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ORIGINAL ARTICLE

Impact of *COMT* haplotypes on functional connectivity density and its association with the gene expression of dopamine receptors

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Abstract

Catechol-*O*-methyltransferase (*COMT*) affects brain connectivity via modulating the dopamine system, with an expected greater effect of haplotypes than single-nucleotide polymorphism (SNP). The action pathway from *COMT* to dopamine to connectivity is theoretically dependent on the gene expression of dopamine receptors. Here, we aimed to investigate the impact of *COMT* haplotypes on brain functional connectivity density (FCD) in hundreds of healthy young subjects, and to disclose the association between the *COMT*-FCD statistical map and the spatial expression of the dopamine receptor genes. We found an inverted U-shaped modulation of *COMT* haplotypes on FCD in the left inferior parietal lobule that is mainly connected to the frontal and parietal cortices, with APS homozygotes exhibiting greater FCD than the other five groups. However, we failed to identify any significant effect of any SNP on FCD. Utilizing gene expression data collected from Allen human brain atlas, we found the *COMT*-FCD statistical map was significantly associated with the expression patterns of the dopamine receptor genes. Our results suggest that *COMT* haplotypes have greater impact on functional connectivity than a single genetic variation and that the association between *COMT* and functional connectivity may be dependent on the gene expression of dopamine receptors.

Keywords Allen human brain atlas · *COMT* · Functional connectivity density · Functional magnetic resonance imaging · Haplotype

Introduction

The enzyme of catechol-*O*-methyltransferase (COMT) catalyzes the degradation of synaptic dopamine in the brain (Mannisto 1999), whereby it affects the structure and function of the brain and then cognition and brain disorders. The *COMT* gene contains several single-nucleotide polymorphisms (SNPs), which modulate brain dopamine concentration by altering *COMT* enzymatic activity. For example, the well-studied SNP (rs4680, Val158Met polymorphism) of *COMT* can result in nearly four-fold difference in enzyme activity (Mannisto 1999), which has been related to individual differences in the brain and cognition and to the susceptibility of psychiatric disorders. Compared to the Met allele, the Val allele is associated with poorer performance of executive cognition (Egan et al. 2001), smaller gray matter volume (GMV) in the anterior cingulate cortex (ACC) (McIntosh et al. 2007), greater activation in the prefrontal cortex (PFC) during cognitive tasks (Egan et al. 2001; McIntosh et al. 2007), and greater resting-state functional connectivity (rsFC) of the PFC (McIntosh et al. 2007; Tunbridge

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et al. 2013; Xu et al. 2016). The rs4680 polymorphism is found to interact with dopamine receptor 2 gene (*DRD2*) to modulate the rsFC of the dorsal ACC in a U-shaped model and the rsFC is negatively correlated with its GMV (Xu et al. 2016). The impact of this polymorphism on working memory is mediated by the activity of the prefrontal–parietal–striatal network (Tan et al. 2007; Li et al. 2016), and the effect of this polymorphism on executive function is mediated by the GMV of the left lateral frontal pole (Xu et al. 2016). In addition to the rs4680, the rs4633 T allele of the *COMT* is also found to be associated with the susceptibility to paranoid schizophrenia (Wang et al. 2009), and *COMT* variants (rs4680, rs4633, and rs6267) are associated with treatment-related symptom improvement in patients with schizophrenia (Chen et al. 2016).

Although converging evidence demonstrates the influence of *COMT* rs4680 on prefrontal function, there exists great discrepancy in the association of this SNP with schizophrenia (Glatt et al. 2003; Fan et al. 2005; Costas et al. 2011; Gonzalez-Castro et al. 2016). The neglect of the joint effect of other *COMT* genetic variations may account for some of the nonsignificant associations (Meyer-Lindenberg et al. 2006). Haplotypes characterized by the linkage disequilibrium (LD) structure of multiple markers are considered more valuable than SNP alone because haplotypes carry more information about the genetic variations attributed to phenotypes (Meyer-Lindenberg et al. 2006; International HapMap C 2005). It has been proved that *COMT* haplotypes have stronger statistical power for examining genetic impact on brain morphology (Meyer-Lindenberg et al. 2006; Lee and Qiu 2016; Honea et al. 2009; Liu et al. 2010; Lorenz et al. 2010).

A pioneer study has identified three common haplotypes named HPS, APS, and LPS, which denote high, middle, and low pain sensitivity (Diatchenko et al. 2005). Compared to the LPS, the HPS causes nearly 20 times lower enzyme activity via altering mRNA secondary structure, resulting in higher synaptic dopamine levels (Nackley et al. 2006), which establishes an association between *COMT* haplotypes and dopamine levels. Using the acute phenylalanine and tyrosine depletion (APTD) method to reduce the dopamine synthesis, the reduced dopamine levels have been associated with the decreased rsFC (Shafiei et al. 2019), which supports an association between dopamine levels and rsFC of the human brain. Although *COMT* haplotypes have shown a greater effect on the white matter connections than the rs4680 alone (Liu et al. 2010), it remains unclear whether and how *COMT* haplotypes influence the brain functional connectivity. In this study, we utilize a data-driven method, the functional connectivity density (FCD) mapping, to evaluate functional connectivity of each voxel throughout the whole brain (Tomasi and Volkow 2010, 2011). The higher FCD indicates the faster information processing speed, and the intermediate phenotype is more sensitive to individual differences (Tomasi and Volkow 2011).

Theoretically, the effect of *COMT* on brain connectivity is dependent on the availability of dopamine receptors because the dopamine would functionally act by combining to its receptors in the brain (Li et al. 2016; Hawrylycz et al. 2012). The availability of dopamine receptors could be roughly estimated by the gene expression of dopamine receptors in the brain, which can be obtained from Allen human brain atlas (AHBA) (Hawrylycz et al. 2012). However, it remains largely unknown on the association between the effect of *COMT* on functional connectivity and the spatial expression patterns of dopamine receptor genes in the brain.

Here, we hypothesize that *COMT* haplotypes would show a greater effect on brain FCD than a single SNP alone and the effect should depend on the spatial expression patterns of dopamine receptor genes in the brain. First, we identified three major *COMT* haplotypes comprising of four SNPs, and then, 191 healthy young adults were grouped according to the six combinations of the three haplotypes. Second, a one-way analysis of covariance (ANCOVA) was performed to identify brain regions with significant FCD differences among the six haplotype groups and among the genotypic groups of each SNP. Third, we performed validation analyses by recalculating FCD using two different connection thresholds and preprocessing data using other two methods. Fourth, we used connection probability map to identify the specific functional connections contributing the significant FCD differences across *COMT* haplotype groups. Finally, we combined AHBA database to investigate the relationship between the FCD difference map and the gene expression of the five dopamine receptors (*DRD1*, *DRD2*, *DRD3*, *DRD4*, and *DRD5*).

Materials and method

Subjects

A total of 323 right-handed healthy young adults aged from 18 to 30 years old were recruited (157 males and 166 females) for this study. These subjects were carefully screened to ensure that they had no history of psychiatric or neurological illness, and no drug or alcohol abuse. To purify the sample, only Chinese Han subjects were included. The study was approved by the Medical Research Ethics Committee of Tianjin Medical University, and all participants provided written informed consent.

Genotyping

For each subject, we extracted genomic DNA from 3000 µl of whole blood using the EZgeneTM Blood gDNAMiniprep

Kit (BiomigaInc, San Diego, CA, USA). The *COMT* rs6269, rs4633, rs4818, and rs4680 were then genotyped in each subject using the method of polymerase chain reaction and ligation detection reaction (Thompson et al. 2004; Yi et al. 2009). The summary of the PCR primer sequences and probes for each SNP is shown in Table S1 and Table S2. Among the 323 subjects, 43 subjects were excluded due to genotyping failure of any of the four SNPs. The genotyping failure was present in 29 subjects for rs4818, 33 subjects for rs6269, 29 subjects for rs4633, and 20 subjects for rs4680. Among the 43 subjects, 15 subjects failed in one of the four SNPs, 14 subjects failed in three of the four SNPs, and 14 subjects failed in all of the four SNPs. The relatively low genotype call rates could be ascribed to the genotyping method, the blood sample contamination, and the conservative exclusion of the ambiguous loci.

Haplotype estimation

The haplotype is specifically referred to a set of statistically associated SNPs on a single chromatid, the information of which is thought to be critical for investigating the genetic risks of many diseases. The genotypic distribution of each of the four *COMT* SNPs was in Hardy–Weinberg equilibrium. After 43 subjects being excluded due to genotyping failure, haplotype analysis was conducted on the remaining 280 healthy young adults. Haploview4.2 software (Barrett et al. 2005) was used to calculate the LD relationship between SNPs and then to define the haplotype blocks. We identified the major haplotypes and their frequencies in our population (Table S3) as well as the individual haplotype assignments using PHASE 2.1 (Stephens et al. 2001; Stephens and Scheet 2005). When the probability of individual haplotype pair exceeded 0.90, the corresponding haplotype combination was assigned. Because we were only interested in subjects with haplotype combinations (LPS/LPS, LPS/APS, LPS/HPS, APS/APS, APS/HPS, and HPS/HPS) of the three haplotypes, only 198 out of 280 subjects were included in further analysis.

Image acquisition

MRI data were acquired using a Signa HDx 3.0 Tesla MR scanner (General Electric). Resting-state functional MRI (fMRI) data were obtained using a single-shot echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR)/echo time (TE) = 2000/30 ms; field of view (FOV) = 240 × 240 mm; matrix = 64 × 64; flip angle (FA) = 90°; slice thickness = 4 mm; no gap; 40 interleaved transverse slices and 180 volumes lasting for 6 min. Sagittal 3D T1-weighted images were collected using a brain volume sequence with the following parameters: 8 TR/TE = 8.1/3.1 ms; inversion time = 450 ms; FA = 13°; FOV = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm, no gap; and 176 sagittal slices. During the fMRI scans, all subjects were instructed to keep still with their eyes closed, to think of nothing in particular, to stay as motionless as possible, and not to fall asleep. After scanning, subjects' conditions were checked to ensure that they met the requirements; otherwise, the fMRI data were abandoned or scanned again.

Data preprocessing

To account for the effects of head motion and to confirm the reliability of our results, three different preprocessing methods were used in this study.

In the first method (6-parameter regression), the fMRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). The first ten volumes for each subject were discarded to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. The remaining 170 volumes were then corrected for the acquisition time delay between slices. Seven subjects were excluded from further analysis because their fMRI data had a maximum displacement in one or more of the three orthogonal directions (x, y, z) of > 2 mm or a maximum rotation (x, y, z) > 2.0°. We also calculated frame-wise displacement (FD), indexing volume-to-volume changes in head position. The FD was obtained from the derivatives of the rigid-body realignment estimates that are used to realign fMRI data (Power et al. 2012, 2013). Next, all fMRI data were spatially normalized to the standard EPI template and resampled to a voxel size of $3 \times 3 \times 3$ mm^3. After normalization, several nuisance covariates (six motion parameters and average fMRI signals of the ventricular and white matter) were regressed out from the data. Finally, datasets were band-pass-filtered with frequency from 0.01 to 0.1 Hz.

The second preprocessing method (12-parameter regression and spike removing) was similar to the first one, except that spike volumes with FD > 0.3 were further removed and the first time derivations of the 6 motion parameters were further regressed out from the fMRI data (Ciric et al. 2017; Satterthwaite et al. 2013).

The third method is named as independent component analysis-based strategy for automatic removal of motion artifacts (ICA-AROMA) (Pruim et al. 2015a, b), which was conducted using tools from the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl) (Jenkinson et al. 2012). The ICA-AROMA first used MELODIC of FSL to decompose the BOLD data into spatially independent components (IC) and then a predetermined, theoretically motivated classifier was applied to identify ICs as noise or signal and the ICs that were classified as noise were removed from the fMRI data. Please see the detailed streamline in supplementary material.

FCD calculation

The FCD of each voxel was calculated using the previously described method (Tomasi and Volkow 2011). The Pearson's linear correlation was applied to calculate the functional connection between voxels, and two voxels with a correlation coefficient > 0.6 were considered functionally connected. This threshold was thought to be the most optimal threshold for the calculation of FCD (Tomasi and Volkow 2011). The FCD at a given voxel x_0 was computed as the total number of functional connections between x_0 and all other voxels. The normalized FCD was obtained through a Z-transform of all the qualified voxels to increase the normality of the distribution. Finally, the FCD maps were spatially smoothed with a $6 \times 6 \times 6$ mm^3 Gaussian kernel. We used a gray matter (GM) mask to restrict the calculation of the FCD to voxels in the GM regions.

Statistical analyses for imaging genetics data

After excluding subjects with genotyping failure ($n = 43$), uninterested haplotypes ($n = 82$), and excessive head motion ($n = 7$), 191/323 subjects were finally included in the investigation of the effect of *COMT* haplotypes on the FCD. After excluding subjects with genotyping failure and excessive head motion, 276 (rs6269), 281 (rs4633), 280 (rs4818), and 286 (rs4680) subjects were included in the investigation of the effect of *COMT* SNPs on the FCD. A one-way analysis of covariance (ANCOVA) was performed to voxel-wisely identify the effect of *COMT* haplotypes on the FCD after controlling for the effects of age, gender, years of education, and FD value. Multiple comparisons were corrected at the cluster level using the family-wise error rate method ($P < 0.05$, FWE corrected, voxel level $P < 0.001$). Then, post hoc analysis was done among the genotypic subgroups. Bonferroni method was used to correct for multiple comparisons ($P < 0.05$). We also validated the reliability of our results using another two connection thresholds of $r = 0.5$ and $r = 0.7$ with the same ANCOVA model and corrected methods. In the validation tests (accounting for the effects of head motion using the method of 12-parameter regression and spike removing and the method of the ICA-AROMA), the uncorrected $P < 0.005$ was used in the voxel-wise analyses.

Connection probability maps

For each significant cluster with FCD differences under each connection threshold, we used this connection threshold to generate the functional connectivity map of the cluster for each subject. Based on these connectivity maps of all subjects, we generated a connection probability map of this cluster under the connection threshold which may represent the connection pattern of this cluster at the exact connection threshold.

Gene expression analysis

Because *COMT* haplotypes showed a nonlinear inverted U-shaped modulation on the FCD, this F-map was not suitable for investigating the linear relationship of spatial distributions between the effect of *COMT* haplotypes on the FCD and the gene expression patterns of dopamine receptors. We merged haplotype groups (LPS/HPS, LPS/APS, and LPS/LPS) in the ascending limb of the inverted U-shaped curve into the low dopamine group, and haplotype groups (APS/HPS and HPS/HPS) in the descending limb of the inverted U-shaped curve into the high dopamine group. And then we extracted two *T*-statistical maps between the APS/APS (middle dopamine) group and the low and high dopamine groups. One represents the linear contrast of the ascending limb of the inverted U-shaped curve; the other represents the linear contrast of the descending limb of the inverted U-shaped curve.

Utilizing *alleninf* toolbox (Gorgolewski et al. 2014) and publicly available gene expression data of six donated brains provided by AHBA (Hawrylycz et al. 2012), we examined the sample-wise correlations between the patterns of dopamine receptor gene expression and unthresholded T-statistical maps of the FCD differences between haplotype groups. First, *alleninf* toolbox extracted the MNI coordinates of each gene expression sampling sites in the whole brain GM mask. Then, we drew spherical ROIs with a radius of 4 mm on the FCD statistical map and averaged values of the statistical map within each ROI. Because there were several probes for dopamine receptor genes, we chose one probe to represent the gene expression by performing the principal component analysis (https://github.com/chrisfilo/alleninf). Finally, correlation coefficients between average ROI values and normalized gene expression values were examined. Detailed procedures can be found elsewhere (Gorgolewski et al. 2014; Albaugh et al. 2017).

Results

Demographic and genetic characteristics

Using the software Haploview v4.0, we found one haplotype block consisting of the four *COMT* SNPs (Fig. 1). Three common haplotypes ACCG, ATCA and GCGG (termed as HPS, APS, and LPS haplotypes) accounted for 83.4% of all the detected haplotypes (0.275 for HPS, 0.274 for APS, and 0.284 for LPS). Only those 191 subjects who carried one of the six haplotype combinations (LPS/LPS, LPS/APS, LPS/

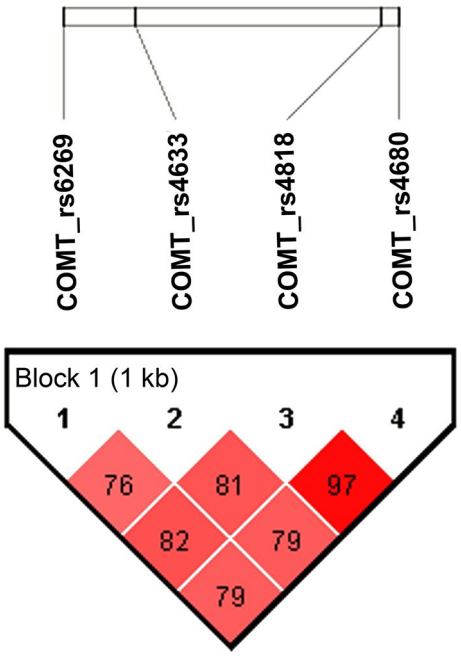

Fig. 1 Linkage disequilibrium (LD) structure of four single-nucleotide polymorphisms (SNPs) within *COMT* in our sample

HPS, APS/APS, APS/HPS, and HPS/HPS), and qualified fMRI data were included in the subsequent analysis. The demographic data of these haplotype groups are summarized in Table 1. There were significant differences among the six *COMT* haplotype groups in the mean FD ($P = 0.005$), but not in age, gender and years of education ($P > 0.05$). For each SNP, *COMT* rs6269, rs4818 and rs4680 did not show significant differences in age, gender, years of education and FD between genotypes; however, there was a significant difference in years of education ($P = 0.001$) between *COMT* rs4633 genotypic groups (Table S4).

Single SNP effects on FCD calculated with a connection threshold of 0.6

After regressing out the effects of age, gender, years of education and FD, we did not find any significant effect of any *COMT* SNP on the FCD with the cluster level FWE correction for multiple comparisons.

Haplotype effects on FCD calculated with a connection threshold of 0.6

The *COMT* haplotype groups showed significant differences ($P < 0.05$, FWE corrected) in the FCD in the left inferior parietal lobule (IPL) (peak MNI coordinate: $x = -42$, $y = -42$, $z = 45$, cluster size = 66 voxels, peak $F = 8.44$, Fig. 2b) after regressing out the effects of age, gender, years of education and FD (Fig. 2b). The mean FCD value of the ROI was extracted from each subject. The left column of Fig. 2e showed the mean FCD of six subgroups, whereas the right column showed the location of each imaging phenotype on the curve and that the distribution of FCD among these subgroups was fitted into an inverted U-shaped model, with the x-axis reflecting the presumed dopamine signaling from low to high (LPS/LPS < LPS/APS < LPS/HPS < APS/APS < APS/HPS < HPS/HPS). Specifically, post hoc analysis showed that the FCD value of APS/APS subgroup was higher than all of the other subgroups (all $P < 0.05$, Bonferroni corrected) and APS/HPS subgroup had significant higher FCD value than LPS/HPS subgroup ($P = 0.014$, Bonferroni corrected).

Validation using FCD calculated with connection thresholds of 0.5 and 0.7

We recalculated FCD values based on two other connection thresholds and repeated the FCD analysis to validate our results derived from the connection threshold of 0.6. The genetic effect was also significant in the left IPL (peak MNI coordinate: $x = -42$, $y = -42$, $z = 45$ and $x = -42$, $y = -48$, $z = 48$, cluster size = 69 and 58 voxels, respectively, peak

Table 1 Demographic information for haplotype analysis

	Haplotype combination						F/χ^2 value	P value
	HPS/HPS ($n = 21$)	APS/HPS ($n = 42$)	APS/APS ($n = 13$)	LPS/HPS ($n = 51$)	LPS/APS ($n = 40$)	LPS/LPS ($n = 24$)		
Age (years)	22.6 (2.1)	22.5 (2.5)	23.1 (2.0)	22.1 (2.1)	22.9 (2.3)	22.4 (2.3)	0.760	0.580
Gender (M:F)	8/13	19/23	8/5	15/36	18/22	13/11	7.241	0.203
Education (years)	16.2 (2.0)	16.1 (2.1)	16.1 (1.6)	15.0 (2.1)	16.2 (1.9)	16.0 (1.9)	0.912	0.475
FD	0.09 (0.04)	0.08 (0.04)	0.07 (0.03)	0.08 (0.03)	0.11 (0.03)	0.08 (0.05)	3.439	0.005

F female, *M* male, *FD* frame-wise displacement

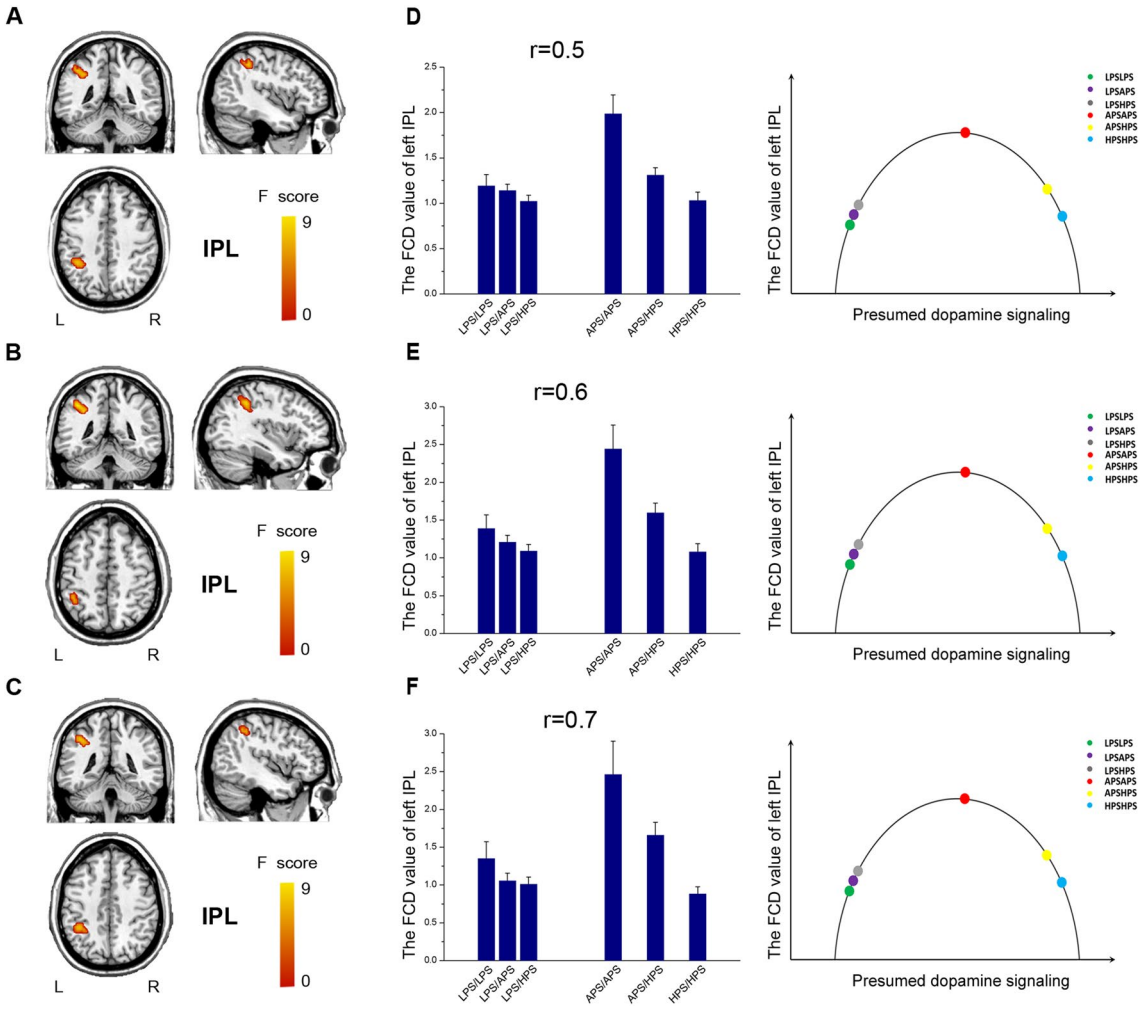

Fig. 2 Effects of *COMT* on the brain FCD under different connection thresholds. **a**–**c** Show brain regions with significant effects of *COMT* haplotypes on the brain FCD with connection thresholds of 0.5, 0.6 and 0.7, respectively. **d**–**f** Illustrate the nonlinear modulation of the presumed dopamine signaling (constructed by *COMT* haplotype groups) on the FCD of the IPL obtained with connection thresholds of 0.5, 0.6 and 0.7, respectively. The horizontal axis of the bar plot represents six haplotype subgroups with the presumed dopamine signaling from low to high. The left bar plots depict the mean value and standard error. The right columns depict the locations of each imaging phenotype on the curve. *COMT* catechol-*O*-methyltransferase, *FCD* functional connectivity density, *IPL* inferior parietal lobule, *L* left and *R* right

$F = 7.81$ and 7.46, Fig. 2a, c) under the connection thresholds of 0.5 and 0.7 with the same ANCOVA model and corrected methods ($P < 0.05$, FWE corrected, voxel $P < 0.001$, Fig. 2a, c). Similarly, the distribution of the FCD of the significant cluster in haplotype subgroups was satisfied for an inverted U-shaped model with the APS/HPS subgroup showing significant higher FCD value (Fig. 2d, f).

Validation using FCD calculated with other preprocessing pipelines

Using the method of 12-parameter regression and spike removing to preprocess the data, *COMT* haplotypes still showed a significant effect on the FCD of the left IPL ($P < 0.005$, uncorrected, peak MNI coordinate: $x = -29$, $y = -54$, $z = 48$, $x = -31$, $y = -54$, $z = 51$, and $x = -32$, $y = -54$, $z = 51$ cluster size = 17,14 and 22 voxels, peak $F = 5.83$, 5.56 and 7.11, respectively) under different connectivity thresholds (Figure S1 A–C) and the effect of the *COMT* on the FCD of the left parietal lobe could not be found in the single variation analysis. Besides, the post hoc analysis consistently re-identified the inverted U-shaped modulation of *COMT* on the FCD through acting on the dopamine levels under different connection thresholds. The APS homozygotes showed the highest FCD value in the left parietal lobe (Figure S1 D–F).

Additionally, based on the fMRI data using ICA-AROMA for motion correction, *COMT* haplotypes still showed a

significant effect on the FCD of the left IPL ($P < 0.005$, uncorrected) under the connection threshold of 0.5 (peak MNI coordinate: $x = -32$, $y = -42$, $z = 40$, cluster size = 17 voxels, peak $F = 5.32$; Figure S2A) and 0.6 (peak MNI coordinate: $x = -34$, $y = -42$, $z = 42$, cluster size = 16 voxels, peak $F = 4.33$; Figure S2B). The effect of the *COMT* on the FCD of the left parietal lobe could not be found in the single variation analysis. In addition, the post hoc analysis consistently re-identified the inverted U-shaped modulation of *COMT* on the FCD through acting on the dopamine levels under different connection thresholds. The APS homozygotes also showed the highest FCD value in the left parietal lobe (Figure S2 C-D).

Connection probability maps

The connection probability maps of the significant cluster at different connection thresholds are shown in Fig. 3. The 20% connection probability maps under the connection thresholds of 0.5, 0.6 and 0.7 consistently showed that the left IPL mainly connected with the bilateral parietal and prefrontal cortices, which belong to the canonical fronto-parietal network (FPN). The 20% connection probability maps under different thresholds using other two preprocessing methods also showed the similar connection pattern of the left IPL (Figure S3 and Figure S4). The percentages of voxels of the whole gray matter that showed more than 20% connection probability with the significant cluster are shown in Table S5. Only 0.60% of the gray matter voxels showed significant connections with the left IPL under the connection threshold of 0.7 using the ICA-AROMA correction.

Association between *COMT* haplotype-FCD statistical maps and the dopamine receptor gene expression

We calculated the associations of spatial distributions between the unthresholded T-maps of the genotypic effect on the FCD and the gene expression patterns of dopamine receptors in whole brain gray matter using AHBA. We found that the FCD differential map between middle (APS/APS) and low (LPS/HPS, LPS/APS and LPS/LPS) dopamine groups was correlated with the gene expression of the *DRD1* ($r = -0.14$; $P = 2.4e{-}14$), *DRD2* ($r = 0.33$; $P = 1.4e{-}71$) and *DRD3* ($r = 0.12$; $P = 3.9e{-}11$) (Fig. 4a–c). Similarly, the FCD differential map between middle (APS/APS) and high (HPS/HPS and APS/HPS) dopamine groups was correlated with the gene expression of the *DRD1* ($r = -0.04$; $P = 0.02$), *DRD2* ($r = 0.29$; $P = 1.3e{-}56$) and *DRD3* ($r = 0.15$; $P = 1.3e{-}14$) (Fig. 4d–f). However, there were no significant correlations ($P > 0.05$) between these two T-maps and the gene expression of the *DRD4* and *DRD5*.

Discussion

In contrast to the lack of significant effects of any single SNP on the FCD, we found a reproducible and significant effect of *COMT* haplotypes on the FCD in the left IPL, indicating that *COMT* haplotypes could explain more variance in FCD than single SNPs. The *COMT* genetic variants could induce a cascade process to affect the brain and cognition. The *COMT* genotypes or haplotypes would result in different *COMT* enzyme activity via affecting the transcription and translation of this gene (Mannisto 1999; Nackley et al. 2006). Since the *COMT* enzyme catalyzes the degradation of synaptic dopamine in the brain (Mannisto 1999), different *COMT* activity would result in different dopamine levels. The dopamine concentration would affect neuronal survival and growth in an inverted U-shaped manner, where only the optimal synaptic dopamine level could facilitate neuronal growth by enhancing the expression of brain derived neurotrophic factor (*BDNF*) (Kuppers and Beyer 2001). In contrast, either excessive lower or higher dopamine level could impair neuronal integrity and survival (Santiago et al. 2000). The neuronal survival and growth would affect the

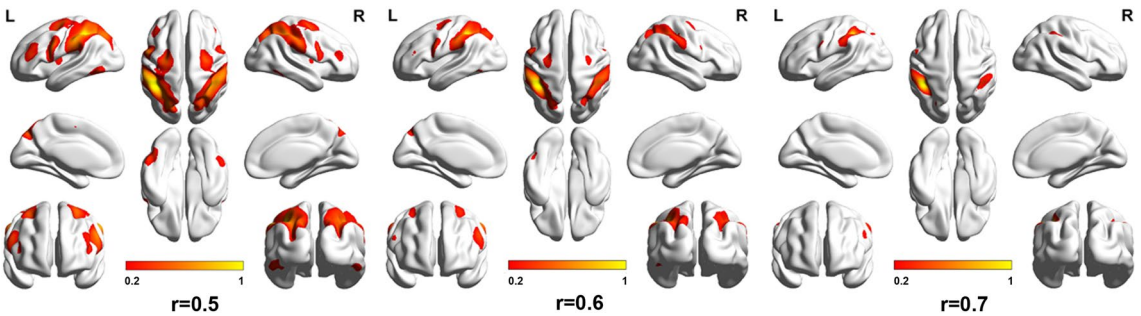

Fig. 3 20% connection probability maps of the left IPL at the threshold 0.5, 0.6 and 0.7. The maps at different connection thresholds consistently show that the left IPL mainly connects with the bilateral parietal and prefrontal cortices. As expected, the brain regions connected with the left IPL shrink as the connection thresholds increase. *IPL* inferior parietal lobule

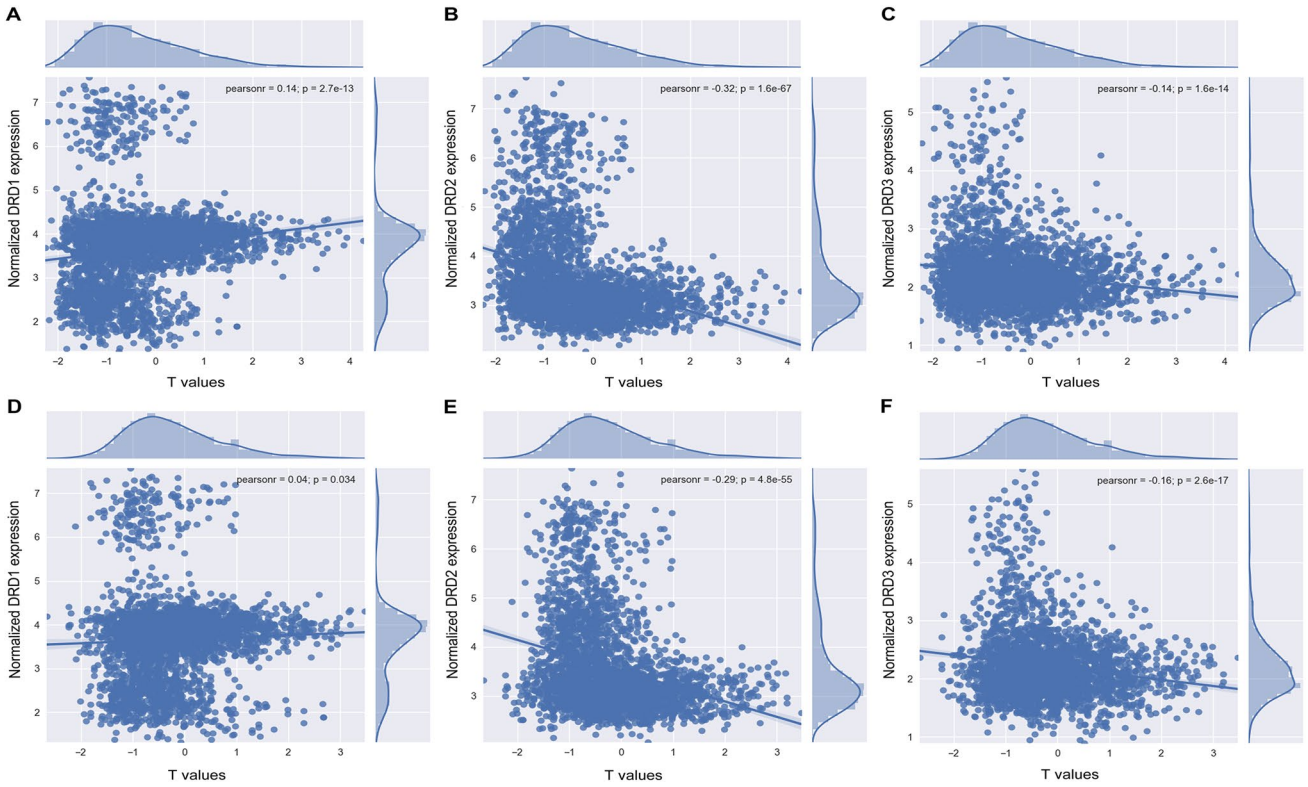

Fig. 4 Scatter plots depicting relationship between the effects of *COMT* haplotypes on FCD and the normalized expression of dopamine receptor genes. The upper row shows correlations between the normalized expression values (*y*-axis) of *DRD1* (**a**), *DRD2* (**b**) and *DRD3* (**c**) and T-statistic values (*x*-axis) corresponding to the group difference between APS/APS and the combination of LPS/HPS, LPS/APS and LPS/LPS. The lower row shows correlations between the normalized expression values (*y*-axis) of *DRD1* (**d**), *DRD2* (**e**) and *DRD3* (**f**) and *T*-statistic values (*x*-axis) corresponding to the group difference between APS/APS and the combination of HPS/HPS and APS/HPS

structural and functional architectures of the human brain, which would further affect the cognitive performance. The above-mentioned mechanisms may help us to understand why *COMT* haplotypes have a much greater effect on the FCD than single SNPs. Compared to a single SNP (such as the rs4680) resulting in 3–4 times of difference in *COMT* enzyme activity (Mannisto 1999), the *COMT* haplotypes (LPS vs. HPS) could cause nearly 20 times of difference in enzyme activity (Nackley et al. 2006). The more drastic changes in *COMT* enzyme activity may lead to more significant difference in extracellular dopamine concentration, which will have more prominent effect on neuronal survival and growth, and finally have a greater effect on brain functional connectivity. In consistent with our findings, several previous studies have revealed a more significant biological effect of *COMT* haplotypes than single SNPs. For examples, *COMT* haplotypes rather than any single SNPs are associated with the activation of the PFC (Meyer-Lindenberg et al. 2006), show significant association with the risk of schizophrenia (Nicodemus et al. 2007), and exhibit a significant modulation on the intelligence-related white matter integrity (Liu et al. 2010).

The most consistent finding of this study was that the APS/APS group showed the significantly highest FCD in the left IPL, which could be validated using different preprocessing methods. Compared to the LPS with the highest enzyme activity and the HPS with the lowest enzyme activity, the APS shows an intermediate enzyme activity (Nackley et al. 2006). According to the role of the *COMT* enzyme in catalyzing the degradation of extracellular dopamine (Mannisto 1999), the LPS, APS and HPS correspond to the lowest, intermediate and highest dopamine levels in the brain, respectively. Because the intermediate dopamine level is best for neuronal survival and growth (Kuppers and Beyer 2001), the APS/APS combination with an intermediate enzyme activity and dopamine level would generate the most optimal environment for neuronal growth, which may account for the highest FCD in the APS/APS group. In contrast, either excessive lower or higher dopamine level would impair neuronal integrity and survival (Santiago et al. 2000), which may explain why both the LPS/LPS group (the highest enzyme activity and the lowest dopamine level) and the HPS/HPS group (the lowest enzyme activity and the highest dopamine level) showed the relatively low FCD. These

findings could be applied to select suitable patients with neuropsychiatric disorders for dopamine-related medications (Giakoumaki et al. 2008; Mattay et al. 2003). For example, patients with LPS/LPS combination (the highest enzyme activity and the lowest dopamine level) would benefit from *COMT* inhibitors by reducing enzyme activity or monoaminergic drugs by increasing synaptic dopamine level. In contrast, the same drugs would cause clinical deterioration in patients with HPS/HPS combination (the lowest enzyme activity and the highest dopamine level) because *COMT* inhibitors would further reduce enzyme activity and monoaminergic drugs would further increase synaptic dopamine level (Mattay et al. 2003; Giakoumaki et al. 2008).

The connection probability map indicates that the left IPL is a node of the FPN and is mainly connected with other prefrontal and parietal regions of the network. The prominent effect of *COMT* haplotypes on prefrontal-parietal connectivity may be explained by the increased importance of *COMT* in dopamine degradation in the prefrontal cortex due to the lack of dopamine transporters in this region (Seamans and Yang 2004; Mannisto 1999). The FPN has been associated with many cognitive functions, such as working memory, executive control and reasoning (Sheffield et al. 2015; Mohr et al. 2016), and thus the FPN is an ideal candidate that mediates the effects of *COMT* haplotypes or SNPs on cognitive performance. It is plausible that the APS/APS combination with an intermediate dopamine level would establish optimal brain architectures and then exhibit the best cognitive performance than the LPS/LPS with the lowest dopamine level and the HPS/HPS with the highest dopamine level. This is consistent with a previous study showing that the haplotype with intermediate enzyme activity and dopamine level show the highest white matter integrity in the PFC and the highest intelligence (Liu et al. 2010).

Dopamine should act on different dopamine receptors to regulate the brain and cognition (Tsang et al. 2015; Guo et al. 2006), it is plausible that the *COMT* effect on the brain connectivity should be dependent on the availability of dopamine receptors, which can be estimated by the gene expression of dopamine receptors in the brain. By investigating the relationship of FCD differential maps between *COMT* haplotypes with dopamine receptor gene expression, we found that the effects of *COMT* haplotypes on the FCD were significantly correlated with gene expression of dopamine receptors. More specifically, brain regions with high expression of *DRD1* and low expression of *DRD2* and *DRD3* tend to have a great effect of *COMT* haplotypes on the FCD. The dopamine receptors (D1-D5 receptors) can be classified into two families (Luquin-Piudo and Sanz 2011; Cristina et al. 1998): D1-like family (stimulatory receptors) including D1 and D5 receptors; and D2-like family (inhibitory receptors) including D2, D3 and D4 receptors. Our expression analysis turned out that FCD differences among *COMT* haplotypic subgroups are positively correlated with the expression of the stimulatory dopamine receptors, but negatively correlated with the expression of the inhibitory dopamine receptors. The distinct distribution and function of dopamine receptors in the brain may contribute to the inverse correlation, with D1 receptors playing a greater role in disinhibiting neuronal activity and initiating behavior, and D2 receptors playing a more significant role in inhibiting neuronal activity (Hall et al. 1994; Parent and Hazrati 1995). Taking together, our findings suggest that the modulation effect of *COMT* haplotypes on the FCD may be dependent on the gene expression of *DRD1*, *DRD2* and *DRD3*.

Several limitations should be noted in this study. First, the current genotyping technology cannot distinguish specific information between two chromatids. Thus *COMT* haplotypes cannot be precisely obtained in unrelated individuals if more than one marker locus is heterozygous and must, therefore, be estimated. Using phase v2.1 software, we could only obtain all of the possible haplotype assignments for each individual and choose the most probable one. However, in our study, for each subject, there always existed one assignment with a probability of exceeding 90%. So we used the most likely haplotypes for each subject in the analysis, which may introduce some minor biases. Second, one can roughly estimate the relative dopamine signaling from low to high is in the order of HPS/HPS, other combinations and LPS/LPS. However, the specific sorting scheme for middle subgroups (HPS/APS, APS/APS, LPS/HPS and LPS/APS) is arbitrary. In other words, we do not know the inner interactions of the three haplotypes in contributing to the dopamine signaling. More systematic studies and other techniques are required to figure out the interactions and to elucidate the underlying mechanisms. Third, we cannot completely exclude the effects of head motion on our results because the significances were reduced when more stringent motion correction methods were used. The merits and demerits of the three methods used in this study are shown in Table S6. However, it is difficult to infer which to be the best one. For example, although 12-parameter regression and spike removing can improve motion correction, this method may lead to overfitting of the data and therefore to removal of signal of interest (Satterthwaite et al. 2013; Yan et al. 2013; Pruim et al. 2015b). Moreover, the ICA-AROMA is the most efficient method for head motion correction (Pruim et al. 2015b); however, the spatial smoothing before the metric calculation in the ICA-AROMA method may result in the loss of details (subtle FCD differences between adjacent voxels) in the FCD maps compared to the recommended preprocessing pipeline (spatial smoothing after the FCD calculation) (Figure S5).

Conclusion

In this study, we explored the effects of single *COMT* SNPs and their haplotypes on the brain FCD in Chinese young adults and found that *COMT* haplotypes rather than single SNPs had a significant effect on the fronto-parietal connectivity, confirming that more variance could be explained by *COMT* haplotypes instead of single SNPs. We further revealed an association between the effects of *COMT* on connectivity and the gene expression of dopamine receptors, disclosing a dependency of *COMT* effects on the availability of dopamine receptors. These results suggest that future studies should include the haplotype analysis as an important supplement for the SNP analysis, and that cross-scale investigation of all components of a neurotransmitter pathway may improve our understanding of its biological effects.

Author contribution statement JT and YL; Methodology: JT, YL, WQ, JX and QS; Formal analysis and investigation: JT, JX, WQ and QX; Writing–original draft preparation: JT, YL and CY; Writing–review and editing: JT and CY; Funding acquisition: CY and TJ; Resources: BL and TJ; Supervision: CY, BL and TJ.

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Compliance with ethical standards

Conflict of interest The authors declare that they have 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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