Association of the COMT Met^{158} allele with trait impulsivity in healthy young adults

MÁRCIO GERHARDT SOEIRO-DE-SOUZA[1], MATTHEW S. STANFORD[2], DANIELLE SOARES BIO[1], RODRIGO MACHADO-VIEIRA[3] and RICARDO ALBERTO MORENO[1]

[1]Mood Disorders Unit (GRUDA), Department and Institute of Psychiatry, School of Medicine, University of São Paulo (HC-FMUSP), São Paulo, Brazil; [2]Department of Psychology and Neuroscience, Baylor University, Waco, TX, USA; [3]Laboratory of Neuroscience LIM-27, Department and Institute of Psychiatry, School of Medicine, University of São Paulo (HC-FMUSP), São Paulo, Brazil

Received November 5, 2012; Accepted February 20, 2013

DOI: 10.3892/mmr.2013.1336

Abstract. Dopamine (DA) is considered to be an important neurotransmitter in the control of impulsive behavior, however, its underlying mechanisms have not been fully elucidated. Catechol-*O*-methyltransferase (COMT) is a key enzyme in the catabolism of DA within the prefrontal cortex (PFC) and has been suggested to play a role in the mediation of impulsive behavior. The COMT single nucleotide polymorphism (SNP) rs4680 (Val^{158}Met) Met allele has been shown to decrease COMT enzyme activity and is associated with improved PFC cognitive function (intelligence and executive functions). Studies have associated the rs4680 genotype with impulsivity as a symptom in attention deficit hyperactivity disorder and substance abuse. However, only a few studies have assessed the effects of rs4680 on impulsiveness in healthy subjects, the results of which remain controversial. The Barratt Impulsiveness Scale (BIS-11) was applied to 82 healthy volunteers (including 42 females) who were genotyped for *COMT* rs4680. Subjects carrying the Met/Met genotype scored higher for the BIS-11 second-order factor Non-planning than carriers of the Val/Val genotype. No interaction between gender*genotype was detected. Age, gender and education had no effect on the results. The *COMT* rs4680 Met/Met genotype was associated with higher impulsivity on the BIS-11 second-order factor Non-planning. These results suggest that COMT enzyme activity may be important in the regulation of impulsiveness among young adults. Further studies involving larger samples should be conducted to confirm the results of the present study.

Correspondence to: Professor Márcio Gerhardt Soeiro-de-Souza, Department and Institute of Psychiatry, School of Medicine, University of São Paulo (HC-FMUSP), Dr. Ovidio Pires de Campos, s/n 05403-010, São Paulo, Brazil
E-mail: mgss@usp.br

Key words: impulsivity, dopamine, catechol-*O*-methyltransferase

Introduction

Impulsivity is a complex construct and one of its main characteristics is a predisposition toward rapid, unplanned reactions to internal or external stimuli, with no regard for the negative repercussions of these reactions on the impulsive individual or on others (1-8). Impulsivity may be studied as a symptom secondary to a psychiatric disorder or a non-pathological characteristic in the general population. The majority of neurobiological studies on impulsivity have operationally defined impulsivity as a symptom of attention deficit hyperactivity disorder (9-15) and/or substance abuse (14,16,17). In these studies, dopamine (DA) was hypothesized to be important in the neurobiology of impulsive behavior (18-24). By contrast, the neurobiology of impulsivity in healthy subjects is less studied and not well elucidated.

Although it has been suggested that DA plays a key role in certain aspects of impulsivity (9,12,25-27), the precise mechanisms involved remain unclear. The majority of evidence that associates DA and impulsivity is derived from pharmacological studies. DA agonists are reported to increase motor impulsivity (27-31), particularly in patients with Parkinson's disease (26,27,32). Patients with DA dysregulation syndrome, an iatrogenic disturbance, have been reported to develop an addiction to DA replacement therapy (4,11-15,33), which leads to impulsive-compulsive behaviors, including gambling, shopping and eating. Certain drugs of abuse enhance extracellular DA levels and consequently increase impulsive behavior (1,10,14,19,20,23). Hyperdopaminergic states, including mania and other psychoses, also exhibit increased impulsive symptoms (9,12,17,19,20,23) which typically respond to antidopaminergic agents. While impulsivity is a complex construct, results from these and other studies suggest that DA affects the expression of impulsivity.

Data from a number of previous studies suggest that the prefrontal cortex (PFC) is important in the control of multiple types of impulsivity (16,21,23,26). Insufficient (hypodopaminergic) and excessive (hyperdopaminergic) D1 receptor stimulation impairs PFC function (18,21,22,24,25,29,34-37), with hyperdopaminergic states resulting in greater

Table I. Sociodemographic and BIS-11 scores by COMT rs4680 genotype.

Variable	Met/Met (n=26)		Val/Met (n=35)		Val/Val (n=21)		F	P-value[c] (2-tailed)	Bonferroni post-hoc
	Mean	SD	Mean	SD	Mean	SD			
Age (years)	24.87	4.55	23.73	5.17	24.57	4.06	2.03	0.13[a]	
Gender (male/female)	14/12		18/17		8/13			0.51[b]	
Years of education	13.54	2.64	14.08	2.03	13.91	2.67	0.31	0.72[a]	
BIS-11 Non-planning	26.81	2.38	25.66	3.19	24.57	2.65	3.67	0.03[a]	Met/Met>Val/Val
BIS-11 Attentional	11.31	1.69	11.77	1.94	11.48	1.69	0.51	0.59[a]	
BIS-11 Motor	15.62	3.31	15.37	2.17	16.71	1.92	1.93	0.15[a]	
BIS-11 total	68.38	4.03	67.63	4.22	67.57	4.81	0.28	0.75[a]	

[a]ANOVA; [b]Chi-square test. [c]Differences between the groups; significance level, P<0.05.

impulsivity (9,12,19,21,25-27,38,39). Catechol-*O*-methyltransferase (*COMT*) is one of the key enzymes involved in the catabolism of extraneuronal DA in glial cells and postsynaptic neurons (27,28,30,39,40) and is therefore an important regulator of PFC DA levels. It has been shown that the *COMT* single nucleotide polymorphism (SNP) rs4680 (also known as Val[158]Met) leads to a 35-50% reduction in *COMT* enzyme activity in Met allele carriers (Met$^+$) compared with non-carriers (4,21,32,33,38). The *COMT* SNP has been associated with cognitive performance in healthy controls and psychiatric patients (1,3-8,19,20,23,41). *COMT* rs4680 Met$^+$ has been associated with better performances in cognitive tests, most notably in working memory, intelligence and executive functions (6,9,11,12-15,20). An analysis of previous *COMT* genetic association studies, particularly those which directly addressed the effects of these variants on dopaminergic tone, has revealed that behavioral inhibition may be central to the effects of *COMT* (14,16,23,42). However, additional studies in healthy humans have failed to confirm the association between impulsiveness and *COMT* genetic variability (18-20,22-24).

The present study aimed to investigate the potential association between impulsiveness, measured by the Barratt Impulsiveness Scale (BIS-11) (9,12,26), and the *COMT* rs4680 functional polymorphism in a sample of healthy volunteers. We hypothesized that individuals with the Met/Met genotype would have higher BIS-11 scores due to decreased COMT enzyme activity in the PFC.

Materials and methods

Patients. The sample comprised 82 healthy volunteers between 18 and 35 years old, who were recruited from the University of São Paulo, Brazil. To be included in this study, subjects were required to have no previously diagnosed psychiatric conditions (present or past) on The Mini International Neuropsychiatric Interview (M.I.N.I.) (28,29). All subjects had no family history of mood or psychotic disorders (first-degree relatives) and no recent use of any pharmacological treatments (last 6 months) or alcohol (last 4 weeks).

The Research Ethics Board of the Hospital das Clínicas University of São Paulo, Brazil, reviewed and approved this study. Written informed consent was obtained from all the subjects.

Assessment of impulsivity. Impulsiveness was assessed using the BIS-11 (26,32), a 30-item self-report questionnaire that has been extensively studied in the literature and confirmed as a reliable instrument for investigating impulsivity. The BIS-11 evaluates six first-order factors (attention, motor, self-control, cognitive complexity, perseverance and cognitive instability) and three second-order factors [Attentional (attention and cognitive instability), Motor (motor and perseverance) and Non-Planning Impulsiveness (self-control and cognitive complexity)]. The total score is obtained by summation of the first- or second-order factors. The items are scored on a four-point scale (1, rarely/never; 2, occasionally; 3, often; and 4, almost always/always). Previous studies which have used the BIS-11 have tended to focus on the total score and second-order factors due to the questionable reliability and validity of the first-order factors (3,5-8,40). The scale was applied under standardized conditions and scored by two trained clinical neuropsychologists.

Genotyping. DNA was extracted from the peripheral blood according to the salting-out method (11-15,33) 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, 1X *Taq*Man Universal Master Mix (Applied Biosystems, Foster City, CA, USA), 1X each primer and probe assay and H_2O. Thermal cycling consisted of an initial denaturation for 10 min at 95˚C, followed by 40 cycles of denaturation at 95˚C for 15 sec 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). The quality control of real-time PCR results was carried out by direct sequencing on an ABI PRISM® 3100 Genetic Analyzer (Applied Biosystems).

Statistical analysis. BIS-11 scores (the total score and three second-order factors) were stratified as a function of the COMT rs4680 genotype (Met/Met, Val/Met or Val/Val). Demographic data and BIS-11 scores were compared among the three genotype groups. Continuous variables were

Table II. Multivariate analysis of covariance using the BIS-11 second-order factors and total scores as dependent variables and age, gender, education, COMT genotype and gender*COMT genotype interactions as covariates.

Dependent variable/covariates	B	df	Std. Error	t	P-value	95% CI (bound) Lower	95% CI (bound) Upper	Partial eta squared	Noncent. parameter	Observed power
BIS-11 Non-planning										
Age	0.09	1	0.088	0.99	0.3	-0.088	0.262	0.013	0.994	0.165
Gender	1.38	1	1.28	1.08	0.3	-1.174	3.926	0.015	1.075	0.186
Education	-0.2	1	0.134	-1.2	0.2	-0.432	0.1	0.02	1.244	0.233
[COMT4680=Met/Met]	**2.57**	1	**1.14**	**2.26**	**0.02**	**0.301**	**4.843**	**0.064**	**2.257**	**0.605**
[COMT4680=Val/Met]	1.62	1	1.052	1.54	0.1	-0.475	3.718	0.031	1.541	0.331
[COMT4680=Val/Val]	0[a]	1								
[COMT4680=Met/Met]*gender	-1.2	1	1.698	-0.7	0.5	-4.619	2.148	0.007	0.727	0.111
[COMT4680=Val/Met]*gender	-1.2	1	1.605	-0.7	0.5	-4.347	2.047	0.007	0.717	0.109
[COMT4680=Val/Val]*gender	0[a]	1								
BIS-11 Attentional										
Age	-0	1	0.054	-0.6	0.6	-0.139	0.077	0.004	0.572	0.087
Gender	0.83	1	0.789	1.05	0.3	-0.741	2.405	0.015	1.054	0.18
Education	-0.1	1	0.082	-1	0.3	-0.249	0.079	0.014	1.031	0.175
[COMT4680=Met/Met]	-0.9	1	0.703	-1.2	0.2	-2.258	0.544	0.02	1.219	0.225
[COMT4680=Val/Met]	0.57	1	0.649	0.88	0.4	-0.723	1.862	0.01	0.878	0.139
[COMT4680=Val/Val]	0[a]	1								
[COMT4680=Met/Met]*gender	1	1	1.047	0.95	0.3	-1.09	3.083	0.012	0.951	0.156
[COMT4680=Val/Met]*gender	-0.8	1	0.99	-0.8	0.4	-2.793	1.151	0.009	0.83	0.13
[COMT4680=Val/Val]*gender	0[a]	1								
BIS-11 Motor										
Age	-0	1	0.078	-0.3	0.7	-0.181	0.128	0.002	0.339	0.063
Gender	1.38	1	1.13	1.22	0.2	-0.877	3.626	0.02	1.217	0.225
Education	0.22	1	0.118	1.85	0.1	-0.017	0.453	0.044	1.85	0.447
[COMT4680=Met/Met]	0.21	1	1.006	0.21	0.8	-1.792	2.218	0.001	0.212	0.055
[COMT4680=Val/Met]	-0.8	1	0.929	-0.8	0.4	-2.621	1.08	0.009	0.83	0.13
[COMT4680=Val/Val]	0[a]	1								
[COMT4680=Met/Met]*gender	-2.6	1	1.499	-1.8	0.1	-5.63	0.344	0.04	1.763	0.413
[COMT4680=Val/Met]*gender	-1.6	1	1.417	-1.1	0.3	-4.385	1.261	0.016	1.103	0.193
[COMT4680=Val/Val]*gender	0[a]	1								
BIS-11 total										
Age	0.03	1	0.136	0.23	0.8	-0.239	0.302	0.001	0.232	0.056
Gender	2.89	1	1.975	1.46	0.1	-1.044	6.827	0.028	1.464	0.304
Education	-0	1	0.206	-0	1	-0.413	0.408	0	0.012	0.05
[COMT4680=Met/Met]	1.62	1	1.759	0.92	0.4	-1.889	5.121	0.011	0.919	0.148
[COMT4680=Val/Met]	0.74	1	1.623	0.46	0.6	-2.494	3.976	0.003	0.456	0.074
[COMT4680=Val/Val]	0[a]	1								
[COMT4680=Met/Met]*gender	-2.4	1	2.62	-0.9	0.4	-7.588	2.855	0.011	0.903	0.145
[COMT4680=Val/Met]*gender	-2	1	2.476	-0.8	0.4	-6.931	2.938	0.009	0.806	0.125
[COMT4680=Val/Val]*gender	0[a]	1								

[a]Val/Val is the parameter genotype; Significance level, P<0.05. Bold, indicates statistically significant variable.

compared using ANOVA, while categorical data were compared using the Chi-square test. BIS-11 second-order factors and the BIS-11 total scores were entered as dependent variables in a multivariate analysis of covariance (MANOVA) model, using age, gender, education, rs4680 genotype and the gender*genotype interaction as covariates. Pearson's test was applied to investigate the possible correlation between BIS-11 factors. Bonferroni testing was used for multivariable error correction. P<0.05 was considered to indicate a statistically significant difference. The PASW Statistics version 18.0 soft-

ware (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

The allelic distribution in the experimental sample was in accordance with the Hardy-Weinberg equilibrium (χ^2=0.65, P=0.58), indicating that the samples were representative. The genotype frequency for rs4680 was 31.7% Met/Met, 42.7% Val/Met and 25.6% Val/Val.

The sample comprised 82 individuals (including 42 females) with a mean age of 23.8±3.9 years and an average of 13.9±2.4 years of schooling. No differences were observed between the genotypes for gender, age or education (Table I).

An ANOVA comparing the BIS-11 second-order factor scores for the Met/Met, Val/Met and Val/Val genotypes revealed a significant difference for the Non-planning factor only (P=0.03). The Bonferroni correction for multiple variables revealed sustained statistical differences for Non-planning scores between the Met/Met and Val/Val genotypes (Met/Met>Val/Val; Table I).

The BIS-11 second-order factors were entered as dependent variables in a MANOVA model, using age, gender, education, genotype and the gender*genotype interaction as covariates. Results revealed that gender*genotype interactions had no impact on any of the second-order factors, gender, age or education. The Non-planning factor was shown to be directly affected by the Met/Met genotype compared with Val/Val and this data remained significant after removing the interaction from the MANOVA model (B=2.57; P=0.02; partial eta, 6.4%; power, 60.5%; Table II)

Pearson's test revealed that the BIS-11 Non-planning had a weak correlation with the BIS-11 Attentional second-order factor (-0.27) and BIS-11 total score (0.46). Additionally, the BIS-11 Motor second-order factor was correlated with the BIS-11 total score (0.58).

Discussion

To the best of our knowledge, this is the first study to report an association between higher self-reported impulsiveness (BIS-11) scores and the presence of the *COMT* SNP rs4680 in healthy volunteers. The BIS-11 second-order factor Non-Planning Impulsiveness (failure to plan ahead) was higher in carriers of the Met/Met genotype compared with those of the Val/Val genotype. Our results corroborate those of studies on impulsive symptoms and COMT in ADHD and substance abuse, indicating that impulsiveness in healthy subjects may have a similar neurobiology to impulsive behavior in psychiatric disorders.

Previous similar studies in healthy humans have failed to confirm the association between impulsiveness and *COMT* genetic variability (14,19,20,23). Forbes *et al* (20) reported that there was no differential impact of COMT on BIS-11 scores in 89 healthy subjects (19,20,23), while Colzato *et al* (23) also identified that there was no association between COMT and impulsivity in 130 healthy adults using the Dickman stop-signal paradigm (23,26). However, Paloyelis *et al* (19) demonstrated an association between variations in the DAT1 genotype (rather than COMT) and the total score based on an adolescent version of the BIS-11 in 36 healthy participants. In the same study, a correlation between COMT and impulsivity was reported for a behavioral measure (delayed discounting), in which individuals carrying the Met/Met genotype scored higher than Val carriers. Behavioral measures of impulsivity have been shown to correlate with self-report measures in a number of (29,34-37), but not all, studies [review by Stanford *et al* (40)].

Previous studies investigating the association between variations of the COMT gene and symptoms of impulsivity have focused on individuals diagnosed with ADHD, conduct disorders and substance abuse (19,21,26,38,39). A number of these studies revealed that the COMT Met allele was associated with increased impulsive behavior. Boettiger *et al* (39) carried out a study on a sample of alcoholics and controls and reported that the Val/Val genotype was associated with higher scores on an immediate reward test and higher activation in the dorsal PFC, as shown by functional magnetic resonance imaging (fMRI) (39,40). DeYoung *et al* (38) and Biederman *et al* (21) used a semi-structured psychiatric interview and reported that the Met allele was associated with ADHD symptoms (21,33,38). In the present study, impulsiveness was operationally defined as a characteristic which is normally distributed in the population, rather than a symptom of a psychiatric disorder.

The BIS-11 Non-planning factor consists of 11 items used to assess the ability of an individual to plan out their behavior and be involved in considering the future. Results in the present study revealed a significantly lower ability to organize and plan future actions in COMT Met homozygous individuals compared with subjects of other genotypes. Since Met carriers are reported to have lower COMT enzyme activity in the PFC, it is plausible to speculate that PFC DA levels may affect this aspect of impulsivity. Notably, previous studies have demonstrated an association between the Non-planning factor and working memory performance (continuous memory scanning task) (19,20,23,41). The results from these studies support the conclusion that Attentional Impulsiveness is correlated with participants deleting no-longer-relevant information from their working memory. Non-planning Impulsiveness was associated with working memory capacity, whereas those with Motor Impulsiveness were shown to have a trend towards having a lower overall capacity and a greater ability to restrict access to working memory. These studies further showed that certain forms of impulsiveness were associated with problems that require different executive control abilities. By contrast, several other studies have reported that COMT Met carriers have a better performance in certain measures of working memory (6,11,20).

The explanation for our results of a positive association between impulsivity and the COMT enzyme polymorphism may be identified by pharmacological and imaging studies. It has been reported that the stimulation of D1 receptors by selective agonists increases risky choices in risk-based decision making tasks, while the blockade of D1 receptors decreases risky choices in preclinical models (23,42). Similarly, DA genetic studies have reported that variants of the gene for the D1 receptor are associated with risky and novelty-seeking behaviors (34-37,43). More recently, a positron emission tomography (PET) study has suggested

that D2 and D3 autoreceptor availability in impulsiveness is mediated in part through its effect on stimulated striatal DA release (19,21,38,39,44). Additionally, conditions which are often associated with impulsivity, including increased aggression and suicide, have also been associated with the *COMT* Met allele (39,45-47). Therefore, assuming that optimal levels of DA in frontal-striatal circuits mediate impulsiveness, factors that disturb this balance in either direction are likely to modify behavior (11,19,21,38,48,49) and cognition (50,51).

Previous studies have tested the genetic correlates of impulsiveness using the BIS-11 (41-50,52-60). Individuals with the short allele polymorphism of the serotonin transporter gene promoter region (5-HTTLPR) had higher impulsivity scores on the BIS-11 (41,52). These differences may be greatest for the Attentional subscale of the BIS-11 (6,11,53). Studies have also reported a significant correlation between the BIS-11 and other aspects of the serotonergic system, including SNPs of the tryptophan hydroxylase-2 (TPH2) gene (42,54), the C allele of the T102C serotonin 2a receptor (43,55) and the T allele at the A-161T locus of the 5-HT1b receptor gene (44,56). A study in children reported a significant negative correlation between MAO activity and the BIS-11 (45-47,57), while another identified no differences among those with low or high activity MAO-A alleles (11,19,48,49,58). No significant associations or group differences have been revealed for the BIS-11 subscale scores and genetic or allelic polymorphisms of the adenosine receptor (50,59) or the α-2A noradrenergic receptor (51,60).

Our results suggest that impulsivity is not a singular construct and that different subtypes of impulsiveness may be dissociated pharmacologically and neurobiologically (2,25,61). Additionally, the present study examined the sub-factors of impulsiveness [as proposed in a review by Stanford *et al* (40)] with an aim to provide a better definition of the association between this multifactorial characteristic and variations in the COMT genotype. Limitations of this study included its small sample size and that the BIS-11 was the only method used to measure impulsivity. Furthermore, only one COMT SNP was tested, since it is the only one with evidence of its functionality.

In conclusion, the present study demonstrated a positive association between the COMT rs4680 SNP and higher self-reported impulsiveness (BIS-11) in healthy young subjects. These results indicate that COMT enzyme activity may play a role in the pathogenesis of impulsivity in healthy subjects, corroborating the findings of previous studies which have investigated impulsivity as a symptom in psychiatric disorders. The established central role of *COMT* in the PFC, together with evidence that implicates specific frontal areas in behavioral inhibition, warrants further investigations to explore the possible role of *COMT* in the neurobiology of impulsiveness.

Acknowledgements

We would like to thank the Institute of Psychiatry at the University of São Paulo, in particular the members of the Mood Disorders Unit (GRUDA) and Laboratory of Neuroscience (LIM27) for their dedication and hard work and all volunteers for their collaboration. This study was financed by the São Paulo Research Foundation (Fundo de Apoio a Pesquisa do Estado de Sao Paulo, FAPESP).

References

1. Robinson TE and Kolb B: Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology 47 (Suppl 1): 33-46, 2004.
2. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM and Swann AC: Psychiatric aspects of impulsivity. Am J Psychiatry 158: 1783-1793, 2001.
3. Lachman HM, Morrow B, Shprintzen R, Veit S, Parsia SS, Faedda G, *et al*: Association of codon 108/158 catechol-O- methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. Am J Med Genet 67: 468-472, 1996.
4. O'Sullivan SS, Evans AH and Lees AJ: Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management. CNS Drugs 23: 157-170, 2009.
5. Weinshilboum RM, Otterness DM and Szumlanski CL: Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. Annu Rev Pharmacol Toxicol 39: 19-52, 1999.
6. Bruder GE, Keilp JG, Xu H, Shikhman M, Schori E, Gorman JM, *et al*: Catechol-O-methyltransferase (COMT) genotypes and working memory: associations with differing cognitive operations. Biol Psychiatry 58: 901-907, 2005.
7. Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T and Goldman D: A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 159: 652-654, 2002.
8. Chen X, Wang X, O'Neill AF, Walsh D and Kendler KS: Variants in the catechol-o-methyltransferase (COMT) gene are associated with schizophrenia in Irish high-density families. Mol Psychiatry 9: 962-967, 2004.
9. Swann AC, Anderson JC, Dougherty DM and Moeller FG: Measurement of inter-episode impulsivity in bipolar disorder. Psychiatry Res 25: 195-197, 2001.
10. Winstanley CA, Eagle DM and Robbins TW: Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. Clin Psychol Rev 26: 379-395, 2006.
11. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, *et al*: Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 98: 6917-6722, 2001.
12. Nolan KA, D'Angelo D and Hoptman MJ: Self-report and laboratory measures of impulsivity in patients with schizophrenia or schizoaffective disorder and healthy controls. Psychiatry Res 187: 301-303, 2011.
13. Joober R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, *et al*: Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. Arch Gen Psychiatry 59: 662-663, 2002.
14. Bilder RM, Volavka J, Lachman HM and Grace AA: The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology 29: 1943-1961, 2004.
15. Diamond A, Briand L, Fossella J and Gehlbach L: Genetic and neurochemical modulation of prefrontal cognitive functions in children. Am J Psychiatry 161: 125-132, 2004.
16. Kim S and Lee D: Prefrontal cortex and impulsive decision making. Biol Psychiatry 69: 1140-1146, 2011.
17. Jentsch JD and Taylor JR: Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl) 146: 373-390, 1999.
18. Kimberg DY, D'Esposito M and Farah MJ: Effects of bromocriptine on human subjects depend on working memory capacity. Neuroreport 8: 3581-3585, 1997.
19. Paloyelis Y, Asherson P, Mehta MA, Faraone SV and Kuntsi J: DAT1 and COMT effects on delay discounting and trait impulsivity in male adolescents with attention deficit/hyperactivity disorder and healthy controls. Neuropsychopharmacology 35: 2414-2426, 2010.
20. Forbes EE, Brown SM, Kimak M, Ferrell RE, Manuck SB and Hariri AR: Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. Mol Psychiatry 14: 60-70, 2009.
21. Biederman J, Kim JW, Doyle AE, Mick E, Fagerness J, Smoller JW and Faraone SV: Sexually dimorphic effects of four genes (COMT, SLC6A2, MAOA, SLC6A4) in genetic associations of ADHD: a preliminary study. Am J Med Genet B Neuropsychiatr Genet 147B: 1511-1518, 2008.

22. Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD and Robbins TW: Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci 20: RC65, 2000.
23. Colzato LS, van den Wildenberg WP, Van der Does AJ and Hommel B: Genetic markers of striatal dopamine predict individual differences in dysfunctional, but not functional impulsivity. Neuroscience 170: 782-788, 2010.
24. Goldman-Rakic PS, Castner SA, Svensson TH, Siever LJ and Williams GV: Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. Psychopharmacology (Berl) 174: 3-16, 2004.
25. Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Lääne K, *et al*: Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315: 1267-1270, 2007.
26. Patton JH, Stanford MS and Barratt ES: Factor structure of the Barratt impulsiveness scale. J Clin Psychol 51: 768-774, 1995.
27. Cools R, Barker RA, Sahakian BJ and Robbins TW: L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 41: 1431-1441, 2003.
28. Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D and Karayiorgou M: Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci USA 95: 9991-9996, 1998.
29. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al*: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 (Suppl 20): 22-33, quiz 34-57, 1998.
30. Robert G, Drapier D, Verin M, Millet B, Azulay JP and Blin O: Cognitive impulsivity in Parkinson's disease patients: assessment and pathophysiology. Mov Disord 24: 2316-2327, 2009.
31. Dang D, Cunnington D and Swieca J: The emergence of devastating impulse control disorders during dopamine agonist therapy of the restless legs syndrome. Clin Neuropharmacol 34: 66-70, 2011.
32. Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL and Weinshilboum RM: Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6: 243-250, 1996.
33. Laitinen J, Samarut J and Hölttä E: A nontoxic and versatile protein salting-out method for isolation of DNA. Biotechniques 17: 316, 318, 320-322, 1994.
34. Swann AC, Bjork JM, Moeller FG and Dougherty DM: Two models of impulsivity: relationship to personality traits and psychopathology. Biol Psychiatry 51: 988-994, 2002.
35. Hinson JM, Jameson TL and Whitney P: Impulsive decision making and working memory. J Exp Psychol Learn Mem Cogn 29: 298-306, 2003.
36. Green L, Myerson J and Ostaszewski P: Amount of reward has opposite effects on the discounting of delayed and probabilistic outcomes. J Exp Psychol Learn Mem Cogn 25: 418-427, 1999.
37. Richards JB, Zhang L, Mitchell SH and de Wit H: Delay or probability discounting in a model of impulsive behavior: effect of alcohol. J Exp Anal Behav 71: 121-143, 1999.
38. DeYoung CG, Getchell M, Koposov RA, Yrigollen CM, Haeffel GJ, af Klinteberg B, *et al*: Variation in the catechol-O-methyltransferase Val 158 Met polymorphism associated with conduct disorder and ADHD symptoms, among adolescent male delinquents. Psychiatr Genet 20: 20-24, 2010.
39. Boettiger CA, Mitchell JM, Tavares VC, Robertson M, Joslyn G, D'Esposito M and Fields HL: Immediate reward bias in humans: fronto-parietal networks and a role for the catechol-O-methyltransferase 158(Val/Val) genotype. J Neurosci 27: 14383-14391, 2007.
40. Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE and Patton JH: Fifty years of the Barratt Impulsiveness Scale: An update and review. Personality and Individual Differences 47: 385-395, 2009.
41. Whitney P, Jameson T and Hinson JM: Impulsiveness and executive control of working memory. Pers Individ Diff 37: 417-428, 2004.
42. St Onge JR and Floresco SB: Dopaminergic modulation of risk-based decision making. Neuropsychopharmacology 34: 681-697, 2009.
43. Comings DE, Gade R, Wu S, Chiu C, Dietz G, Muhleman D, *et al*: Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. Mol Psychiatry 2: 44-56, 1997.
44. Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, *et al*: Dopaminergic network differences in human impulsivity. Science 329: 532, 2010.
45. Han DH, Park DB, Na C, Kee BS and Lee YS: Association of aggressive behavior in Korean male schizophrenic patients with polymorphisms in the serotonin transporter promoter and catecholamine-O-methyltransferase genes. Psychiatry Res 129: 29-37, 2004.
46. Han DH, Kee BS, Min KJ, Lee YS, Na C, Park DB and Lyoo IK: Effects of catechol-O-methyltransferase Val158Met polymorphism on the cognitive stability and aggression in the first-onset schizophrenic patients. Neuroreport 17: 95-99, 2006.
47. Nedic G, Nikolac M, Sviglin KN, Muck-Seler D, Borovecki F and Pivac N: Association study of a functional catechol-O-methyltransferase (COMT) Val108/158Met polymorphism and suicide attempts in patients with alcohol dependence. Int J Neuropsychopharmacol 14: 377-388, 2011.
48. Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, *et al*: Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch Gen Psychiatry 60: 889-896, 2003.
49. Williams-Gray CH, Hampshire A, Robbins TW, Owen AM and Barker RA: Catechol O-methyltransferase Val158Met genotype influences frontoparietal activity during planning in patients with Parkinson's disease. J Neurosci 27: 4832-4838, 2007.
50. Soeiro-de-Souza MG, Bio DS, David DP, Rodrigues dos Santos D Jr, Kerr DS, Gattaz WF, Machado-Vieira R and Moreno RA: COMT Met (158) modulates facial emotion recognition in bipolar I disorder mood episodes. J Affect Disord 136: 370-376, 2012.
51. Soeiro-de-Souza MG, Machado-Vieira R, Soares Bio D, Do Prado CM and Moreno RA: COMT polymorphisms as predictors of cognitive dysfunction during manic and mixed episodes in bipolar I disorder. Bipolar Disord 14: 554-564, 2012.
52. Baca-García E, Salgado BR, Segal HD, Lorenzo CV, Acosta MN, Romero MA, *et al*: A pilot genetic study of the continuum between compulsivity and impulsivity in females: the serotonin transporter promoter polymorphism. Prog Neuropsychopharmacol Biol Psychiatry 29: 713-717, 2005.
53. Sakado K, Sakado M, Muratake T, Mundt C and Someya T: A psychometrically derived impulsive trait related to a polymorphism in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) in a Japanese nonclinical population: assessment by the Barratt impulsiveness scale (BIS). Am J Med Genet B Neuropsychiatr Genet 121B: 71-75, 2003.
54. Lopez de Lara C, Brezo J, Rouleau G, Lesage A, Dumont M, Alda M, *et al*: Effect of tryptophan hydroxylase-2 gene variants on suicide risk in major depression. Biol Psychiatry 62: 72-80, 2007.
55. Bjork JM, Moeller FG, Dougherty DM, Swann AC, Machado MA and Hanis CL: Serotonin 2a receptor T102C polymorphism and impaired impulse control. Am J Med Genet 114: 336-339, 2002.
56. Zouk H, McGirr A, Lebel V, Benkelfat C, Rouleau G and Turecki G: The effect of genetic variation of the serotonin 1B receptor gene on impulsive aggressive behavior and suicide. Am J Med Genet B Neuropsychiatr Genet 144B: 996-1002, 2007.
57. Paaver M, Nordquist N, Parik J, Harro M, Oreland L and Harro J: Platelet MAO activity and the 5-HTT gene promoter polymorphism are associated with impulsivity and cognitive style in visual information processing. Psychopharmacology (Berl) 194: 545-554, 2007.
58. Passamonti L, Fera F, Magariello A, Cerasa A, Gioia MC, Muglia M, *et al*: Monoamine oxidase-a genetic variations influence brain activity associated with inhibitory control: new insight into the neural correlates of impulsivity. Biol Psychiatry 59: 334-340, 2006.
59. Alsene K, Deckert J, Sand P and de Wit H: Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 28: 1694-1702, 2003.
60. Sequeira A, Mamdani F, Lalovic A, Anguelova M, Lesage A, Seguin M, *et al*: Alpha 2A adrenergic receptor gene and suicide. Psychiatry Res 125: 87-93, 2004.
61. Evenden JL: Varieties of impulsivity. Psychopharmacology (Berl) 146: 348-361, 1999.