Sex-dependent effect on the association of *COMT* Val^{158}Met polymorphism with schizophrenia clinical symptoms and cognitive impairment

Hang Xu (xuh@psych.ac.cn)
Institute of Psychology Chinese Academy of Sciences
Yongjie Zhou
Shenzhen Kangning Psychiatric Hospital: Shenzhen Kangning Hospital
Jiesi Wang
Institute of Psychology Chinese Academy of Sciences
Meihong Xiu
Beijing Huilongguan Hospital
Dachun Chen
Beijing Huilongguan Hospital
Weiwen Wang
Institute of Psychology Chinese Academy of Sciences
Li Wang
Institute of Psychology Chinese Academy of Sciences
Xiangyang Zhang
Institute of Psychology Chinese Academy of Sciences

Research Article

Keywords: Schizophrenia, Catechol-O-methyl transferase (COMT), Val158Met (rs4680), Sex difference, Cognitive function

Posted Date: August 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-817886/v1

Abstract

Catechol-O-methyltransferase (*COMT*) Val^{158}Met (rs4680) polymorphism is thought to be involved in the pathogenesis of schizophrenia, which is related to the regulation of dopamine transmission in the prefrontal cortex. Recent studies have shown that the influence of *COMT* Val^{158}Met variation is sexually dimorphic. This study aims to explore the possible effect of the interaction between *COMT* Val^{158}Met polymorphism and sex on patients' clinical characteristics and cognitive function. 367 inpatients with chronic schizophrenia (246 males and 121 females) and 419 healthy controls (172 males and 247 females) are recruited. The cognitive performances are assessed by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and the *COMT* Val^{158}Met polymorphism is genotyped. The psychopathological symptoms of the patients are assessed by the Positive and Negative Syndrome Scale (PANSS). We find that: 1) sex difference in the allele frequency and genotype distribution of *COMT* Val^{158}Met are found only in schizophrenia patients; 2) there is sex × *COMT* genotype interaction in positive symptoms, immediate memory, attention, and RBANS total score indexes in patients with schizophrenia; 3) mainly in the male patients' sample, Val/Val carriers exhibit more positive symptoms and more severe cognitive impairment than Met carriers. These findings suggest that *COMT* Val^{158}Met polymorphism is associated with the risk and severity of schizophrenia in a sexually dimorphic way, which is helpful to understand the factors that may lead to different manifestations of male and female patients with schizophrenia.

Introduction

Schizophrenia is a devastating mental disorder, with a lifetime prevalence rate of approximately 0.4% worldwide [1]. The burden of disease is high, however, the biological background of the pathophysiology of schizophrenia has not been fully understood [1, 2]. The core features of schizophrenia are characterized by three domains, including heterogeneous positive and negative symptoms (such as hallucinations, delusions, and reduced expression of emotions or motivation), and cognitive dysfunction (such as difficulties with concentration, working memory, and decision making) [3].

Furthermore, sex differences in schizophrenia have also received attention in terms of age of onset, course of the disease, symptomatology, treatment outcome, and neurological abnormalities [4–6]. There is evidence that the risk ratio of men suffering from schizophrenia is about 1.4 times higher than that of women [2, 7]. In terms of clinical symptoms, male patients exhibit more negative symptoms, while female patients display more affective, paranoid, and periodic psychiatric symptoms [4]. The underlying molecular mechanism of sex differences for the features of schizophrenia remains unclear.

Several candidate genes are associated with sexual dimorphism in schizophrenia, including the catechol-O-methyl transferase (*COMT*) Val^{158}Met gene (Bollettini et al. 2018). A large amount of evidence indicates that *COMT* encodes a major catabolic enzyme involved in DA metabolism and has been widely studied in patients with schizophrenia. The human *COMT* gene is located at position 11.21 on chromosome 22, which is a region closely related to mental illness. Single nucleotide polymorphism (SNP) rs4680 (Val^{158}Met) is one of the widely studied polymorphisms of the *COMT* gene, which transforms from valine (or allele G) to methionine (or allele A) (Val^{158}Met). *COMT* Val^{158}Met regulates the dopaminergic transmission in the prefrontal cortex (PFC), where it accounts for more than 60% of the metabolic degradation of dopamine [8]. At normal body temperature, the COMT activity of Val allele carriers is three times higher than that of Met allele carriers. Higher COMT activity leads to lower DA signal, so the Val allele may cause physiological impairment of the prefrontal lobe [9]. Given the importance of COMT in regulating dopamine, the *COMT* Val^{158}Met gene polymorphism has been associated with dopamine-related disorder (such as schizophrenia) and cognitive dysfunction, and the response to treatment [10, 11]. For example, Val/Val patients with schizophrenia show more severe psychiatric symptoms [12],more positive/negative symptoms [13–15], and worse performance in working memory tasks [16]. Met allele load can predict improvement in cognitive performance and positive/negative symptoms after antipsychotic treatment [12, 17, 18]. *COMT* is considered to have sex-specific effects on various transcriptional regulation of estrogens and other mechanisms [19]. Recent studies have reported the sexually dimorphic effect of Val^{158}Met polymorphism on brain morphology. The decrease in COMT enzyme activity increases the thickness of PFC in male, but not female mice and humans [20, 21]. Consistent with neuroanatomical changes, *COMT* Val^{158}Met polymorphism is associated with sex differences in PFC-dependent working memory in patients, which means that men with Met allele show better working memory [21]. It has also been reported that there is an effect of high-activity allele loading on negative symptoms, disorganization, and cognition (such as executive function and verbal IQ) in males [22, 23], while the Met allele is associated with lower stress effects in females [24].

In addition to the sex factor, ethnicity seems like also an influencing factor considering the relationship between *COMT* Val^{158}Met polymorphism and schizophrenia. A recent meta-analysis of 32816 subjects indicates an association between *COMT* Val^{158}Met polymorphism and schizophrenia in the general population. The risk is higher in Caucasians than in Asians [25]. However, studies in the Chinese Han population have found inconsistent results between Val^{158}Met polymorphism and schizophrenia. For example. Sun et al. found no significant genotypic association between Val^{158}Met polymorphism and clinical symptoms or cognitive function [26], while Li et al. found that Val^{158}Met polymorphism may be associated with negative symptoms of schizophrenia in Han Chinese. [13, 27]. One possible reason for this

inconsistency is that many of these studies do not consider the sex-gene interaction [26, 28]. Therefore, at present, there is no study from China to investigate the effect of sex × *COMT* genotype interaction on symptoms and cognitive function in patients with schizophrenia.

Based on the above background, this study aims to explore the effect of sex × *COMT* genotype interaction on the characteristics and cognitive function of Chinese Han patients with schizophrenia.

Methods

Subjects

We recruited 367 inpatients (246 males and 121 females) from the Beijing Huilongguan Hospital, a Beijing city-owned psychiatric hospital. These patients were all Han Chinese and met the criteria for schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). The diagnosis was independently confirmed by two experienced psychiatrists. The patients met the following criteria: a) aged between 20 to 75 years old, with more than five years of education; b) had a course of disease for at least 5 years; c) received a stable dose of oral antipsychotic drugs for more than one year. Antipsychotic treatment was monotherapy, including clozapine (47.5%), risperidone (25.0%), chlorpromazine (4.9%), sulpiride (8.2%), perphenazine (6.6%), haloperidol (4.5%), nimesulide (2.9%), and quetiapine (0.4%). We excluded patients with major physical diseases or any acute or chronic diseases affecting the immune, endocrine, metabolic or nervous systems (such as cerebrovascular disease, cancer, lung disease, or diabetes), as well as pregnant or breast-feeding women. Their average age was 50.16 ± 9.80 years (ranging from 19 to 73 years), and their average course of the disease was 27.66 ± 7.79 years (ranging from 14 to 55 years). The average education level was 9.71 ± 2.52 years. 181 males and 63 females of those patients completed the cognition assessment. In the same period, a total of 419 healthy Han Chinese was recruited from the local area in Beijing, including 172 males and 247 females. Any healthy subjects with a history of medical abnormalities or common mood disorders or substance abuse/dependence were excluded. The age, education level, marriage of patients and healthy subjects matched. Their average age was 46.21 ± 13.18 years (ranging from 16 to 70 years). The average education level was 9.2 ± 3.32 years. None of them suffered from substance/alcohol dependence/abuse except for smoking. 168 males and 229 females completed the cognitive assessment. The informed consent form was obtained from all participants. The study protocol was approved by the Institutional Review Board, Beijing Hui-Long-Guan Hospital.

Clinical assessment

Four psychiatrists simultaneously participated in a training course to evaluate the Positive and Negative Syndrome Scale (PANSS). After training, the inter-observer correlation coefficient of the PANSS total score was maintained above 0.8 to ensure the reliability and consistency of the evaluation.

The cognitive function of all subjects was assessed by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A) [29]. The clinical validity and test-retest reliability were confirmed in the Chinese general population and patients with schizophrenia [30]. It provides a total score and five subscores of cognitive function, including immediate memory, visuospatial/constructional, language, attention, and delayed memory. The Chinese version of RBANS showed good validity (Cronbach's α coefficient of the total scale, immediate memory, visuospatial, language, attention, and delayed memory were 0.9, 0.86, 0.68, 0.67, 0.85, and 0.80, respectively) and good test-retest reliability in China [30].

Blood sampling and Genotyping

After an overnight fast, venous blood was collected from the forearm vein of the subjects using the anticoagulant ethylene diamine tetraacetic acid (EDTA) tubes between 7:00 and 9:00 am. Genomic DNA was extracted from whole blood samples. Following the standard protocol, the *COMT* Val^{158}Met polymorphism was identified by using Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) (Sequenom Inc., San Diego, CA, USA). The amplification primers were: sense: 5'-TCACCATCGAGATCAACCCC-3', antisense: 5'-GAACGTGGTTGTAACACCTG-3'. In addition, 5% of the samples were genotyped for error checking, with a reproducibility of 0.99. *COMT* Val^{158}Met polymorphism genotyping was carried out by a technician who was blind to the clinical status of the subjects [31].

Statistical analysis

Statistical analyses were carried out using the Statistical Package of Social Sciences version 24 (SPSS, Inc., USA) for Windows. Differences between groups were compared using ANOVA/MANCOVA for continuous variables and chi-square test for categorical variables. Hardy–Weinberg equilibrium was performed to examine genotype deviation. The interaction analysis of diagnosis, sex, and *COMT* Val^{158}Met polymorphism on cognitive functions adopted the three-way MANCOVA, with age and education as covariates. The interaction effects of sex and genotype on cognitive functions in healthy control and patients were analyzed by two-way MANCOVA. The one-way MANCOVA was adopted to analyze the differences between genotypes of the same gender. The age, age of onset, and education were defined as covariates in the patients. Age and education were defined as covariates in healthy control. The FDR correction was performed for multiple tests and post

hoc analysis. The Cohen's d method was used to calculate the standardized effect size. Descriptive summary statistics were expressed as mean ± standard deviation (SD), and differences with p<0.05 were considered to be significant.

Results

Demographic characteristics and genotypic data

The demographic characteristics of the subjects are shown in Table 1. One-way ANOVA indicated that there was a significant age difference ($F_{(1,781)}$ =32.83, p<0.01), but not in education between patients and healthy controls. In addition, there was a significant sex difference in age in the healthy control group ($F_{(1,417)}$ =6.59, p<0.05), and significant sex difference in educations in both healthy control and patients ($F_{(1,413)}$ =4.17, p<0.05; $F_{(1,365)}$ =5.35, p<0.05). There was no significant difference in the age of onset between male patients and female patients.

The *COMT* Val^{158}Met genotype distribution was consistent with Hardy–Weinberg equilibrium in healthy controls (c^2=2.83, df=1, p=0.24) and patients (c^2=0.03, df=1, p=0.98). The distribution of *COMT* Val^{158}Met genotype and allele were summarized in Table 1.There was no significant difference in *COMT* Val^{158}Met genotype (c^2=2.27, df=2, p>0.05) and allele distribution (c^2=0.52, df=1, p>0.05) between the healthy controls and patients. However, there were significant sex differences in the *COMT* Val^{158}Met genotype (c^2=10.3, df=2, p<0.01) and allele frequency in patients (c^2=4.16, df=1, p<0.05), showing that male patients had a higher proportion of Met alleles. However, there was no such a sex difference in healthy controls (c^2=0.82, df=2, p>0.05; c^2=0.03, df=1, p>0.05, respectively).

Interaction of diagnosis, sex and *COMT* Val^{158}Met genotype on the cognitive function

As shown in Table 2, three-way MANCOVA indicated the interaction analysis results of the diagnosis, sex, and genotype. The main effects of diagnosis were significant in all cognitive indexes (all p or FDR corrected p<0.05; Cohen's f=0.54, 0.23, 0.49, 0.30, 0.70,0.47 respectively in immediate memory, visuospatial/constructional, language, attention, delayed memory, and total score). There was significant sex effect in delayed memory ($F_{(1,631)}$=5.18, p<0.05, FDR corrected p=0.02, Cohen's f=0.18). There was significant COMT genotype effect on language ($F_{(1,631)}$=4.92, p<0.05, FDR corrected p=0.03, Cohen's f=0.18). There was significant diagnosis×sex interaction in delayed memory ($F_{(1,631)}$=5.58, p<0.05, FDR corrected p=0.09, Cohen's f=0.19), and diagnosis×COMT interaction in language ($F_{(1,631)}$=4.77, p<0.05, FDR corrected p=0.10, Cohen's f=0.17), and sex×COMT interaction ($F_{(1,631)}$=4.54, p<0.05, FDR corrected p=0.09, Cohen's f=0.19) in immediate memory ($F_{(1,631)}$=4.54, p<0.05, FDR corrected p=0.11, Cohen's f=0.17), but those differences did not pass the correction.

Interaction of sex and *COMT* Val^{158}Met genotype on the clinical characteristics of schizophrenia patients

The interaction of sex and *COMT* Val^{158}Met polymorphism on the clinical characteristics of patients with schizophrenia were summarized in Table 3. After adjusting for age and education, two-way MANCOVA showed that there was a significant sex × genotype interaction effect on the positive subscale score ($F_{(1,238)}$=7.29, p<0.05, FDR corrected p=0.04, Cohen's f=0.35), but not on the negative subscale, general psychopathology subscale or PANSS total scores (all p>0.05). In addition, there were no main effects of sex or genotype on the PANSS subscales and total scores (all p>0.05). One-way MANCOVA showed that in male patients, there was a significant genotype effect on the positive subscale ($F_{(1,173)}$=5.42, p<0.05, FDR corrected p=0.03, Cohen's f=0.50). However, there was no genotype effect in female patients (p>0.05). Further *post hoc* analysis (Fig 1A) indicated that male patients with Met homozygote and heterozygote had a significantly lower score than female patients with Met homozygote and heterozygote genotypes (p<0.01). Male patients with Val/Val genotype had more positive symptoms than Met carriers (Val/Met vs. Met carrier: 13.3±4.8 vs. 11.6±4.6, p<0.05), while in female patients, Met carriers exhibited more positive symptoms slightly (12.3±5.4 vs. 14.7±7.3, p=0.07).

Interaction of sex and *COMT* Val^{158}Met genotype on cognitive performance in healthy control and schizophrenia patients

In patients, two-way MANCOVA with age, age of onset, and education as covariates indicated that there were significant sex effect on immediate memory ($F_{(1,235)}$=3.98, p<0.05, FDR corrected p=0.06, Cohen's f=0.26), delayed memory ($F_{(1,235)}$=6.91, p<0.01, FDR corrected p=0.02, Cohen's f=0.34), and total score ($F_{(1,235)}$=4.33, p<0.05, FDR corrected p=0.06, Cohen's f=0.27). Moreover, there was a significant genotype effect on language ($F_{(1,235)}$=6.57, p<0.05, FDR corrected p=0.01, Cohen's f=0.33). There was a significant sex × genotype interaction on immediate memory ($F_{(1,235)}$=4.44, p<0.05, FDR corrected p=0.07, Cohen's f=0.33), attention ($F_{(1,235)}$=4.92, p<0.05, FDR corrected p=0.05, Cohen's f=0.29), and total score ($F_{(1,235)}$=4.21, p<0.05, FDR corrected p=0.04, Cohen's f=0.27).

One-way MANCOVA showed that in male patients, there was significant genotype effect on all the cognitive indexes: immediate memory ($F_{(1,175)}$= 12.9, p<0.01, FDR corrected p=0.002, Cohen's f=0.54), visuospatial/constructional ($F_{(1,175)}$= 5.9, p<0.05, FDR corrected p=0.03, Cohen's f=0.37), language ($F_{(1,175)}$= 4.4, p<0.05, FDR corrected p=0.05, Cohen's f=0.32), attention ($F_{(1,175)}$=4.6, p<0.01, FDR corrected p= 0.05, Cohen's f=0.32), delayed memory ($F_{(1,175)}$=4.3, p<0.01, FDR corrected p= 0.05, Cohen's f=0.31), and total score ($F_{(1,175)}$=9.0, p<0.01, FDR corrected

p=0.01, Cohen's f=0.45). However, in female patients, there were no significant differences between genotypes in any of the cognitive indexes. Further *post hoc* analysis showed that male patients with Val homozygotes had the lowest score in nearly all the cognitive indexes (Fig1 B,C,D,E,G,F).

In the healthy controls, we did not find any significant sex effects, genotype effects, or sex × genotype interactions on cognitive performance (all *p*>0.05). Further *post hoc* analysis showed that in either male or female healthy controls, there was no significant genotype effect on any cognitive indexes (all *p*>0.05).

Discussion

In this study, we investigate the interaction of *COMT* Val^{158}Met polymorphism and sex on clinical characteristics and cognitive performance of patients with schizophrenia and healthy controls in a Chinese population. The main findings of this study are as follows: 1) there are no significant differences in allele frequency and genotype distribution of *COMT* Val^{158}Met between healthy people and schizophrenia patients. At the same time, sex differences in the allele frequency and genotype distribution of *COMT* Val^{158}Met are found only in patients with schizophrenia. 2) in patients, there are sex × genotype interactions in terms of positive symptoms, immediate memory, attention, and RBANS total score. 3) in the patients' sample, the male patients with Val/Val exhibit more positive symptoms and more severe cognitive dysfunction compared with male Met carriers.

Our results reveal that there are no significant differences in allele and genotype frequencies of *COMT* Val^{158}Met polymorphism between patients with schizophrenia and healthy control. This result is in line with many other studies conducted in East Asian populations [14, 32, 33]. However, the *COMT* Val^{158}Met polymorphism is found to play an important role in susceptibility to schizophrenia in Caucasian and African Americans [6, 10, 34, 35]. A meta-analysis report shows that there is no evidence of a significant association among the Asian populations, while the risk of disease in Caucasians with the Val allele is increased up to 10–23% [25]. These pieces of evidence suggest that the association between *COMT* Val^{158}Met polymorphism and schizophrenia may be race-specific. Furthermore, recent studies have shown that the genetic variations of *COMT* are associated with sex-dependent effects on enzyme activity, brain function, and pathological processes, suggesting that sex may be the key to understanding COMT-dependent effects [20]. In this study, we find that compared with healthy people, the distribution of Val^{158}Met gene polymorphism had significant sex differences in the allele and genotype frequencies of patients. Studies conducted in the Asian population have reached a generally consistent conclusion that *COMT* Val^{158}Met polymorphisms may not contribute to susceptibility to schizophrenia [26, 33]. However, previous studies may have ignored the impact of sex differences.

Previous studies have reported the potential association between *COMT* and negative symptoms in the Asian populations [27, 28], but some studies have not [26]. The current study does not find an association between negative symptoms and *COMT* in our patient samples, but *COMT* Val^{158}Met polymorphism has a sexually dimorphic effect on positive symptoms. Consistent with our study, Goghari et al reported that male patients with Val homozygotes demonstrated greater positive symptoms than those male patients with Met carriers [15]. The dopamine hypothesis of schizophrenia assumes that positive symptoms can be attributed to the hyperactivity of dopamine D2 receptors in the subcortical and limbic brain regions, while negative symptoms can be attributed to the hypo functionality of dopamine D1 receptors neurotransmission in PFC [36]. However, little is known about the relationship between the *COMT* Val^{158}Met polymorphism and dopamine receptors.

The relationship between cortical dopamine and PFC-dependent functions is inverted-U-shaped [37, 38], and too high or too low dopamine is associated with impaired function. The Val/Val genotype may be associated with a low D1/high D2 status [37]. Dopamine has been shown to play an important role in the PFC-mediated cognition [39]. Evidence from *COMT* knockout mice and pharmacological investigations have confirmed the importance of COMT for dopaminergic clearance in PFC [9, 20, 21]. Since the COMT efficacy of the Val alleles is three to four times higher than that of Met alleles, this difference may shape cognitive performance. In our study, male patients with homozygous Val alleles show worse cognitive performance in immediate and delayed memory, which is consistent with some previous studies. For example, Bilder et al. reported that the *COMT* Met allele was associated with better performance in processing speed and attention ability in patients with chronic schizophrenia [40]. Matsuzaka et al. found that Val/Val carriers scored the lowest in working memory tasks [16]. Shukla et al. found that Val homozygotes were related to poor performance on the dorsolateral-prefrontal-cortex-dependent task [41]. This sex-*COMT* interaction on cognitive function has also been verified in transgenic mice [42]. The activity levels of the COMT enzyme are also influenced by sex, showing that male subjects and Val alleles are associated with higher enzyme activity and possibly lower PFC dopamine levels [43]. Therefore, one possible explanation is that the co-regulation of COMT by sex and Val^{158}Met variants may lead to sex differences in schizophrenia. Although relatively little is known about how the genetic variation of Val^{158}Met affects brain structure and function, a recent study has found that male subjects with Met/Met have higher subcortical volumes [20]. Male and female patients have different association patterns between the *COMT* gene and disease phenotype. The COMT effect is relatively weak among women [44]. Notably, the sex-dependent effects on cognition were not observed in normal healthy people.

In summary, our results suggest that the Val allele of *COMT* Val^{158}Met genotype is closely associated with the positive symptoms and cognitive dysfunction of Chinese male patients with schizophrenia. There are several limitations in the current study. 1) The influence of drugs cannot be ruled out. 2) This study only examined one candidate gene, while other potential polymorphisms may be involved in the psychopathological symptoms of schizophrenia. 3) Due to the limited sample size, we cannot separate the homozygous Met/Met group and the heterozygous Val/Met group from the 'Met allele carriers'. Therefore, larger sample size is needed to confirm our findings, and more studies are necessary to elucidate the mechanism in depth. In conclusion, this study reveals that *COMT* Val^{158}Met polymorphism has a sexually dimorphic effect on the severity of schizophrenia and helps to understand the factors that may lead to different manifestations between male and female patients with schizophrenia.

Declarations

Contributors

Xiangyang Zhang designed the study, managed study supervision. Meihong Xiu, Dachun Chen and Yongjie Zhou interviewed the participants and conducted the clinical assessment. Hang Xu analyzed the data and drafted the manuscript. Hang Xu, Xiangyang Zhang, Weiwen Wang, Li Wang, and Jiesi Wang revised and completed the paper.

Conflict of interest

The authors declare they have no competing interests in this research.

Acknowledgments

This work was supported by the grants from the National Natural Science Foundation of China (81371477), China Postdoctoral Science Foundation (E0BH0110), the Special Research Assistant Program of CAS (E0ZZ0210), and the Chinese Academy of Sciences and the Key Laboratory of Mental Health, Institute of Psychology.

References

1. Simeone JC et al (2015) An evaluation of variation in published estimates of schizophrenia prevalence from 1990 horizontal line 2013: a systematic literature review. BMC Psychiatry 15:193
2. McGrath J et al (2008) Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30:67–76
3. Zai G et al (2017) A review of molecular genetic studies of neurocognitive deficits in schizophrenia. Neurosci Biobehav Rev 72:50–67
4. Leung A, Chue P (2000) Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand Suppl 401:3–38
5. Goldstein JM et al (2013) Sex differences in the genetic risk for schizophrenia: history of the evidence for sex-specific and sex-dependent effects. Am J Med Genet B Neuropsychiatr Genet 162B(7):698–710
6. Hoenicka J et al (2010) Gender-specific COMT Val158Met polymorphism association in Spanish schizophrenic patients. Am J Med Genet B Neuropsychiatr Genet 153B(1):79–85
7. Aleman A, Kahn RS, Selten JP (2003) Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psychiatry 60(6):565–571
8. Karoum F, Chrapusta SJ, Egan MF, *3-Methoxytyramine is the major metabolite of released dopamine in the rat frontal cortex: reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a simple two pool model.* J Neurochem (1994) **63**(3): p. 972-9
9. Egan MF et al (2001) Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A 98(12):6917–6922
10. Pelka-Wysiecka J et al (2013) BDNF rs 6265 polymorphism and COMT rs 4680 polymorphism in deficit schizophrenia in Polish sample. Pharmacol Rep 65(5):1185–1193
11. Woodward ND, Jayathilake K, Meltzer HY (2007) COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia. Schizophr Res 90(1–3):86–96
12. Molero P et al (2007) Clinical involvement of catechol-O-methyltransferase polymorphisms in schizophrenia spectrum disorders: influence on the severity of psychotic symptoms and on the response to neuroleptic treatment. Pharmacogenomics J 7(6):418–426
13. Li WJ et al., *Association of Catechol-O-methyltransferase gene polymorphisms with schizophrenia and negative symptoms in a Chinese population.* American Journal of Medical Genetics Part B-Neuropsychiatric Genetics, 2012. **159b**(4): p. 370–375

14. Nunokawa A et al (2007) No associations exist between five functional polymorphisms in the catechol -O-methyltransferase gene and schizophrenia in a Japanese population. Neurosci Res 58(3):291–296
15. Goghari VM, Sponheim SR (2008) Differential association of the COMT Val158Met polymorphism with clinical phenotypes in schizophrenia and bipolar disorder. Schizophr Res 103(1–3):186–191
16. Matsuzaka CT et al (2017) Catechol-O-methyltransferase (COMT) polymorphisms modulate working memory in individuals with schizophrenia and healthy controls. Braz J Psychiatry 39(4):302–308
17. Bertolino A et al (2004) Interaction of COMT (Val(108/158)Met) genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. Am J Psychiatry 161(10):1798–1805
18. Huang E et al., *Catechol-O-Methyltransferase Val158Met Polymorphism and Clinical Response to Antipsychotic Treatment in Schizophrenia and Schizo-Affective Disorder Patients: a Meta-Analysis*. Int J Neuropsychopharmacol, 2016. 19(5)
19. Harrison PJ, Tunbridge EM (2008) Catechol-O-methyltransferase (COMT): a gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. Neuropsychopharmacology 33(13):3037–3045
20. Bollettini I et al (2018) Sexually divergent effect of COMT Val/met genotype on subcortical volumes in schizophrenia. Brain Imaging Behav 12(3):829–836
21. Sannino S et al (2015) COMT Genetic Reduction Produces Sexually Divergent Effects on Cortical Anatomy and Working Memory in Mice and Humans. Cereb Cortex 25(9):2529–2541
22. Stefanis NC et al (2004) Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. Biol Psychiatry 56(7):510–515
23. Barnett JH et al (2007) Gender-specific effects of the catechol-O-methyltransferase Val108/158Met polymorphism on cognitive function in children. Am J Psychiatry 164(1):142–149
24. Hill LD et al (2018) Catechol-O-methyltransferase Val158Met polymorphism associates with affect and cortisol levels in women. Brain Behav 8(2):e00883
25. Gonzalez-Castro TB et al (2016) The Role of a Catechol-O-Methyltransferase (COMT) Val158Met Genetic Polymorphism in Schizophrenia: A Systematic Review and Updated Meta-analysis on 32,816 Subjects. Neuromolecular Med 18(2):216–231
26. Sun Z et al (2018) Association between COMT gene polymorphisms, clinical symptoms, and cognitive functions in Han Chinese patients with schizophrenia. Psychiatr Genet 28(3):47–54
27. Mao Q et al (2016) Association of catechol-O-methyltransferase Val(108/158) Met genetic polymorphism with schizophrenia, P50 sensory gating, and negative symptoms in a Chinese population. Psychiatry Res 242:271–276
28. Wang Y et al (2010) Analysis of association between the catechol-O-methyltransferase (COMT) gene and negative symptoms in chronic schizophrenia. Psychiatry Res 179(2):147–150
29. Randolph C et al (1998) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 20(3):310–319
30. Zhang BH et al., *Repeatable battery for the assessment of neuropsychological status as a screening test in Chinese: reliability and validity*. Chinese Mental Health Journal, 2008
31. Wang J et al (2021) The interactive effect of genetic polymorphisms of IL-10 and COMT on cognitive function in schizophrenia. J Psychiatr Res 136:501–507
32. Kong FZ et al (2011) [An association study of COMT gene polymorphisms with schizophrenia]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 28(2):208–211
33. Yu R et al (2007) Association analysis of COMT polymorphisms and schizophrenia in a Chinese Han population: a case-control study. Am J Med Genet B Neuropsychiatr Genet 144B(4):570–573
34. Diez-Martin J et al., *[COMT Val158Met polymorphism and schizophrenia in a series of Spanish patients]*. Med Clin (Barc), 2007. **128**(2): p. 41 – 4
35. Boot E et al (2011) Dopamine metabolism in adults with 22q11 deletion syndrome, with and without schizophrenia–relationship with COMT Val(1)(0)(8)/(1)(5)(8)Met polymorphism, gender and symptomatology. J Psychopharmacol 25(7):888–895
36. Toda M, Abi-Dargham A (2007) Dopamine hypothesis of schizophrenia: making sense of it all. Curr Psychiatry Rep 9(4):329–336
37. Schacht JP (2016) COMT val158met moderation of dopaminergic drug effects on cognitive function: a critical review. Pharmacogenomics J 16(5):430–438
38. Cools R, D'Esposito M (2011) Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry 69(12):e113–e125
39. Williams HJ, Owen MJ, O'Donovan MC (2007) Is COMT a susceptibility gene for schizophrenia? Schizophr Bull 33(3):635–641

40. Bilder RM et al (2002) Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. Biol Psychiatry 52(7):701–707
41. Shukla AA et al (2016) COMT val158met polymorphism and molecular alterations in the human dorsolateral prefrontal cortex: Differences in controls and in schizophrenia. Schizophr Res 173(1–2):94–100
42. Papaleo F et al (2012) Effects of sex and COMT genotype on environmentally modulated cognitive control in mice. Proc Natl Acad Sci U S A 109(49):20160–20165
43. Elton A et al (2017) COMT Val(158)Met Polymorphism Exerts Sex-Dependent Effects on fMRI Measures of Brain Function. Front Hum Neurosci 11:578
44. Voisey J et al (2012) HapMap tag-SNP analysis confirms a role for COMT in schizophrenia risk and reveals a novel association. Eur Psychiatry 27(5):372–376

Tables

Table2: **Interaction of diagnosis, sex, and *COMT* Val^{158}Met genotype on the cognitive function**

Variables	Immediate memory		Visuospatial/constructional		Language		Attention		Delayed memory		RBANS total score	
	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*
Diagnosis(D)	46.66	0.00**	7.99	0.00**	38.18	0.00**	14.61	0.00**	76.70	0.00**	34.52	0.00**
SEX	3.37	0.07	1.33	0.25	0.03	0.85	0.01	0.94	5.18	0.02*	2.54	0.11
COMT	1.15	0.28	0.02	0.90	4.92	0.03*	0.44	0.51	0.17	0.68	0.21	0.65
D×SEX	0.34	0.56	0.31	0.58	0.18	0.67	0.00	1.00	5.58	0.02*	1.44	0.23
D×COMT	1.85	0.17	0.56	0.45	4.77	0.03*	0.11	0.74	1.05	0.31	1.43	0.23
SEX×COMT	4.54	0.03*	2.97	0.09	0.53	0.46	2.68	0.10	2.62	0.11	2.40	0.12
D×SEX×BDNF	1.28	0.26	1.36	0.24	0.26	0.61	1.15	0.28	1.81	0.18	1.02	0.31

Three-way MANCOVA with age and education as the covariates; *p*: *<0.05 ** <0.01.

Due to technical limitations, Table 1 and 3 are only available as a download in the Supplemental Files section.

Figures

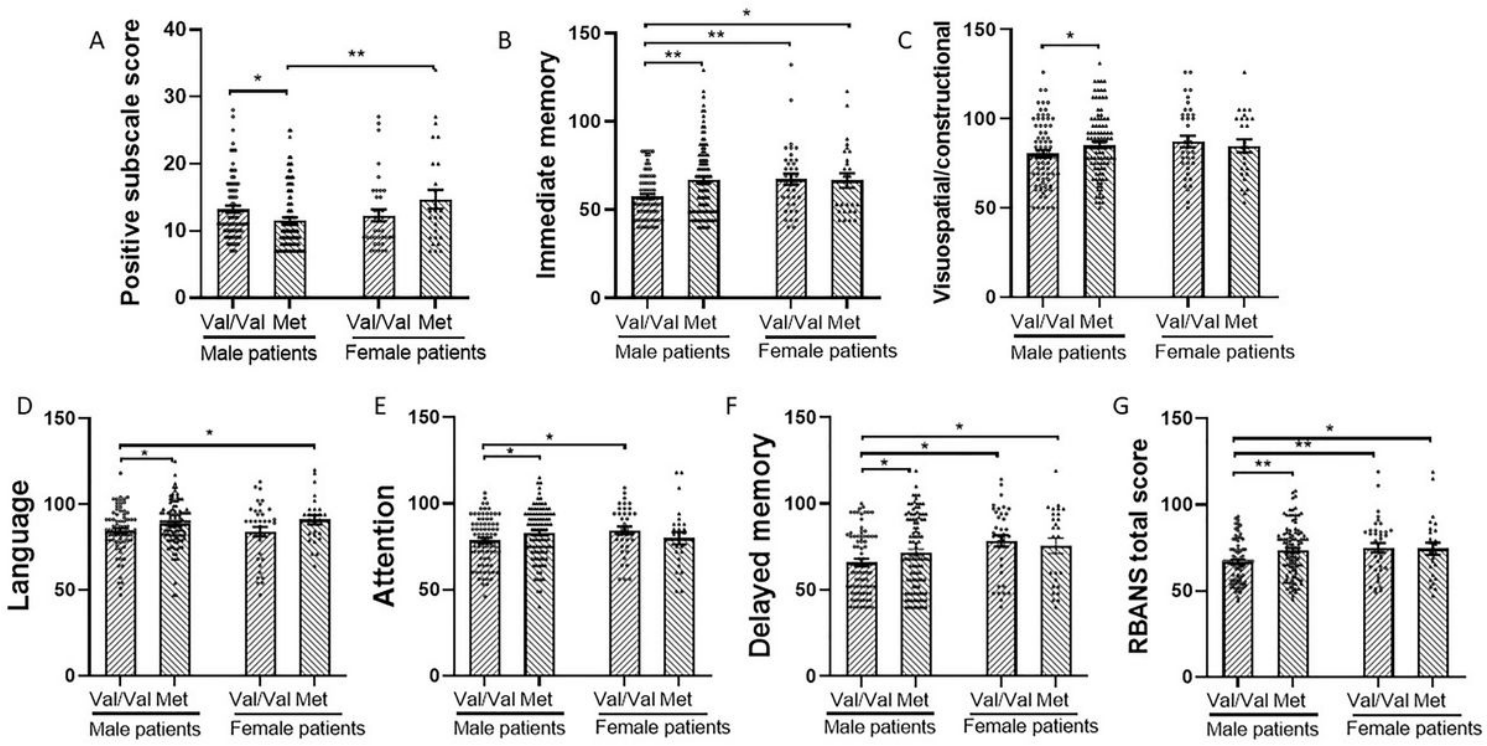

Figure 1

Comparisons between COMT Val158Met genotype and sex with post hoc test on PANSS positive subscale score (A), immediate memory (B), Visuospatial/constructional (C), Language (D), Attention (E), Delayed memory (F), and RBANS total score (G) indexes. Error bars: standard error of the mean. p: *<0.05 ** <0.01. Met means Met carrier.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1and3.docx