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ORIGINAL RESEARCH

ZNF804A rs1344706 interacts with *COMT* rs4680 to affect prefrontal volume in healthy adults

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Abstract The biological function of *ZNF804A* rs1344706, the first genome-wide supported risk variant of schizophrenia, remains largely unknown. Based on the upregulating effect of *ZNF804A* on the expression of *COMT*, we hypothesize that *ZNF804A* may affect grey matter volume (GMV) by interacting with *COMT*. Voxel-based morphometry was applied to analyze the main and interaction effects of *ZNF804A* rs1344706 and *COMT* rs4680 on brain GMV in 274 healthy young human subjects. The GMV of the left dorsolateral prefrontal cortex (DLPFC) showed a significant *COMT* rs4680 × *ZNF804A* rs1344706 interaction, manifesting as an inverted U-shape modulation by the presumed dopamine signaling. In *COMT* Met-allele carriers, the *ZNF804A* TG heterozygotes showed greater GMV in the left DLPFC than both GG and TT homozygotes. In *COMT* Val/Val homozygotes, however, the *ZNF804A* TG heterozygotes exhibited smaller GMV in the left DLPFC than GG homozygotes and comparable GMV with TT homozygotes. These findings suggest that *ZNF804A* affects the GMV of the prefrontal cortex by interacting with *COMT*, which may improve our understanding of neurobiological effect of *ZNF804A* and its association with schizophrenia.

Keywords *ZNF804A* · *COMT* · Single nucleotide polymorphism · Grey matter volume · Magnetic resonance imaging

Introduction

As a complex and polygenic hereditary disorder, schizophrenia has been linked to multiple genetic variations (Purcell et al. 2009; Kauppi et al. 2015; Walton et al. 2013). Among these genetic variations, a single nucleotide polymorphism (SNP) in zinc finger protein 804A (*ZNF804A,* rs1344706*,* G > T) is consistently associated with schizophrenia in Caucasian (Esslinger et al. 2009; O'Donovan et al. 2008). Recently, one large scale meta-analysis has shown that the allelic effects of *ZNF804A* rs1344706 are in the same direction between Asian and European populations (Xiao et al. 2016). Although biological function of this SNP remains largely unknown, *ZNF804A* rs1344706 has been suggested to be linked to schizophrenia by regulating the expression of risk genes of schizophrenia, including catechol-O-methyltransferase (*COMT*), *PRSS16*, *PDE4B* and *DRD2* (Girgenti et al. 2012). For example, the expression of *ZNF804A* can interact with the premotor region of *COMT* and result in an increase in transcript level of *COMT* (Girgenti et al. 2012), suggesting a potential genotypic interaction between *ZNF804A* and *COMT* on phenotypes.

COMT catalyzes the degradation of synaptic dopamine in the brain, especially in the prefrontal cortex (PFC) because of the lack of dopamine transporter in the PFC synapses (Mannisto and Kaakkola 1999; Seamans and Yang 2004). Compared with Val/Val homozygotes of *COMT* rs4680, Met-allele carriers have a fourfold lower enzymatic activity resulting in higher extracellular dopamine concentration

Qiang Xu and Yongqin Xiong contributed equally to the work.

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(Mannisto and Kaakkola 1999; Seamans and Yang 2004; Chen et al. 2004a, b; Lachman et al. 1996). An optimal dopamine signaling promotes neuronal growth and differentiation by inducing the expression of brain-derived neurotropic factor (BDNF) (Kuppers and Beyer 2001), which is vital for neurodevelopment of the brain, such as the hippocampal volume (Ho et al. 2007; Szeszko et al. 2005). However, insufficient or excessive extracellular dopamine signaling can impair the neuronal integrity and survival (Honea et al. 2009; Kuppers and Beyer 2001; Noh et al. 1999). As a result, the modulation of extracellular dopamine signaling on cognitive and imaging phenotypes is nonlinear, in which both the lowest and highest dopamine levels may play an unfavorable effect (Seamans and Yang 2004; Tian et al. 2013; Zhao et al. 2015).

Similar to the effect of *COMT* rs4680, *ZNF804A* rs1344706 also affects the PFC volume in both schizophrenia patients and healthy subjects (Schultz et al. 2014; Lencz et al. 2010; Wei et al. 2015). However, the neurobiological mechanisms underlying the *ZNF804A* effect remain largely unknown. Because *ZNF804A* can upregulate the transcription of *COMT* (Girgenti et al. 2012) and *COMT* can affect grey matter volume (GMV) of the brain (Tian et al. 2013; Honea et al. 2009), we hypothesize that *ZNF804A* may indirectly affect brain GMV by modulating the expression of the *COMT*.

To test the hypothesis, we performed voxel-wise GMV analysis to identify *COMT* rs4680 × *ZNF804A* rs1344706 interactions in 274 Chinese Han healthy young individuals. The GMV was selected because the heritability of structural properties is much greater than that of functional properties (Winkler et al. 2010; Glahn et al. 2010; Hibar et al. 2015). Based on the upregulating effect of *ZNF804A* on *COMT* (Girgenti et al. 2012) and the modulatory effect of *COMT* on dopamine signaling (Mannisto and Kaakkola 1999; Seamans and Yang 2004; Chen et al. 2004a, b Lachman et al. 1996), we can roughly estimate the extracellular dopamine signaling in the human brain. For instance, subjects with *COMT* Val/Val and *ZNF804A* TG would show the lowest dopamine signaling; in contrast, subjects with Met-allele/GG would have the highest dopamine signaling.

Materials and methods

Subjects

A total of 323 right-handed healthy young human subjects (157 males and 166 females, mean age = 22.7 years, range = 18–31 years) participated in the study. Participants were screened carefully to guarantee that they had no history of neurological or psychological diseases, mental retardation, traumatic brain injury, alcoholism or drug dependency and abuse, psychiatric treatment or visible brain lesions, and had no contraindication for MRI examinations. Only Chinese Han subjects were included in the study to purify the sample. All subjects were strongly right-handed judged by the Chinese edition of the Edinburgh Handedness Inventory (Oldfield 1971). After a full explanation of the study, all subjects provided written informed consent. The protocol was approved by the Ethics Committee of Tianjin Medical University.

Cognitive tests

The Chinese Revised Wechsler Adult Intelligence Scale (WAIS-RC) was used to measure the Full-scale Intelligence Quotient (FIQ) (Gong 1982). The working memory was evaluated using the n-back task outside of MR scanner (Owen et al. 2005). Detailed procedures of the task were described previously (Ding et al. 2012). The accuracy rate of the 3-back task was used to assess working memory performance.

Genotyping

Genomic DNA was extracted from white blood cells with the EZgene TM Blood gDNA Miniprep Kit according to standard protocols. *COMT* rs4680 was genotyped using the PCR and ligation detection reaction (LDR) method (Thomas et al. 2004; Yi et al. 2009). The PCR primer sequences for *COMT* were as follows: forward, 5′ GGGCCTACTGTG GCTACTCA 3′; and reverse: 5′ CCCTTTTTCCAGGT CTGACA 3′. Detailed procedures were described previously (Zhao et al. 2015). *ZNF804A* rs1344706 was genotyped using the iPLEX Gold Assay following the manufacturer's instructions and using primers (*ZNF804A* amplification primer 1: 5′-ACGTTGGATGCCAGATAGATATCCAAGAAG-3′; primer 2: 5′- ACGTTGGATGTCAAAGCCTTATCTCTTCAC-3′; *ZNF804A* extension primer: AGATCTCCAAGAAG TTGATTCTGAT. Detailed procedures please see (B. Liu et al. 2014). According to the genotypes of the *COMT* rs4680 and *ZNF804A* rs1344706, we divided subjects into six genotypic subgroups: Val/Val/TG, Val/Val/TT, Val/Val/GG, Met-allele/TG, Met-allele/TT and Met-allele/GG.

Image acquisition

MR images were acquired using a Signa HDx 3.0-Tesla MR scanner (General Electric, Milwaukee, WI, USA). For minimizing head motion and reducing scanner noise, tight but comfortable foam padding and ear plugs were used during scanning. Sagittal 3D T1-weighted images were acquired using a brain volume sequence with the following parameters: repetition time/echo time = 8.1/3.1 ms; inversion time = 450 ms; flap angle =13°; field of view =256 mm × 256 mm; matrix =256 × 256; slice thickness = 1 mm; no gap; and 176 sagittal slices.

Structural data preprocessing

All structural images were carefully checked slice by slice to ensure image quality and to exclude gross anatomical abnormalities. The structural MR images were segmented into grey matter (GM), white matter and cerebrospinal fluid using the Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Following segmentation, a GM template was generated from the entire image datasets using diffeomorphic anatomical registration through the exponentiated Lie algebra (DARTEL) technique. After an initial affine registration of the GM template to the tissue probability map in the Montreal Neurological Institute (MNI) space, non-linear warping of GM images was performed to the GM template in the MNI space with a resolution of 1.5-mm^3. The non-linear components derived during spatial normalization were used to modulate the GM value of each voxel (F. Liu et al. 2012). Finally, to compensate for residual between-subjects anatomical differences, the GMV images were smoothed using a Gaussian kernel of 8 mm full-width-at-half-maximum (FWHM).

Voxel-based morphometry (VBM) analysis

We performed analysis of covariance (ANCOVA) with a fully factorial (genotype-by-genotype) design with age, gender and years of education as nuisance variables to compare voxel-wise GMV differences between the two genotypic groups. Non-stationary cluster extent correction was utilized to correct inhomogeneity of local smoothness which might result in misestimate of cluster size (Kurth et al. 2015). We first set an initial voxel-wise threshold of $P = 0.0001$, and then we used the family wise error (FWE) method ($P < 0.05$) with non-stationary cluster size correction. If the interaction was significant, the significant clusters were picked as brain regions of interest (ROIs). We extracted each ROI by drawing a sphere (r = 3 mm) centered at the peak MNI coordinates of the ROI. The mean GMVs of these ROIs were compared across six genotypic subgroups.

Statistical analysis

Statistical analyses for the demographic, cognitive and behavioral data were performed using Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, IL, USA) for Windows. A two-way (*COMT* and *ZNF804A*) analysis of variance (ANOVA) was used to evaluate the main effects of each SNP and their interactions for demographic, cognitive and psychological data ($P < 0.05$).

Two schemes were used to define the order of the six genotypic groups with dopamine signaling from low to high under different hypotheses on the effects of *ZNF804A* rs1344706 and *COMT* rs4680. If the *ZNF804A* rs1344706 has a stronger effect than *COMT* rs4680, the presumed dopamine signaling from low to high would be: Val/Val/TG < Met-allele/TG < Val/Val/TT < Met-allele/TT < Val/Val/GG < Met-allele/GG. On the contrary, if the *COMT* rs4680 has a stronger effect than *ZNF804A* rs1344706, the presumed dopamine signaling from low to high would be: Val/Val/TG < Val/Val/TT < Val/Val/GG < Met-allele/TG < Met-allele/TT < Met-allele/GG. We used the quadratic curve fitting analysis to test which scheme is more plausible based on the inverted U-shape modulation of dopamine on the GMV of the brain (Tian et al. 2013).

Results

Demographic and genotypic data

After excluding of 37 participants with genotyping failure, one participant with poor image quality and 12 participants without cognitive data, a total of 274 healthy young Chinese Han participants finally included in the study. The genotypic distributions of both *COMT* rs4680 and *ZNF804A* rs1344706 were in Hardy-Weinberg equilibrium (*COMT*: $P = 0.987$, *ZNF804A*: $P = 0.484$). There were no significant differences ($P > 0.05$,details in Table 1) in gender, age, year of education, FIQ and working memory performance among the six genotypic groups.

Table 1 Demographic and behavioral data of the 274 finally included healthy young participants

Subgroups (COMT/ZNF804A)	n	Age (years)	Years of education	Gender (M:F)	FIQ	Accuracy 2-back (%)	Accuracy 3-back (%)
Met-allele/TT	32	23.1(2.6)	15.8(2.1)	18:14	116.3(12.6)	88.8(5.4)	81.8(6.0)
Met-allele/TG	70	22.5(2.3)	15.6(2.1)	38:32	116.9(8.8)	88.1(5.7)	81.4(7.3)
Met-allele/GG	45	22.5(2.9)	15.2(2.3)	19:26	114.2(8.8)	87.4(5.5)	81.1(6.1)
Val/Val/TT	34	22.9(2.3)	16.0(2.0)	15:19	118.7(6.8)	89.3(5.4)	83.5(5.5)
Val/Val/TG	61	23.0(2.5)	15.8(1.7)	25:36	117.1(9.0)	89.6(5.7)	81.5(6.6)
Val/Val/GG	32	22.0(2.2)	15.4(2.0)	16:16	117.0(9.0)	89.8(5.4)	81.9(6.9)
F values	274	1.056	0.980	0.802	1.599	1.352	0.670
P values	274	0.385	0.430	0.549	0.161	0.243	0.646

COMT catechol-O-methyltransferase, *F* female, *FIQ* Full-scale Intelligence Quotient, *M* male, *ZNF804A* zinc finger protein 804A

VBM analysis

We found a significant *COMT* rs4680 × *ZNF804A* rs1344706 interaction ($P = 0.048$, FWE corrected at the cluster level) on the GMV in the left dorsolateral prefrontal cortex (DLPFC) (Peak MNI coordinates: x = −18, y = −4.5, z = −69; cluster size =257 voxels; peak $F_{(2,265)} = 13.95$; Fig. 1a). However, there was no significant main effect of either *COMT* rs4680 or *ZNF804A* rs1344706 on brain GMV at the same statistical threshold. The GMV of the left DLPFC (Peak MNI coordinates = −18, −4.5, 69, a sphere with $r = 3$ mm) of each participant was extracted for the post hoc comparisons.

Post-hoc analysis

The GMV of the left DLPFC exhibited a non-linear modulation by the presumed dopamine signaling (Fig. 1b). In *COMT* Met-allele carriers, *ZNF804A* TG heterozygotes showed greater GMV in the left DLPFC than GG ($P = 0.047$, Bonferroni corrected) and TT homozygotes ($P = 0.0002$, Bonferroni corrected). However, there was no significant GMV difference between GG and TT homozygotes ($P = 0.081$, uncorrected). In *COMT* Val/Val homozygotes, *ZNF804A* TG heterozygotes exhibited smaller GMV in the left DLPFC than GG ($P = 0.041$, Bonferroni corrected) but not than TT homozygotes ($P = 0.465$, Bonferroni corrected). There was no significant GMV difference between GG and TT homozygotes ($P = 0.408$, uncorrected).

The quadratic curve fitting analysis is statistically significant ($P = 0.000086$, Fig. S1A) and consistent to the inverted U-shape theory of dopamine signaling when we ordered the six genotypic groups by assuming that the *COMT* rs4680 has a stronger effect than *ZNF804A* rs1344706. On the contrary, the quadratic curve fitting analysis is not statistically significant ($P = 0.123$, Fig. S1B) when the order was based on the

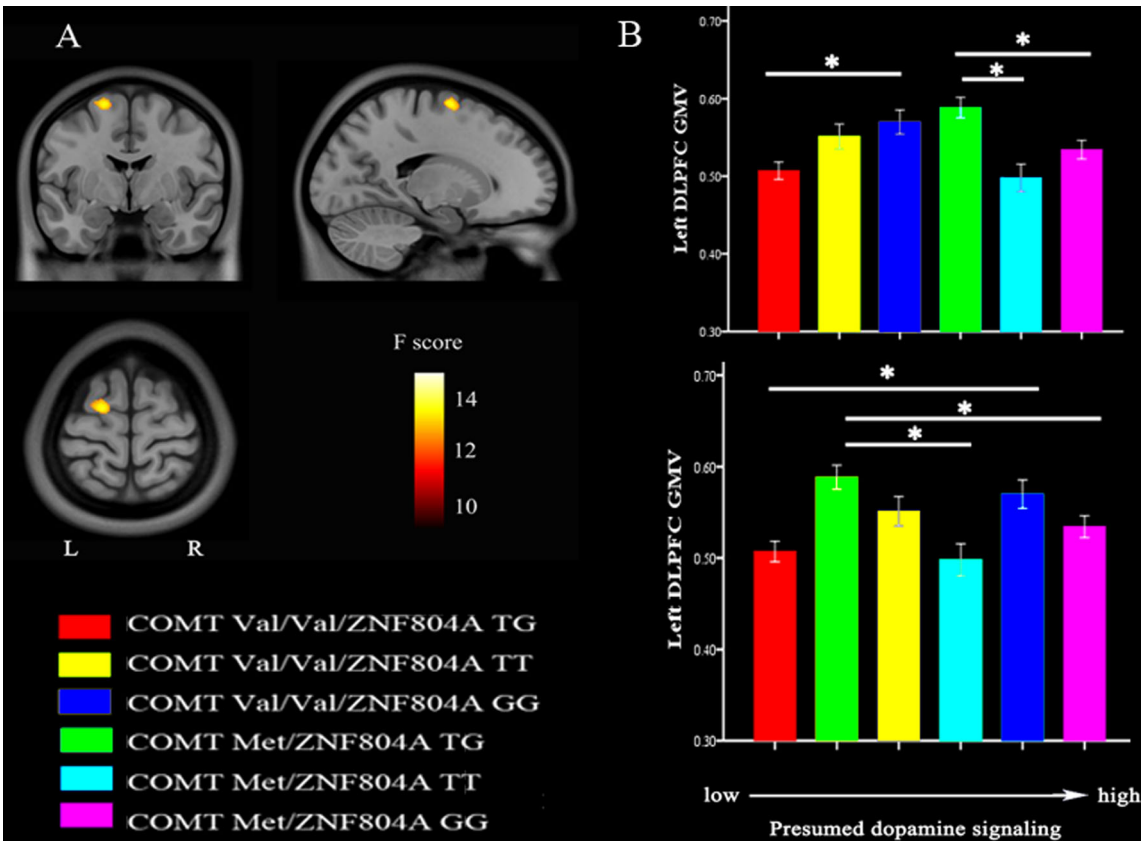

Fig. 1 Interaction effect of *COMT* rs4680 and *ZNF804A* rs1344706 on the GMV of the DLPFC. **a** represents the brain region with significant *COMT* rs4680 × *ZNF804A* rs1344706 interaction on GMV ($P = 0.048$, FWE corrected at the cluster level). Color bar shows the F scores. **b.** the *upper panel of B* represents the intergroup difference of the GMV in the left DLPFC, exhibiting an inverted U-shape modulation when assuming the *COMT* rs4680 has a stronger effect than *ZNF804A* rs1344706. The *lower panel of B* represents the intergroup difference of the GMV in the left DLPFC, not satisfying the inverted U-shape modulation when assuming that the *ZNF804A* rs1344706 has a stronger effect than *COMT* rs4680. The *horizontal axis* of the bar plot represents six genotypic subgroups of *COMT* rs4680 and *ZNF804A* rs1344706 arranged by extracellular dopamine signaling from low to high. The *vertical axis* represents the GMV (mean ± SE) in the DLPFC of each genotypic subgroup. COMT, catechol-O-methyltransferase; DLPFC, dorsolateral prefrontal cortex; FWE, family wise error; GMV, grey matter volume; L, left; R, right; ZNF804A, zinc finger protein 804A

hypothesis that the *ZNF804A* rs1344706 has a stronger effect than *COMT* rs4680.

Discussion

It is well known that the dopamine signaling modulates phenotypes (i.e., neuronal growth, brain volume, cognition, and so on) in an inverted U-shape manner (Fallon et al. 2013; Giakoumaki et al. 2008; Qin et al. 2012; Meyer-Lindenberg et al. 2005; Zhao et al. 2015; Honea et al. 2009; Tian et al. 2013). That is, only the optimal dopamine signaling predicts favorable outcome, in contrast, either too low or too high dopamine signaling predicts bad outcome. The underlying mechanism is dopamine signaling level-dependent neurotrophic and neurotoxic effects (Honea et al. 2009; Kuppers and Beyer 2001; Noh et al. 1999). In the ascending branch of the inverted U-shape curve, dopamine plays neurotrophic effect and the outcome becomes favorable with the enhancing dopamine signaling. In contrast, dopamine plays neurotoxic effect in the descending branch of the curve and the outcome becomes unfavorable with the enhancing dopamine signaling. In the roof of the curve, the dopamine signaling is optimal and the outcome is the most favorable.

In the human brain, the extracellular dopamine signaling is difficult to be measured *in vivo*. However, it can be roughly estimated by the genotypic information. COMT accounts for a large portion of extracellular dopamine concentration in the PFC because of the lack of dopamine transporter in the PFC synapses (Mannisto and Kaakkola 1999; Seamans and Yang 2004). It is clear that Met-allele carriers of *COMT* rs4680 can reduce the expression of the COMT and result in lower enzymatic activity, lower efficient dopamine degradation, and higher dopamine signaling than Val/Val homozygotes (Mannisto and Kaakkola 1999; Chen et al. 2004a, b; Lachman et al. 1996; Seamans and Yang 2004). However, the effect of *ZNF804A* rs1344706 on dopamine signaling is rather complex. The expression of *ZNF804A* is higher in T-allele carriers than in GG homozygotes (Schultz et al. 2014; Riley et al. 2010; Williams et al. 2011). In the PFC, the *ZNF804A* TG heterozygote can induce over-expression of the rs12476147 T-allele via a cis-regulatory mechanism, further resulting in the over-expression of *ZNF804A* (Guella et al. 2014; Guella and Vawter 2014). Consequently, the presumed *ZNF804A* expression level from low to high was: GG < TT < TG. The *ZNF804A* may be associated with dopamine signaling through up-regulating the transcript level of the *COMT* (Girgenti et al. 2012). According to the genotypes of the *COMT* rs4680 and *ZNF804A* rs1344706, we proposed two sorting schemes. Based on the inverted U-shape hypothesis of dopamine signaling on the GMV (Tian et al. 2013), the quadratic curve fitting analysis suggests that the more reasonable sorting scheme is Val/Val/TG < Val/Val/TT < Val/Val/GG < Met-allele/TG < Met-allele/TT < Met-allele/GG in the presumed dopamine signaling from low to high. Cautiously, this statement needs to be validated by biological investigations.

In the present study, we found an inverted U-shaped modulation of the presumed dopamine signaling on the GMV of the left DLPFC, which can be well explained by the dopamine-dependent neurotrophic and neurotoxic effects (Honea et al. 2009; Noh et al. 1999; Kuppers and Beyer 2001). Both *COMT* rs4680 and *ZNF804A* rs1344706 have been reported to affect the PFC volume of the human brain (Honea et al. 2009; Tian et al. 2013; Lencz et al. 2010). Although we have known that *COMT* rs4680 affects the PFC via modulating the dopamine concentration in this region (Tian et al. 2013; Honea et al. 2009), it remains largely unknown how *ZNF804A* rs1344706 affects the PFC. We found that the effect of *ZNF804A* rs1344706 on the prefrontal volume can be well incorporated into COMT-dependent modulation model of the dopamine signaling. That is, *ZNF804A* rs1344706 may affect the PFC volume by interacting with *COMT* rs4680. This is consistent with a pioneer study reporting that *ZNF804A* can regulate the transcription of the *COMT* gene (Girgenti et al. 2012).

In summary, following the clue of neurobiological association between *ZNF804A* and *COMT*, we provided the first evidence for an epistatic interaction between *ZNF804A* rs1344706 and *COMT* rs4680 on the GMV of the left DLPFC, which may improve our understanding on the biological mechanism underlying the genome-wide supported variant *ZNF804* rs1344706 of schizophrenia on the prefrontal anatomy.

Compliance with ethical standards

Funding This study was funded by the Natural Science Foundation of China (Grants number: 81425013, 81271551, 91132301, 81501451 and 81301201).

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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