Association study between COMT ^{158}Met and creativity scores in bipolar disorder and healthy controls

Estudo de associação entre COMT ^{158}Met e criatividade em sujeitos com transtorno bipolar e controles saudáveis

Márcio Gerhardt Soeiro-de-Souza[1], Robert Post[2], Rodrigo Machado-Vieira[3], Carolina Martins do Prado[3], Ricardo Alberto Moreno[1], Hagop Akiskal[4], Kareen K. Akiskal[5]

[1] Mood Disorders Unit (Gruda), Department and Institute of Psychiatry, School of Medicine, University of São Paulo (IPq-HC-FMUSP), Brazil.
[2] Bipolar Collaborative Network, United States of America.
[3] Laboratory of Neuroscience (LIM27), IPq-HC-FMUSP), Brazil.
[4] International Mood Center, San Diego, California, USA.
[5] International Mood Center San Diego, California and Paris, France.

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Abstract

Background: Bipolar disorder (BD) patients have been reported to be associated higher creativity abilities, and recent data tend to support the hypothesis that dopaminergic system that could be associated with creativity. Catechol-O-methyltransferase (COMT) is one of the major enzymes involved in the metabolic degradation of dopamine. The *COMT* gene polymorphism (rs4680 or Val^{158}Met) Met *allele* is reported to cause decreased activity of this enzyme in prefrontal cortex and improve performance in several cognitive domains. **Objective:** The objective of this study was to evaluate the influence of Val^{158}Met on creativity in BD type I and healthy controls. **Methods:** Ninety-seven healthy volunteers and 120 BD type I were genotyped for *COMT* rs4680 and tested for creativity (Barrow Welsh Art Scale – BWAS) and intelligence Wechsler Abbreviated Scale of Intelligence (WASI). **Results:** COMT Met allele positively influenced creativity scores in healthy controls but not in BD subjects during mood episodes and euthymia. The presence of *allele* Met did not influence IQ scores. No influence of IQ total score on creativity was observed. Limitations: control group presented higher IQ scores and euthymic group was under medication use. **Discussion:** Our research suggests positive effect of COMT rs4680 (allele Met) on creativity scores in healthy controls. One possible interpretation is that creativity is more likely to be associated with lesser degrees of bipolarity. The fact that the same results were not observed in BD may be associated to dysfunctions in the dopaminergic system that characterizes this disorder. Further studies with larger samples and other types of BD should explore the role of the dopaminergic system in creativity.

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Keywords: Dopamine, creativity, catechol-O-methyltransferase, bipolar disorder, mania, depression.

Resumo

Contexto: O transtorno bipolar (TB) geralmente é associado a pessoas com maiores habilidades criativas, e dados recentes apontam que o sistema dopaminérgico pode estar relacionado à criatividade. A enzima catecol-O-metiltransferase (COMT) é um dos principais agentes envolvidos na degradação metabólica da dopamina. O gene da *COMT* apresenta um polimorfismo (rs4680 ou Val^{158}Met) no qual o alelo Met se associa a uma diminuição da atividade enzimática da COMT, levando a um melhor desempenho em testes cognitivos. **Objetivo:** O objetivo deste estudo foi avaliar a influência do polimorfismo funcional Val^{158}Met na criatividade de pacientes com TB e em controles. **Métodos:** Noventa e sete voluntários saudáveis e 120 pacientes com TB tipo I foram genotipados para *COMT* rs4680 e testados para criatividade (*Barrow Welsh Art Scale* – BWAS) e inteligência (*Wechsler Abbreviated Scale of Intelligence* – WASI). **Resultados:** O alelo Met da COMT associou-se a maiores pontuações na escala de criatividade na amostra de controles saudáveis, mas o mesmo não foi observado em pacientes com TB. A presença do alelo Met não influenciou a pontuação de QI em nenhum dos grupos. O grupo controle apresentava QI médio maior que o grupo TB; o grupo TB estava em uso de múltiplas medicações no momento das avaliações. **Conclusão:** Nossos resultados sugerem influência positiva do alelo Met do COMT rs4680 na criatividade de controles saudáveis. Isso sugere que a criatividade seja uma função possivelmente associada a menores graus de bipolaridade do que nos pacientes com TB tipo I. O fato de não termos observado influência do alelo Met nos resultados dos pacientes com TB pode ser justificado pelo fato de que justamente alterações nesse sistema sejam uma das características básicas do TB. É necessário maior número de estudos com maiores tamanhos amostrais para explorar mais detalhadamente o papel do sistema dopaminérgico na criatividade.

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Palavras-chave: Dopamina, criatividade, catecol-O-metiltransferase, transtorno bipolar, mania, depressão.

Introduction

Bipolar disorder (BD), especially in its softer expressions[1,2], is associated with professional success and increased creativity[3]. Although Jamison[3] contends that the relationship between creativity and BD may be at the trait or temperament level[4] and it is influenced by cognitive function and symptoms[5]. Little is known about the biological underpinnings of creativity in BD, although psychological, neuropsychological and functional imaging studies in healthy subjects have indicated the potential role of the dopaminergic system[6-9].

Dopaminergic pathways project into numerous brain areas implicated in the pathophysiology of BD[10]. Historically, dopaminergic models of BD have been dichotomous and support both dopamine (DA) excess in mania and deficiency in depression[11]. However, most

Address correspondence to: Márcio Gerhardt Soeiro de Souza. Rua Dr. Ovídio Pires de Campos, s/n, Cerqueira César – 05403-010 – São Paulo, SP, Brazil. Phone: (55 11) 2661-6648/
Fax: (55 11) 2661-7894. E-mail: mgss@usp.br

of these models were conceptualized based on indirect evidence drawn from pharmacological and animal studies[10]. DA has been strongly implicated in motivation and reward systems[12]. Moreover, high DA has been reported to decrease inhibition of incoming stimuli from the surrounding environment[13,14], a trait characteristic of creative individuals of higher intelligence[15]. Also, the ability to generate many different ideas about a topic in a short period (divergent thinking), a key aspect of creativity[16], is present in mania and influenced by dopaminergic function. Furthermore, a recent study has reported an association between divergent thinking and DA receptor polymorphisms[17].

Catechol-O-methyltransferase (COMT) is one of the main enzymes involved in the catabolism of DA[18] and thus constitutes an important regulator of prefrontal cortical (PFC) dopaminergic levels[19]. The *COMT* gene single nucleotide polymorphism (SNP) rs4680 (also known as Val[158]Met) leads to a 35% to 50% reduction in the COMT enzyme in Met *allele* carriers (Met+)[18]. *COMT* SNP rs4680 Met+ has been linked to better performance on cognitive tests[20-23] probably to an increment in PFC DA due to lower COMT activity. To our knowledge, only one study has investigated the association of *COMT* and creativity in healthy controls, and reported negative results[17].

The objective of this research was to investigate the role of COMT functional polymorphism Val[158]Met in creativity scores of healthy controls, and BD patients in euthymia and during mood episodes. We hypothesized that carriers of the Met *allele* would have higher creativity scores than Met non-carriers due to lower COMT activity in the PFC.

Material and methods

Subjects

The patients sample comprised one-hundred-nineteen individuals with BD I, aged between 18 and 40 years old in euthymia (N = 42), manic (N = 44) or depressive (N = 33) episode according to DSM-IV TR criteria[24]. In the euthymic group 78.6% were using lithium, 52.4% were using anticonvulsants, 23.8% were using second generation antypsychotics, 16.7% were using antidepressants and 4.8% were using benzodiazepines ate the time of neuropsychological evaluation. Patients experiencing mood episodes were medication free. They were participants in the *LICAVAL* clinical trial[25] and were evaluated immediately after a wash-out period of four weeks for antidepressants, mood stabilizers and antipsychotics, or of eight weeks for *depot* medications. Diagnosis were determined by trained psychiatrists using the Structured Clinical Interview (SCID-I)[26] for DSM-IV TR[24]. The Young Mania Rating Scale (YMRS)[27], and the Montgomery-Asberg Depression Rating Scale (MADRS)[28] were used to evaluate the intensity of symptoms. Subjects with neurological disorders, previous head trauma, any illness requiring medical intervention, currently substance abuse, or who had undergone electroconvulsive therapy in the preceding six months, were excluded.

Ninety-seven healthy subjects, age 18-35 years, were recruited at the University of São Paulo (mostly medical students) to our controls group. Inclusion criteria were no psychiatric diagnosis (present or past) according to the evaluation by trained psychiatrists using The Mini International Neuropsychiatric Interview (M.I.N.I.)[29], negative family history of mood or psychotic disorders (first degree), no use of any psychopharmacological agent, and no substance abuse over the last three months.

Creativity and intelligence assessment

Creativity test was out under standard conditions and scored by two trained neuropsychologists. Since it is known that intelligence and creativity are reported to be correlated (up to $r = 0.50$)[30], it was necessary to rule out the possibility that significant associations between creativity and polymorphisms might merely reflected a relationship to intelligence. Intelligence Quotient (IQ) was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI)[31]. Creativity was assessed using the Barrow Welsh Art Scale (BWAS). The BWAS[32] is an empirically derived metric consisting of 86 black and white images that individuals rate as "like" or "dislike", with higher scores reflecting preference for more asymmetrical and complex figures over more symmetrical and simple figures. Preference for more asymmetrical and complex figures is higher among artists than non-artists according to BWAS scores[33]. The BWAS scale could also reflect cognitive/affective contributions to creativity, as it involves not only visual processing, but also affective processing ("like" or "dislike"). Indeed, BWAS scores have been linked not only to creativity measured by other means but also to emotionality[34].

Genotyping

DNA was extracted from peripheral blood according to the salting-out protocol[35] and genotyped for *COMT* rs4680 using real-time PCR allelic discrimination. PCR amplification for rs4680 was performed in 5 µl reactions with 5 ng of template DNA, 1× TaqMan Universal Master Mix (Applied Biosystems, Foster City, CA), 1× each primer and probe assay, and H_2O. Thermal cycling consisted of first denaturation for 10 min at 95 °C, followed by 40 cycles of denaturation at 95 °C for 15 s and annealing at 60 °C for 1 min. The *allele*-detection process and allelic discrimination were performed for 1 min at 60 °C on a 7500 Real-Time System (Applied Biosystems, Foster City, CA). Quality control of Real time PCR results was done by direct sequencing on a ABI PRISM® 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA).

Statistical analysis

Groups of subjects were classified into four groups (euthymia, mania, depression and controls). Chi-square test was used for comparison of categorical data, and the ANOVA for continuous data. Turkey test was used for multivariable bias correction. BWAS total score was entered as a dependent variable in a MANOVA model using age, gender, education, rs4680 allele Met and WASI-IQ as covariates. The MANOVA model was separately tested in each of the four groups to test the effect of covariates in BWAS. The PASW statistics version 19.0 software (SPSS Inc., Chicago, Illinois) was used for all analyses.

Ethics

The research ethics board of Hospital das Clínicas of the University of São Paulo approved the study. Written informed consent was obtained from all subjects.

Results

The COMT genotype distribution in the experimental was in accordance with the Hardy-Weinberg equilibrium ($\chi^2 = 0.79$ $p = 0.56$) indicating that the samples were representative. Allelic distribution in the sample was 49.1% for allele Val and 50.8% for allele Met. Sociodemographic data of all four groups is presented in table 1.

Univariate analysis of variance (MANOVA) in which the total score BWAS was entered as a dependent variable and age, gender, education, rs4680 allele Met and WASI-IQ as covariates revealed an influence of age (B = -0.84 p = 0.05) and allele Met (B = 7.05 p = 0.03) in BWAS score in healthy controls (Table 2). No influence of gender, education or IQ in BWAS was observed in controls. The same MANOVA model in mania group revealed that gender influenced BWAS score (B = 9.8 p = 0.02). Females in the manic group presented higher creativity scores. In the same manic group a trend was observed for the influence of allele Met on BWAS scores

Table 1. Comparison of sociodemographic characteristics, WASI-IQ, BWAS scores and allele Met prevalence in controls, euthymia, mania and depression groups

	Gender (female/male)	Age	Education	WASI-IQ	BWAS	allele Met (Met+/Met-)
Controls (N = 97)	52/45					74/23
Mean		24.3	13.9	110.5	24.1	
Std. Deviation		4.7	2.4	16.0	13.1	
Euthymia (N = 42)	27/15					33/19
Mean		32.9	12.6	99.3	27.3	
Std. Deviation		10.9	3.1	12.9	12.0	
Mania (N = 44)	35/9					29/15
Mean		29.3	12.2	95.2	25.3	
Std. Deviation		5.3	3.5	14.1	11.4	
Depression (N = 33)	18/15					20/13
Mean		26.9	12.6	97.3	17.3	
Std. Deviation		5.2	2.4	12.3	10.4	
ANOVA						
F		18.5	4.3	15	3.8	
Sig		< 0.001	0.006	< 0.001	0.01	
Turkey		M>D<E>C	M=D=E<C	M=D=E<C	M>D<E>C	
Chi-Squared	0.02					0.14

Significance level p < 0.05.

Table 2. MANOVA model: BWAS total score was entered as a dependent variable and age, gender, education, rs4680 allele Met and WASI-IQ were entered as covariates

Dependent Variable: BWAS							
	Parameter	B	Std. Error	t	Sig.	Partial Eta Squared	Observed Power
Controls							
(N = 97)	Age	-0.84	0.42	-2.01	0.05	5%	51%
	Gender	-4.01	2.74	-1.46	0.15	3%	30%
	Education	0.60	0.60	1.00	0.32	1%	17%
	rs4680 allele Met	7.05	3.12	2.26	0.03	6%	61%
	WASI-IQ	-0.05	0.11	-0.50	0.62	0%	8%
Mania							
(N = 44)	Age	0.07	0.31	0.22	0.83	0%	6%
	Gender	9.86	4.10	2.40	0.02	14%	65%
	Education	-0.49	0.54	-0.90	0.37	2%	14%
	rs4680 allele Met	-6.40	3.58	-1.79	0.08	8%	41%
	WASI-IQ	0.02	0.14	0.13	0.89	0%	5%
Depression							
(N = 33)	Age	-0.06	0.41	-0.15	0.88	0%	5%
	Gender	-1.99	4.30	-0.46	0.65	1%	7%
	Education	-1.29	0.95	-1.35	0.19	8%	25%
	rs4680 allele Met	6.74	4.48	1.51	0.15	10%	30%
	WASI-IQ	0.08	0.19	0.43	0.67	1%	7%
Euthymia	Age	0.08	0.21	0.39	0.70	1%	7%
(N = 42)	Gender	1.74	4.93	0.35	0.73	0%	6%
	Education	-0.25	0.84	-0.30	0.77	0%	6%
	rs4680 allele Met	-0.22	7.17	-0.03	0.98	0%	5%
	WASI-IQ	0.19	0.20	0.93	0.36	3%	15%

(B = -6.4 p = 0.08). No influence of age, education or IQ on BWAS total score was observed on the manic group.

In the depression and euthymic groups the same MANOVA model revealed that none of the covariates influenced BWAS total score (Table 2).

Discussion

This is the first study investigating the role of COMT Val[158]Met in creativity output in bipolar I disorder. Moreover, this is also the first study to report a positive association between *COMT* rs4680, specifically *allele* Met, and higher scores on the BWAS in the healthy population. Carriers of *allele* Met present lower COMT enzyme activity in PFC[18,19], and in the present study this same group was shown to have higher BWAS scores in the healthy control group. This

finding confirms the recent hypothesis that *COMT* numbers among the candidate genes for creativity[17]. In the other hand, in BD the Met *allele* did not influence creativity in mood episodes or euthymia.

These findings reinforce the putative role of DA in creative abilities hypothesized based on pharmacological studies. In Parkinson's disease (PD), the emergence of poetic talent[36] and "compulsive" augmentation of artistic productivity[37] have been reported in dopaminergic replacement therapy[36]. Furthermore, DA antagonists, such as typical antipsychotics, are reported to suppress creativity[38]. Functional imaging studies have shown that the creative thinking process is associated with increased PFC activity[8,39]. These reports are consistent with findings of reviews of creativity studies suggesting that the dopaminergic system, including the PFC, is associated with creativity[8,40]. Also, results of studies on COMT functional SNPs and the differential effects of D1 and D2 receptor binding, have clarified this association. The *allele* Met, associated with low-activity COMT, has been theoretically linked to decreases in phasic and increases in tonic DA transmission subcortically, and in increases DA concentrations cortically. This is associated with increased D1 and decreased D2 transmission in the PFC[41], which have in turn been associated with higher creative achievement or psychosis[15]. Moreover this same SNP have been reported to modulate cognitive function in BD during mood episodes[42].

Dopaminergic and other transmitter relationships to creativity have also been suggested in studies involving non-bipolar patients. A recent study reported an association between divergent thinking and dopamine receptor polymorphism. Higher creativity scores were observed in carriers of the A1 *allele*[17]. The A1 *allele* of DRD2 (rs1800497) has a 30%-40% reduction in DA-D2 receptor density[43]. In the same study, these authors reported that carriers of the A *allele* of the serotonin polymorphism TPH1 A779C also had higher creativity scores[17]. In another study involving a sample of healthy subjects, Kéri studied a polymorphism in the promoter region of neuregulin 1 and found that the T *allele* was associated with higher creative scores[44]. Thus, further examination of the possible neurobiological underpinnings of the link between bipolar disorder and creativity are warranted, especially in those with lesser degrees of bipolarity at the trait level. Dopaminergic function should be investigated in cyclothymic and related temperaments, which the work of Akiskal *et al.* well as supportive evidence from Stanford[45], and supportive evidence from Italian work[46], suggest might be an underlying ingredient in creative work[4]. Andreasen and Canter's early work had also implicated cyclothymic tendencies or disorder[47].

Andreasen and Powers' work also raised the possibility that over-inclusive thinking is characteristic for both mania and schizophrenia[48]. In bipolar disorder the thought processes are less extreme than in schizophrenia and might even be somewhat different qualitatively, and it may be that the overall thought impairment characteristic of schizophrenia restricts the execution of creativity.

There are many difficulties inherent to systematic studies of creativity, particularly methodological problems concerning the reliability and validity of creativity measures, and disagreements over the definition of creativity. The BWAS is not the only measure of creativity and other measures should be explored before drawing more definitive conclusions. In the present study, it was decided to examine the correlation between scores on a widely used scale for measuring creativity and the presence of functional polymorphism of *COMT* (rs4680), which likely influences PFC cognition, in a homogeneous sample of university students. Our results are also consistent with those reported in the literature investigating the role of DA and *COMT* in PFC function and cognition. However, no influence of *COMT* on IQ was evident, and BWAS and IQ scores were unrelated, further suggesting some degree of specificity in the association of COMT with creativity.

This study is the first to report findings that suggest the effects of *COMT* gene polymorphism may not be limited to isolated basal cognitive abilities, but could partially account for greater cognitive abilities related to creativity in healthy controls. In the other hand, we found evidence that creativity during BD episodes and euthymia is not associated with COMT DA catabolism activity in the PFC. Further studies involving larger samples should be conducted in an effort to replicate our findings. In addition, given the strong and consistent body of evidence indicating an association of bipolar spectrum disorders with creativity[1,4,46], examining the association of *COMT* polymorphism with creativity in this population is now warranted.

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