Revista Brasileira de Psiquiatria. 2017;39:302–308
Associação Brasileira de Psiquiatria
doi:10.1590/1516-4446-2016-1987

ORIGINAL ARTICLE

Catechol-O-methyltransferase (*COMT*) polymorphisms modulate working memory in individuals with schizophrenia and healthy controls

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Objective: Cognitive impairment is a core feature of schizophrenia, related to dopaminergic dysfunction in the prefrontal cortex (PFC). It is hypothesized that functional single nucleotide polymorphism (SNP) rs4680 of the catechol-O-methyltransferase (*COMT*) gene could mediate the relationship between cognition and dopamine activity in the PFC. Other *COMT* SNPs could also play a role.
Methods: We evaluated the role of three *COMT* SNPs (rs737865, rs165599, and rs4680) in schizophrenia and their impact on three working memory tasks. For genetic association analyses, 212 individuals with schizophrenia and 257 healthy controls (HCs) were selected. The Visual Working Memory (VWM) Task, Keep Track Task, and Letter Memory Task were administered to 133 schizophrenics and 93 HCs.
Results: We found a significant association of rs737865, with the GG genotype exerting a protective effect and the GA haplotype (rs4680/rs165599) exerting a risk effect for schizophrenia. *COMT* rs4680 AA carriers and rs737865 AA carriers scored lowest on the Keep Track Task. When the genotype*group interaction effect was evaluated, rs165599 exerted opposite effects for VWM and Keep Track task performance in patients and controls, with AA carriers scoring lowest on both tests among controls, but highest among patients.
Conclusion: These data support the hypothesis that *COMT* polymorphisms may be associated with schizophrenia and modulate cognition in patients and controls.

Keywords: Cognition; dopamine; gene

Introduction

Schizophrenia is a multifactorial and debilitating disease with a high heritability rate (approximately 80%).[1] It affects four to seven people per 1,000 worldwide.[2] Despite broad phenotypic heterogeneity, cognitive impairments have been considered profound and clinically relevant since the original descriptions.[3] Deficits usually described in patients involve several cognitive functions, such as memory, attention, working memory (WM), problem solving, processing speed, and social cognition.[4] Cognition in schizophrenia has been widely studied in recent decades, prompted by evidence that it is a determinant of quality of life and everyday functioning in patients.[5] Reduced cognitive performance is already evident at the first episode of psychosis, which implies that cognitive dysfunction is a likely neurobiological marker of schizophrenia even before the onset of illness.[6,7]

The dopamine hypothesis, based on evidence from pharmacological and in vivo imaging studies, is considered the final common pathway for psychotic symptoms in schizophrenia.[8] The enzyme catechol-O-methyltransferase (COMT) metabolizes several catecholamines, but is especially relevant to dopaminergic transmission in the prefrontal cortex (PFC), in which it is a key element to dopamine availability.[9] COMT is encoded by a single gene (also *COMT*) located on chromosome 22q11.2, a region that is commonly missing in 22q11.2 microdeletion syndrome, which has long been associated with predisposition for schizophrenia.[10] The enzymatic activity of COMT is altered by a guanine (G) to adenine (A) single nucleotide polymorphism (SNP) known as Val158Met or rs4680 in the *COMT* gene sequence, resulting in a trimodal distribution (high activity in the Val/Val genotype, intermediate activity in Val/Met, and low activity in Met/Met) and a three- to four-fold difference in COMT activity (Val/Val vs. Met/Met).[11] Studies on the *COMT* Val158Met polymorphism and vulnerability to schizophrenia have produced

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Submitted Apr 21 2016, accepted Sep 05 2016, Epub Mar 02 2017.

conflicting results. Previous meta-analyses do not support an association between *COMT* Val158Met and schizophrenia,[12-14] whereas one meta-analysis found a small but significant effect for homozygotes as the risk variant over heterozygotes in both mixed and Caucasian cohorts.[15] Nevertheless, Gatt et al.,[16] in a recent review of meta-analyses, highlights that Val vs. Met comparisons were null when considering larger samples and mixed or Asian samples.

Cognitive abilities related to the functional integrity of the frontal lobe and its neural networks throughout the brain (WM and executive functioning) might be related to hypodopaminergia in the PFC. Manipulation of dopaminergic tone in the PFC is crucial for executive and WM performance.[17] Thus, genetically determined variations in COMT activity might affect the availability of dopamine in prefrontal synapses,[9] and, thus, affect cognitive abilities, including WM performance, independently from proneness to schizophrenia.

COMT is one of the most investigated genes in schizophrenia, and its role in cognition has also been studied. Samples of healthy individuals showed associations, either positive[18,19] or negative, between *COMT* genotypes and cognition.[20] In schizophrenia samples, there have also been reports of positive[21-23] and negative associations.[24] In studies that showed positive associations, schizophrenia patients demonstrated a similar pattern to healthy controls (HCs): Met (G) homozygotes seem to have better cognitive performance relative to Val (A) carriers. A meta-analysis of the cognitive effects of *COMT* Val158Met,[25] however, concluded that there is weak evidence of association between this polymorphism and cognitive function.

Notably, functional variation in the *COMT* gene is not limited to the rs4680 SNP, but rather includes other polymorphisms, such as a P2 promoter region SNP (rs2097603) and a 3′ region SNP (rs165599). These three SNPs show nonlinear interacting effects on prefrontal efficiency during WM task performance, in agreement with predictions of resultant cortical dopaminergic catabolic rates, and highlight the complexity of genetic contributions to functional neuroimaging phenotypes, even within a single gene.[26] Many studies have focused on the Val158Met polymorphism, neglecting other SNPs in the gene. Studies assessing thousands of SNPs at once, such as genome-wide association studies (GWAS), need a large sample size, which is limited by the time-consuming nature of neuropsychological tests.

Within this context, the aim of this study was to further investigate the role of three *COMT* SNPs (rs737865, rs165599, and rs4680) in schizophrenia and on performance in WM tasks in a sample of patients and controls.

Methods

Subjects

A total of 212 patients and 257 HCs were recruited from Programa de Esquizofrenia (PROESQ) and Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), Universidade Federal de São Paulo (UNIFESP), Brazil. The diagnosis of schizophrenia was confirmed by the Structured Clinical Interview for DSM-IV applied by trained psychiatrists. HCs had no family history of severe psychiatric illness and no current or previous psychiatric disorders.

All subjects underwent blood collection for genetic analyses and a sample of 124 patients was assessed with the Positive and Negative Syndrome Scale (PANSS). Psychopathological dimensions (negative, positive, excited, and anxiety/depression) were classified according to PANSS ratings.[27] These individuals had no history of a diagnosed neurological disorder or medical condition known to be associated with neuropsychological impairment (e.g., epilepsy, stroke). The UNIFESP Ethics Committee approved the research protocol, and participants entered the study only after giving written informed consent.

DNA isolation and COMT *genotyping*

Whole blood was collected into tubes containing 0.1% ethylenediaminetetraacetic acid (EDTA), and genomic DNA isolation was performed using the Gentra Puregene Kit (Qiagen, Germantown, United States) according to the manufacturer's protocol.

All three *COMT* polymorphisms (rs737865, rs165599, and rs4680) were genotyped by TaqMan probe-based real-time polymerase chain reaction (PCR) assays (Life Technologies, Foster City, United States) performed under standard conditions. For each reaction, at least one positive control for each genotype was included.

Neuropsychological tests

Three tests assessing the ability to update information, part of WM function, were administered by trained psychologists to 133 patients and 93 controls. Previous studies have shown that these tasks are sensible choices for discriminating the cognitive performance of subjects with schizophrenia and healthy comparators.[28] The IQ of each participant was also assessed.

In the Visual Working Memory (VWM) task,[29] a subject is asked to pay attention to a computer screen where one to four 3×3 matrices are displayed. A stimulus appears within each matrix for 2 seconds and arrows then start indicating special manipulations that the subject will be asked to perform with the stimuli within each matrix. For example, an arrow pointing to the upward position followed by an arrow pointing to the left indicates that the stimulus should be displaced one row above and one column to the left from its original position. There is no time limit for each answer, but the test stops after consecutive errors. This test was based on the experimental tasks designed by Salthouse et al.[30]

The Keep Track task, adapted from Yntema,[31] first shows several target categories (animals, colors, countries, distances, metals, and relatives) on the computer screen. Then, 15 words are presented verbally in random order for 1,500 milliseconds each. The target categories remain on the screen. Each list had two or three exemplars

from each of the six possible categories. Participants had to remember the last word presented belonging to the remaining target categories (the first three trials had four categories and the last three had five).

The Letter Memory task, adapted from Morris & Jones,[32] was the third updating measure. In this task, letters are presented serially and individually. Participants had to recall the last two letters presented in each presented list. However, they had to rehearse the last two letters out loud by mentally adding the most recent letter, dropping the third letter back, and then saying the new string of two letters out loud. This instruction was given to ensure that participants were performing continuous updating. Although previous studies have used sequences ranging from four to nine words, we had to define this length because most of the patients could not start performance with larger sequences.

For all three tests, higher values denote better performance.

Statistical analysis

First, Hardy-Weinberg equilibrium (HWE) was verified using the chi-squared test. For cognitive analysis, we used square root transformation. To associate each genotype and allele to schizophrenia, we used logistic regression. Then, we constructed a general linear model (GLM) using each cognitive variable as a dependent variable, genotypes of each SNP and group (patient or control) as independent variables, and IQ as covariate to explore SNP and group effects on cognitive variables individually or their interaction (genotype*group), investigating whether the association of each genotype with the relevant dependent variable differed between cases and controls. Linkage disequilibrium (LD) was assessed with SNP Stats[33] (http://bioinfo.iconcologia.net/snpstats/start.htm?) and haplotypes were estimated using PLINK. To test for association between haplotypes and schizophrenia, we performed logistic regression, and for association between haplotypes and cognitive variables, we used a GLM, considering haplotypes and groups as independent variables and IQ as covariate, with the Bonferroni post-hoc procedure. We also investigated the haplotype*group interaction effect on cognitive variables.

Results

The clinical and demographic characteristics of the study population are described in Tables 1 and 2. No differences in gender, age, ethnicity, handedness, or education were found between cases and controls.

Association between COMT *SNPs and schizophrenia*

Allele and genotype frequencies for each group, as well as p-values for HWE, are described in Supplementary Table 1 (online-only). Only rs737865 genotype distribution in the patient group deviated from HWE (p = 0.001). However, when combining schizophrenia and control

Table 1 Characteristics of the study population

	Schizophrenia		Control		
Variable	N	n	N	n	p-value
Gender	212		257		
Male		146		158	0.095
Female		66		99	
Ethnicity	198		239		
Caucasian		116		160	0.071
Non-Caucasian		82		79	
Handedness	131		92		
Right		122		86	0.919
Left		9		6	
Variable	N	Mean (SD)	N	Mean (SD)	p-value
Age (years)	212	36.03 (10.61)	257	37.12 (12.19)	0.301
Education (years)	131	10.83 (3.14)	92	11.41 (2.56)	0.130

SD = standard deviation.

Table 2 Characteristics of the schizophrenia group

Variable	N	Mean (SD)
Age at onset (years)	127	22.65 (6.53)
Duration of illness (years)	105	15.31 (9.01)
PANSS - negative symptoms	124	24.25 (7.11)
PANSS - positive symptoms	123	16.65 (5.75)
PANSS - excited	123	7.22 (2.38)
PANSS - anxiety/depression	124	9.22 (3.31)

PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

Table 3 Association between each single nucleotide polymorphism and cognitive variables

Response variable	Group		rs165599		rs4680		rs737865		Group* rs165599	Group* rs4680	Group* rs737865
	Mean (SD)	Statistics	Mean (SD)	Statistics	Mean (SD)	Statistics	Mean (SD)	Statistics			
VWM Task	Patients: 2.31 (0.82) Controls: 2.87 (0.80)	$p = 0.001^{\dagger}$; $\eta^2 = 0.047$; power = 0.911	AA: 2.48 (0.85) AG: 2.63 (0.83) GG: 2.44 (0.90)	$p = 0.214$; $\eta^2 = 0.014$; power = 0.328	AA: 2.50 (0.85) AG: 2.52 (0.85) GG: 2.58 (0.88)	$p = 0.467$; $\eta^2 = 0.007$; power = 0.179	AA: 2.53 (0.90) AG: 2.59 (0.79) GG: 3.40 (0.51)	$p = 0.071$; $\eta^2 = 0.026$; power = 0.528	$p = 0.033^{*}$; $\eta^2 = 0.031$; power = 0.646	$p = 0.226$; $\eta^2 = 0.013$; power = 0.317	$p = 0.345$; $\eta^2 = 0.005$; power = 0.156
Keep Track Task	Patients: 3.60 (0.53) Controls: 4.06 (0.39)	$p < 0.001^{\ddagger}$; $\eta^2 = 0.151$; power = 1.000	AA: 3.80 (0.47) AG: 3.81 (0.56) GG: 3.75 (0.53)	$p = 0.597$; $\eta^2 = 0.005$; power = 0.135	AA: 3.63 (0.57) AG: 3.79 (0.50) GG: 3.86 (0.53)	$p = 0.032^{*}$; $\eta^2 = 0.031$; power = 0.649	AA: 3.76 (0.51) AG: 3.87 (0.52) GG: 4.22 (0.51)	$p = 0.048^{*}$; $\eta^2 = 0.030$; power = 0.589	$p = 0.032^{*}$; $\eta^2 = 0.031$; power = 0.647	$p = 0.885$; $\eta^2 = 0.001$; power = 0.069	$p = 0.639$; $\eta^2 = 0.001$; power = 0.075
Letter Memory Task	Patients: 10.67 (1.27) Controls: 11.32 (0.85)	$p = 0.001^{\dagger}$; $\eta^2 = 0.047$; power = 0.911	AA: 10.95 (1.19) AG: 11.00 (1.11) GG: 10.82 (1.22)	$p = 0.529$; $\eta^2 = 0.006$; power = 0.156	AA: 10.79 (1.27) AG: 10.92 (1.06) GG: 11.03 (1.23)	$p = 0.293$; $\eta^2 = 0.011$; power = 0.268	AA: 10.92 (1.17) AG: 10.96 (1.17) GG: 11.71 (0.890)	$p = 0.313$; $\eta^2 = 0.012$; power = 0.255	$p = 0.213$; $\eta^2 = 0.014$; power = 0.328	$p = 0.416$; $\eta^2 = 0.008$; power = 0.201	$p = 0.613$; $\eta^2 = 0.001$; power = 0.080

η^2 = effect size; SD = standard deviation; VWM = Visual Working Memory.
*$p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

groups, no significant deviation from HWE was found (p = 0.087); hence, this polymorphism was included in our analyses.

Using logistic regression, we found a significant association between *COMT* rs737865 genotypes and schizophrenia (p = 0.017). Considering the AA genotype as reference, the GG genotype seemed to exert a protective effect (p = 0.034; odds ratio [OR] = 0.200; 95% confidence interval [95%CI] = 0.045-0.884). However, we did not observe a significant association between rs737865 alleles and schizophrenia (p = 0.926). For the other SNPs, we did not find significant associations between genotypes (rs4680: p = 0.702; rs165599: p = 0.348) or alleles (rs4680: p = 0.583; rs165599: p = 0.155) and schizophrenia.

Haplotype analysis showed that rs4680 and rs737865 SNPs were in moderate LD (D′ = 0.715), as were rs4680 and rs165599 (D′ = 0.604). On the other hand, rs737865 and rs165599 showed a weak LD (D′ = 0.083). Therefore, only haplotype blocks constructed with rs4680 and rs737865 or those constructed with rs4680 and rs165599 were considered for the analyses. Haplotype frequencies are described in Supplementary Table 2 (online-only). We found a significant association between G-A (rs4680/rs165599) haplotype and schizophrenia compared to G-G haplotype (p = 0.014; OR = 1.64; 95%CI = 1.11-2.42). No significant association between haplotype blocks constructed with rs4680 and rs737865 and schizophrenia was found.

Association between COMT *SNPs and WM*

The main effects when comparing cognitive variables and groups or genotypes are described in Table 3. We found a significant decrease in all three WM task scores (VWM, Keep Track, and Letter Memory) in patients when compared to controls (Table 3). Analyzing the association between SNPs and cognitive variables, we found a significant association between rs4680 and Keep Track task scores (Table 3), with AA (Val/Val) subjects performing worse than GG (Met/Met) subjects (post-hoc Bonferroni p = 0.042). The same association was identified for rs737865, with AA carriers performing worse than GG carriers for the Keep Track task (post-hoc Bonferroni p = 0.043). However, when the interaction between these SNPs and group (genotype*group) was analyzed, we did not find a significant association (Table 3).

Although rs165599 was not associated with any of the cognitive variables, considering the interaction genotype* group, there was a significant difference (Table 3 and Figure 1), with AA carriers performing worse in the control group and GG carriers performing worse in the patient group for both the VWM and Keep Track tasks.

Comparing haplotypes and cognitive variables, we found a significant association with Keep Track Task performance (p = 0.017), showing that G-A (rs4680/rs165599) (mean = 3.89; standard deviation [SD] = 0.49) subjects had higher scores than A-A carriers (mean = 3.74; SD = 0.51) (post-hoc Bonferroni p = 0.043). Moreover, haplotype blocks with rs737865 and rs4680 were also associated with Keep Track Task performance (p = 0.040), with A-A (rs737865/rs4680) carriers performing worse

(mean = 3.76; SD = 0.51) than G-G haplotype carriers (mean = 3.92; SD = 0.53) (post-hoc Bonferroni p = 0.034). All p-values comparing haplotypes and each cognitive variable are described in Supplementary Table 3 (online-only).

Discussion

In this study, we evaluated the association between three *COMT* SNPs and the diagnosis of schizophrenia and cognitive performance on WM tasks. We found a significant association between rs737865 genotypes and schizophrenia, with the GG genotype exerting a protective effect and GA a risk effect. In a large study of an Israeli Ashkenazi Jewish population, Shifman et al.[34] reported that the polymorphisms rs737865 and rs165599 were highly associated with the disease, suggesting that more than one functional polymorphism should affect susceptibility to schizophrenia at the *COMT* locus. For the other SNPs, we did not find associations on comparisons of genotypes and alleles individually, similarly to previous studies in Brazilian[35] and Greek[36] populations.

When analyzing the haplotypes constructed with rs4680 and rs165599 SNPs, we did find a significant association, with the G-A haplotype (rs4680/rs165599) being a risk factor for schizophrenia when compared to the G-G haplotype. According to the literature, several haplotypes instead of individual alleles may be associated with schizophrenia due to differences in LD among populations.[37] Previous studies have implicated associations of the rs4680/rs165599 haplotypes with schizophrenia and reported an effect opposite from that observed in our sample, with G-G (rs4680/rs165599) and A-G-G (rs737865/rs4680/rs165599) being the risk haplotypes and G-G-A (rs737865/rs4680/rs165599) the protective haplotype.[34,36,38] Both SNPs seem to exert a functional effect, since rs4680 has an effect on COMT activity and rs165599 has an impact on *COMT* expression.[39] Clinical studies of *COMT* have revealed that the Met allele (G) was associated with better performance on tests of prefrontally mediated cognition.[22,23,40-42] Moreover, in a postmortem human brain study, Chen et al.[43] demonstrated that Val (A) is a predominant factor that determines higher COMT activity, which results in lower prefrontal dopamine signaling and, by this mechanism, leads to relatively impaired prefrontal cortical function. Hence, we could hypothesize that the G/Met-allele (rs4680), which induces a low activity, in combination with the G-allele (rs165599), which leads to reduced expression of *COMT*,[39] might exert a protective effect, explaining the higher frequency of the G-G haplotype in controls than in patients in our sample.

Regarding the cognitive variables, patients performed worse in all three WM tests (VWM, Keep Track Task and Letter Memory Task), and *COMT* SNPs might be influencing cognitive performance. We found that both rs4680 and rs737865 seem to be associated with Keep Track Task performance, independently of group status (i.e., schizophrenia or HC), with AA carriers (for either rs4680 or rs737865) scoring lowest. This result is in line with previous studies that reported positive results in both healthy and schizophrenia samples.[18,19,21-23] This association seems to be even stronger in the haplotype analysis, with a similar effect, i.e., A-A carriers (A allele of rs4680; A allele of rs165599) scoring lower than G-A carriers (G allele of rs4680; A allele of rs165599). A similar effect was found for haplotypes constructed with rs737865 and rs4680, with A-A haplotype carriers (A allele of rs737865; A allele of rs4680) scoring lower than G-G- carriers (G allele of rs737865; G allele of rs4680). Our results are consistent with those of Meyer-Lindenberg et al.,[26] who demonstrated how haplotype analysis should be superior in predicting WM task performance and prefrontal function. When we evaluated the genotype*group interaction, rs165599 exerted opposite effects for VWM and Keep Track Task performance in patients and controls: AA carrier status was associated with the lowest scores for both tests in controls, but the highest scores in patients (Figure 1).

Our study has limitations that must be considered. First, the sample size was small and statistical power was weak, especially for a genetic association study; however, we analyzed cognitive data, which limited the number of participants assessed. Despite selecting 212 patients with schizophrenia and 257 HCs, only 133 patients and 93 HCs underwent cognitive testing, due to logistic issues. Nevertheless, our sample has power to support that the *COMT* polymorphisms may be associated to schizophrenia

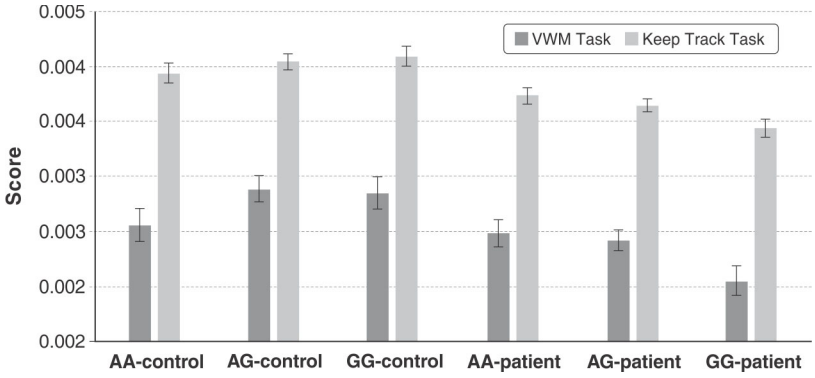

Figure 1 Interaction effect between group and rs165599, which was significant for both Visual Working Memory (VWM) Task and Keep Track Task.Scores presented as square roots.

diagnosis and modulate cognitive performance in both, people with schizophrenia and healthy subjects. Second, the effect sizes were small, which is a common limitation of gene association studies. Further studies should be performed with larger samples. Finally, we acknowledge that the role of COMT in schizophrenia has been widely investigated in past decades, and that the heterogeneity of past research and complexity of schizophrenia phenotypes must be taken into consideration for our conclusions.

Our results are consistent with the major role of COMT in modulating dopamine flux in the PFC and its association with schizophrenia and cognitive function. Regarding this association with the disorder, we found a significant effect of rs737865 genotypes in schizophrenia and of rs4680/rs165599 haplotypes, with an effect opposite to that observed in European populations. The effect of individual SNPs on cognition was supported by previous studies, indicating a worse performance of A-allele genotypes and haplotypes of rs4680 on WM tasks. In addition, the GG genotype and G-allele haplotypes of rs737865 seemed to exert a protective effect on risk of schizophrenia and be associated with higher scores on the Keep Track Task. An interaction effect was also found for group*rs165599, showing the importance of investigating both patients and healthy subjects.

This was the first association study to analyze *COMT* haplotypes and cognition in a Brazilian sample of patients with schizophrenia. The significance of our positive findings encourages further investigations.

Acknowledgements

This research was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (grants 2007/58736-1 and 2011/50740-5), Brazil. The authors gratefully acknowledge the enormous contributions made to this project by the patients, their families, and staff at UNIFESP.

Disclosure

The authors report no conflicts of interest.

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