, the present research did not include a sample of SZ patients. Nevertheless, our results may be applicable to SZ because the two SNPs have been separately shown with effects between healthy individuals and SZ patients. Therefore, our findings in healthy individuals could provide some indications for patients. Second, although we suggest that the effects of genetic variation on corticolimbic circuitry may be implicated in neuropathophysiology, it is likely that the development of symptoms also depends on other interacting factors, such as genetic or environmental factors. More studies are needed to clarify these processes and directly assess the effects on SZ patients. A larger sample is needed to verify our results.

Conclusions

In conclusion, our findings imply that *ZNF804A* rs1344706 and *COMT* rs4680 are associated with brain activity of corticolimbic neural circuitry. We first investigated the epistatic interaction between *ZNF804A* rs1344706 and *COMT* rs4680 in the functional activation of the bilateral DLPFC, which may improve our further understanding on the pathophysiological mechanism underlying functional abnormalities in the prefrontal-corticolimbic circuitry in schizophrenia.

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Conflicts of interest The authors have no conflicts of interest to declare.

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