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Association between catechol-*O*-methyltransferase genetic variation and functional connectivity in patients with first-episode schizophrenia

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ABSTRACT

Dopamine in the prefrontal cortex (PFC) plays an important role in cognitive performance and regulates by catechol-*O*-methyltransferase (COMT) expression. To clarify the effect of COMT genotype on cognitive function in patients with schizophrenia, we performed DNA genotyping, cognitive evaluations, and functional magnetic resonance imaging (fMRI) in antipsychotic-naïve patients with first-episode schizophrenia (FES) and matched healthy control subjects. We found that all cognitive domains were impaired in patients with FES compared with healthy subjects. Moreover, COMT genotype influenced the verbal learning performance in healthy subjects, but not in patients with FES. Resting-state fMRI data revealed that patients with FES exhibited higher functional connectivity degree centrality in the medial PFC and lower degree centrality in the parietal-occipital junction than healthy subjects. Furthermore, patients with FES who were COMT *Met* allele carriers had higher degree centrality in the medial PFC than those with the *Val*/*Val* genotype. In contrast, in healthy controls, *Met* allele carriers exhibited higher degree centrality than healthy controls with the *Val*/*Val* genotype in the left hippocampus and left amygdala. There was a negative correlation between the degree centrality value in medial PFC and score of the Hopkins Verbal Learning Test-Revised (HVLT-R) in FES patients with the *Met* allele. Our findings suggest that COMT genotype differentially influences pathways related to cognitive performance in patients with FES versus healthy individuals, providing an important insight into schizophrenia pathophysiology.

1. Introduction

Cognitive deficits are recognised as a core feature of schizophrenia and have an important influence on treatment outcomes and social functional recovery. Cognitive deficits cause significant financial as well as humanistic burden on patients (Millier et al., 2014). Primate, rodent, and human neuroimaging studies have consistently reported that prefrontal dopamine (DA) plays a major role in regulating cognitive functions (Barch and Ceaser, 2012; Callicott et al., 2000). The DA level in the prefrontal cortex (PFC) is mainly associated with the activity of catechol-*O*-methyltransferase (COMT), which is an important enzyme involved in the degradation of catecholamines, such as DA, from the synaptic cleft (Gong et al., 2017; Zilles et al., 2012). The COMT gene is located on chromosome 22q11 and is regulated by a single nucleotide polymorphism, $Val^{158}Met$ (Lachman et al., 1996). The $Val^{158}Met$ polymorphism results in decreased enzymatic activity and increased synaptic DA concentration in *Met* carriers (Mannisto and Kaakkola, 1999).

Several studies have reported that increased DA levels in the PFC associated with the *Met* allele result in a cognitive advantage. Shashi et al. (2006) investigated the cognitive performance of children with chromosome 22q11 deletion syndrome (22q11DS), which is a common microdeletion syndrome associated with an elevated risk of schizophrenia. The authors found that children with 22q11DS with the *Met* allele had a better cognitive performance than those with the *Val*/*Val* genotype. Furthermore, previous studies have indicated that chronic patients

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with schizophrenia and with the *Met* allele had better cognitive functioning in processing speed and attention domains than subjects with the *Val*/*Val* genotype (Egan et al., 2001; Twamley et al., 2014).

However, studies investigating the influence of the COMT *Val*^{158}*Met* polymorphism on cognition have failed to reach a consensus. Klaus et al. (2017) found that the COMT genotype did not have a significant influence on executive function in healthy adult males, whereas, Tsuchimine et al. (2013) reported that healthy individuals with the *Val*/*Val* genotype showed a better cognitive performance in the executive function domain than those with the *Met* allele. In addition, Matsuzaka et al. (2017) found that *Met* allele carriers scored lower on a working memory task than *Val*/*Val* genotype carriers, in both patients with schizophrenia and healthy individuals. These conflicting results may be explained by Bilder's tonic-phasic DA hypothesis, which states that *Met* alleles of the COMT *Val*^{158}*Met* polymorphism increase tonic DA transmission and reduce phasic DA transmission, thus enhancing the stability of cognitive control, such as that of attention. On the contrary, this hypothesis states that the *Val*/*Val* genotype enhances the plasticity of cognitive control and hence improve executive functioning (Bilder et al., 2004). However, Mata et al. (2008) have suggested that the COMT *Val*^{158}*Met* polymorphism has no effect on any cognitive domains in patients with first-episode schizophrenia (FES). Notably, most previous research investigating the role of COMT variation in schizophrenia have evaluated chronic patients, such that the results may have been confounded by the influence of concurrent antipsychotic drug administration on synaptic DA (Eisenberg et al., 2010). Therefore, we recruited both patients with FES and healthy matched control subjects to verify Bilder's tonic-phasic DA hypothesis.

Various neuroimaging techniques have been applied to investigate the relationship between cognitive impairment, brain abnormalities, and the COMT *Val*^{158}*Met* polymorphism in patients with schizophrenia and healthy subjects (Ira et al., 2013). Most studies have focused on differences in regional brain activity (mainly in the PFC) during cognitive tasks (Ehrlich et al., 2010; Krach et al., 2010). Several studies have reported that patients with schizophrenia who carry the *Val*/*Val* genotype showed greater activation in the PFC during working memory tasks than those carrying the *Met* allele (Cools and D'Esposito, 2011; Egan et al., 2001; Lopez-Garcia et al., 2016). Other studies have reported grey matter morphological differences between COMT genotypes; Li et al. (2015) identified a decreased grey matter volume in the left superior frontal gyrus of *Val*/*Val* allele carriers, both healthy individuals and patients with schizophrenia, compared with *Met* allele carriers. Markett et al. (2016) assessed the influence of the COMT *Val*^{158}*Met* polymorphism on brain-wide functional connectivity (FC) in healthy participants and found that the *Val*/*Val* allele carriers had increased degree centrality (DC) in the default mode network (DMN) and a decreased DC in the somatomotor network.

The DC approach was developed as a data-driven method for determining regional degrees of FC and to identify major cortical and subcortical FC hubs (Di Martino et al., 2013). Recently, this method has been used to investigate major depressive disorder (Shen et al., 2015; Zhang et al., 2016), obsessive compulsive disorder (Gottlich et al., 2015), and Alzheimer's disease (Guo et al., 2016).

In the present study, we used the DC method to investigate the influence of the COMT *Val*^{158}*Met* polymorphism on brain FC in antipsychotic-naïve patients with FES and matched healthy subjects. This investigation was motivated by two hypotheses, as follows: (1) Dose COMT affect cognition in a manner associated with FC, consistent with Bilder's tonic-phasic DA hypothesis? (2) Is cognitive impairment in patients with FES associated with altered PFC FC and the COMT genotype?

2. Subjects and methods

2.1. Subjects

Fifty-six drug-naïve patients with FES or schizophreniform psychosis were recruited from the Shanghai Mental Health Center. Patients were diagnosed using the Structured Clinical Interview for the DSM-IV Patient Edition (SCID-I/P) and met the criteria for schizophrenia or schizophreniform psychosis. Fifty-six healthy comparison subjects matched for age, sex, and years of education were recruited from the local community via poster advertisements. All healthy subjects completed the SCID Non-Patient Edition (SCID-I/NP) to verify the absence of psychiatric illnesses in themselves and their first-degree relatives. The exclusion criteria for all subjects were a history of seizures, illicit substance use or substance abuse disorders, and pregnancy. The study protocol was approved by the Shanghai Mental Health Center Ethics Committee. All participants provided written informed consent prior to study participation.

2.2. Clinical and cognitive assessments

All patients underwent psychopathological assessment using the 24-item Brief Psychiatric Rating Scale (BPRS) expanded version (Lukoff et al., 1986; Ventura and Gugerty, 1993) and completed the Chinese version of the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), which has been validated with normative data from a representative Chinese sample (Shi et al., 2015).

The MCCB is a consensus cognitive battery developed for use in clinical trials, and includes 10 cognitive tests: the Trail Making Test (TMT), Brief Assessment of Cognition in Schizophrenia (BACS), Hopkins Verbal Learning Test-Revised (HVLT-R), Wechsler Memory Scale-Third Edition (WMS-III), University of Maryland Letter-Number Span (LNS), Neuropsychological Assessment Battery (NAB), Brief Visuospatial Memory Test-Revised (BVMT-R), Category Fluency: Animal Naming, The Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) and Continuous Performance Test-Identical Pair (CPT-IP), which evaluate seven cognitive domains: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition. The LNS was excluded in the Chinese version because there is no corresponding alphabet in Chinese. Moreover, because some subjects were younger than 18 years old, we excluded the Mayer-Salovery-Caruso Emotional Intelligence test. Hence, eight neurocognitive tests of the MCCB were selected to use in our study (Table 2) Total testing time (without including rest breaks) was about 35 min.

2.3. Genotyping

We extracted genomic DNA from 3000 μL of whole blood using the Flexi Gene DNA Kit for each subject. The extracted DNA was quantified using a Nano Drop™ 2000 (Thermo Fisher Scientific™, Waltham, MA, USA) and the single nucleotide polymorphism (SNP) analysis was performed using the Kompetitive Allele Specific PCR genotyping system (KASP). Briefly, DNA samples were diluted to a final concentration of 10–20 ng per reaction and the total KASP genotyping mix reaction volume was 10 μL (1 μL diluted DNA, 5 μL 2× KASP Master mix, 0.07 μL primer mix (Roche), and 3.93 ddH_2O). The primer sequences for COMT were as follows: forward: 5'-GGGCCTACTGTGGCTACTCA-3′; reverse:

5'-CCCTTTTTCCAGGTCTGACA-3′.

Subjects who were homozygous and heterozygous for the *A*-allele (*Met*) were merged into a group of *A*-allele carriers and compared with homozygotic individuals for the *G*-allele (*Val*). There are three known COMT rs4680 genotypes: *Met*/*Met*, *Met*/*Val*, and *Val*/*Val*. Subjects with the *Met*/*Met* genotype and the *Met*/*Val* genotype were merged into a group of *Met* allele carriers to address skewed genotypic distributions as per a previous method (Li et al., 2009; Li et al., 2016; Tian et al., 2013).

2.4. MRI data acquisition

MRI was performed using a 3.0-T Siemens Verio MRI scanner (Erlangen, Germany) with a 32-channel head coil. Functional MRI (fMRI)

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