Original Article

COMT Val158Met polymorphism is associated with ecstasy (MDMA)-induced psychotic symptoms in the Turkish population

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ABSTRACT

الأهداف: دراسة تعدد الأشكال الجيني في اضطراب استخدام *(COMT)* من خلال مقارنة توزيعات النمط الجيني بين مرضى MUD والضوابط الصحية مع الأخذ في الاعتبار المعلمات السريرية.

المنهجية: تم قبول 82 مريضًا من مرض الطين على التوالي في عيادة الطب النفسي الخارجية في مايو 2019 إلى يناير 2020 ، وتم تضمين 95 متطوعًا سليمًا في دراسة الحالات والشواهد. استخدمنا تفاعل البلمرة المتسلسل (PCR) وتعدد الأشكال لطول جزء التقييد (RFLP) لتحديد تعدد الأشكال *COMT* Val158Met.

النتائج: كان توزيع التركيب الوراثي *COMT* Val158 وترددات الأليل لمجموعة مرضى MUD مختلفة بشكل كبير عن مجموعة التحكم الصحية. كان للنمط الوراثي نسبة الأرجحية=2.692 فترة الثقة= 1.272-5.698؛ وترددات Met allele (نسبة الأرجحية=1.716، فترة الثقة= 1.118-2.633) القيمة الحصائية p=0.013؛ أعلى بشكل ملحوظ في المجموعة الضابطة من مرضى MUD. عندما مقارنة توزيعات النمط الجيني *COMT* Val158Met وتردد الأليل بين مجموعتين وفقًا للأعراض الذهانية في مجموعة مرضى MUD، كانت توزيعات النمط الجيني *COMT* Val158Met مختلفة بشكل كبير بين مجموعات المرضى. كانت النسبة المئوية للمرضى الذين يعانون من النمط الوراثي Val/Val أقل بشكل ملحوظ في مرضى MUD الذين يعانون من أعراض ذهانية من مرضى MUD بدون أعراض ذهانية (نسبة الأرجحية: 2.625؛ 95% Cl: 1.069–6.446؛ p=0.033).

الخلاصة: وجد أن تعدد الأشكال الجيني COMT Val158Met مرتبط بالمرضى الأتراك المشخصين بMUD والأعراض الذهانية التي يسببها MDMA.

Objectives: To investigate catechol-O-methyltransferase *(COMT)* Val158Met gene polymorphism in MDMA use disorder (MUD) by comparing genotype distributions between MUD patients and healthy controls considering clinical parameters.

Methods: Eighty-two MUD patients' were consecutively admitted to the outpatient psychiatry clinic in May 2019-January 2020, and 95 healthy volunteers were included in the case-control study. We used the polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) to determine *COMT* Val158Met polymorphism.

Results: The *COMT* Val158Met genotype distribution and allele frequencies of the MUD patient group were significantly different from the healthy control group. The Met/Met genotype (OR: 2.692; 95% Cl: 1.272-5.698; p=0.008) and Met allele frequencies (OR: 1.716; 95% Cl: 1.118-2.633; p=0.013) were significantly higher in the control group than in MUD patients. When the *COMT* Val158Met genotype and allele frequency distributions were compared between 2 groups according to the psychotic symptoms in the MUD patient group, the *COMT* Val158Met genotype distributions were significantly different between the groups of patients. The percentage of patients with the Val/Val genotype was significantly lower in MUD patients with a psychotic symptom than the MUD patients without a psychotic symptom (OR: 2.625; 95% Cl: 1.069–6.446; p=0.033).

Conclusion: The *COMT* Val158Met gene polymorphism was found to be related to the MUD-diagnosed Turkish patients and MDMA-induced psychotic symptoms.

Neurosciences 2022; Vol. 27 (1): 24-30
doi: 10.17712/nsj.2022.1.20210045

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Received 13th April 2021. Accepted 14th September 2021

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3,4-methylenedioxymethamphetamine (MDMA), a ring-substituted amphetamine derivative, is a popular recreational drug best known as 'ecstasy.' This group of chemicals, which includes 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxyethylamphetamine (MDE), are named phenylethylamines and characterized by a mixture of hallucinogenic and psychostimulant effects.[1] The MDMA binds to all presynaptic monoamine transporters, most strongly to the serotonin transporter, and causes serotonin and dopamine's rapid and potent release from presynaptic terminals.[2] Therefore, MDMA-related psychopathologies may be related to excitotoxicity, mitochondrial dysfunction, or oxidative stress in serotonergic and dopaminergic systems.[3] Short-term neuropsychiatric consequences of MDMA can be counted as increased self-acceptance, self-confidence, reduced inhibitions, and heightened sexual sensitivity.[4] The long-term neuropsychological outcomes of MDMA were investigated in several types of research but have shown different results. The most common findings were anxiety, depression, psychotic symptoms, memory, and attention deficits.[5]

Catechol-O-methyltransferase *(COMT)* enzyme has a role in the degradation of dopamine and different catecholamines, and the *COMT* gene is expressed from chromosome 22q11.2. Decreased *COMT* enzyme activity is related to valine's amino acid change to methionine caused by a guanine-to-adenine substitution at codon 158 of the *COMT* gene.[6] In the brain, the *COMT* Val158Met (rs4680) polymorphism has been determined to change the activity of *COMT*, which probably causes alteration in dopamine neurotransmission and may end with behavioral abnormalities since dopamine takes a unique position in addiction.[7] Besides, there are studies of Val158Met for psychiatric disorders such as bipolar disorder (BD), schizophrenia (SCZ), and substance use disorder (SUD) that have shown contradictory results.[8-10] Many researchers showed statistically significant relationships of the *COMT* Val158Met polymorphism in subphenotypes of psychiatric disorders such as SCZ patients with homicidal or aggressive behavior or BD with rapid cycling.[11,12] Again, although some reports indicate a positive association between *COMT* polymorphisms and addiction, most studies have not detected a link between them.[13-15] The lack of evidence in a relationship suggests additional studies about the association of the *COMT* gene with SUD.

Therefore, we hypothesized that the *COMT* Val158Met polymorphism might be related to the MUD and some clinical parameters such as the comorbidity of the alcohol or cigarette use disorder, the presence of attempted suicide, and psychotic symptoms. We aimed to investigate the association between the MUD and *COMT* Val158Met gene polymorphism by comparing healthy controls and considering clinical parameters.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company. This research was partially funded by the Istanbul University BAP-YOP (TYL-2019-34316) program.

Methods.

Patient selection. The patients diagnosed with MUD (n=82) were consecutively admitted to the outpatient clinic of the Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurology Training and Research Hospital in May 2019-January 2020; additionally, 95 gender-, age-, and ethnicity-matched healthy participants were included in case-control research. This study was according to the ethical standards on human experimentation confirmed by the Helsinki Declaration and approved by the Clinical Research Ethics Committee of Istanbul Faculty of Medicine (04.02.2019/140).[16] We instructed the participants concerning the study's aim, materials, and methods and acquired their written informed consent. In addition, we applied the researchers' detailed interview data form about clinical information. We confirmed the patients' diagnosis with a positive urine test (urine drugs-of-abuse screening amphetamine/MDMA (CEDIA) test; >500 ng/ml) and excluded any psychiatric diagnosis from the healthy control group according to the DSM-5 criteria.

Psychotic symptoms. Psychotic symptoms were described as a score of 4 or greater on any Brief Psychiatric Rating Scale items of suspiciousness, unusual thought content, or hallucinations in the past month.[13]

DNA analyses. We collected blood samples from participants to isolate their DNA material at the Istanbul Faculty of Medicine Laboratory of Medical Biology. We used the polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) method to analyze the *COMT* Val158Met polymorphism. F: 5'-ACTGTGGCTACTCAGCTGTG-3' and R: 5'-CCTTTTTCCAGGTCTGACAA-3' were used as a primer to determine *COMT* Val158Met polymorphism.[17]

Statistical analyses. Descriptive statistics included mean, standard deviation, percentage. We used the Pearson chi-square test to analyze discrete variables and genotype distributions in participants. The Shapiro-Wilk test of normality was carried out on continuous variables to verify the fit of the data to a normal distribution.

Comparison of clinical parameters according to the genotype were performed by Kruskal Wallis testing since the variables did not have a normal distribution (SPSS version 21.0, IBM Corp. released 2012; Armonk, NY, USA). Allele and genotype frequencies of *COMT* Val158Met for both MUD patients and the control group were in concordance with the Hardy-Weinberg Equilibrium (HWE). We accepted the statistical significance as $p<0.05$ for the outcomes of all analyses. In addition, we performed the power analysis was performed with the "G*power" software (version 3.0.5, http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/), post hoc goodness of fit $\chi 2$ test, with an "-error" probability of 0.05. The potential assumable impacts of population stratification bias in the studied population were estimated with the formulas of Lee and Wang.[18]

Table 1 - Sociodemographic characteristics and clinical parameters of patients.

Ecstasy (MDMA) use disorder	
(Years)	**Mean±SD**
Age	27.40±6.96
Age of onset	16.84±4.21
Duration of disorder	11.29±7.46
Sex	**n** (%)
Female	0 (0)
Male	82 (100)
Education	
Literate	4 (4.9)
Primary School	18 (22.0)
Secondary School	40 (48.8)
High School	19 (23.2)
University	1 (1.2)
COMT Val158Met	
Met/Met	12 (14.6)
Val/Met	34 (41.5)
Val/Val	36 (43.9)
Tobacco - No	1 (1.2)
Usage - Yes	81 (98.8)
Alcohol - No	50 (61)
Usage - Yes	32 (39)
Psychotic - No	37 (45.1)
Symptom - Yes	45 (54.9)
Attempted - No	56 (68.3)
Suicide - Yes	26 (31.7)

SD - standard deviation, MDMA - 3,4-Methylenedioxymethamphetamine, COMT - Catechol-O-methyltransferase

Results. ***COMT Val158Met genotyping.*** The patients diagnosed with MUD were evaluated according to sociodemographic characteristics and clinical parameters, as shown in **Table 1**. According to the *COMT* Val158Met genotype distribution, 14.6% (n=12) of the patients diagnosed with MUD had Met/Met, 41.5% (n=34) had Val/Met, and 43.9% (n=36) had Val/Val genotypes. Thirty-one point six percent (n=30) of the control group had Met/Met, 33.7% (n=32) had Val/Met, and 34.7% (n=33) had Val/Val genotypes. When the *COMT* Val158Met (Met/Met, Val/Met, Val/Val) genotype and the allele frequency (Met, Val) distributions of MUD patients were compared with the control group, there was a significant difference between groups. The Met/Met genotype frequency was higher in the control group compared to MUD (OR: 2.692; 95% Cl: 1.272-5.698; p=0.008). The *COMT* Val158Met allele frequency distributions of MUD patients were also significantly different from those of the control group; the Met allele frequency was higher in the control group than MUD (OR: 1.716; 95% Cl: 1.118-2.633; p=0.013) (**Table 2**).

Comparison of distributions of MUD patients' COMT Val158Met polymorphism due to clinical parameters. Comparing the *COMT* Val158Met genotype and the allele frequency distributions between the 2 groups according to the presence of the alcohol or cigarette usage, attempted suicide, and psychotic symptom in the patient group demonstrated that the *COMT* Val158Met genotype distributions of MUD patients were significantly different between the groups of patients due to the presence of the psychotic symptom (**Table 3**). While the percentage of patients with the Val/Val genotype was significantly higher in MUD patients without a psychotic symptom than the MUD patients with a psychotic symptom (OR: 2.625; 95% Cl: 1.069–6.446; p=0.033), the percentage of patients with the Val/Met genotype was significantly lower in MUD patients without a psychotic symptom than the MUD patients with a psychotic symptom (OR: 3.889; 95% Cl: 1.498–10.094; p=0.004). When clinical parameters (mean of age, age of onset, and duration of MUD) were compared between the three genotype groups in reference to the *COMT* Val158Met genotype of the patients with MUD, there was not found to be a significant difference between the groups (p>0.05)

Discussion. Our case-control study compared the distributions of *COMT* Val158Met gene polymorphism in MUD patients with control subjects. We found significant differences between the distributions of *COMT* Val158Met genotype and the allele frequency distributions. Several pieces of evidence suggest that *COMT* variation affects prefrontal cortex dopamine regulation and modulates features of behavior, cognition, and emotions.[19] Since disturbance of corticostriatal dopamine signaling is a core aspect of neuropsychiatric disorders, including SUD, ADHD,

Table 2 - Comparison of genotype distributions of *COMT* Val158Met polymorphism in patients with the control.

Genotype	MDMA	Control	OR	95% CI	*P*-value
COMTVal158Met	n=[a] (%)	n=95 (%)			
Met/Met	12 (14.6)	30 (31.6)	2.692*	1.272-5.698*	0.008*
Val/Met	34 (41.5)	32 (33.7)	0.717*	0.389-1.322*	0.286*
Val/Val	36 (43.9)	33 (34.7)	0.680*	0.371-1.248*	0.212*
Allele					
Met	58 (35.4)	92 (48.4)			
Val	106 (64.6)	98 (51.6)	1.716*	1.118-2.633*	0.013*

MDMA, 3,4-Methylenedioxymethamphetamine; [a]n= 82; OR, odds ratio; CI, confidence interval; *Pearson chi-square

Table 3 - Comparison of genotype distributions of *COMT* Val158Met in patients due to psychotic symptoms.

Psychotic Symptoms /Genotype	Yes	No	OR	95% CI	*P*-value
COMTVal158Met	n= [a] (%)	n=37 (%)			
Met/Met	5 (11.1)	7 (18.9)	0.536*	0.155-1.854*	0.320*
Val/Met	25 (55.6)	9 (24.3)	3.889*	1.498-10.094*	0.004*
Val/Val	15 (33.3)	21 (56.8)	2.625*	1.069-6.446*	0.033*
Allele					
Met	35 (38.9)	23 (31.1)			
Val	55 (61.1)	51 (68.9)	1.411*	0.737-2.702*	0.298*

COMT, Catechol-O-methyltransferase; [a]n= 45; OR, odds ratio; CI, confidence interval; *Pearson chi-square

BD, and SCZ, the *COMT* Val158Met single-nucleotide polymorphism is among the commonly examined genetic polymorphisms in literature.[20,21] Schilt et al[22] reported that the ecstasy's negative memory effect is moderated by the *COMT* Val158Met gene. In addition, Met-allele carrier patients were slightly more susceptible to the impacts of ecstasy on verbal learning than homozygous Val-patients. However, a study examining a possible association between ecstasy use and verbal fluency in subjects to find a potential implication of genetic factors has been reported no genotype effect for *COMT* Val108/158Met.[23]

In our study, the participants carrying the Met/Met genotype or the Met allele had a lower risk of developing MUD. When we review the researches on other stimulant use disorders and *COMT* gene polymorphisms in the literature, the *COMT* Val108/158Met polymorphism was related to methamphetamine use, with the Val allele being the risk allele for stimulant use disorder in the Chinese population.[24] Similar to our findings, in a comprehensive meta-analysis, Taylor published that in Asians, the Val allele was related to SUD.[25] In contrast to these researches, in African– Americans, the *COMT* Val108/158Met polymorphism (rs737865, rs4680) was associated with cocaine use disorder such that Met allele carriers are at an increased risk of becoming dependent on the drug.[19] Again, Hosak et al[26] showed a significantly higher mean novelty-seeking score among the Met allele patients than the patients with Val/Val homozygotes. However, 2 other studies did not report a connection between the methamphetamine use disorder and *COMT* Val108/158Met polymorphism in American or Japanese patients.[27,28] The explanation for these different results can be a variable prevalence of the *COMT* Val allele among various ethnic groups.[26] It was published that participants with the low-activity Met158 allele showed better performance on a neurocognitive test than participants with the high-activity Val158 allele.[29] Mattay et al[30] reported that the prefrontal cortex's performance was enhanced by amphetamine in participants with the high activity allele; however, those with the low activity allele are more likely to have unfavorable influences on the prefrontal cortex function when given amphetamine, which suggested another explanation that the low activity allele may have a protective effect against stimulant use disorder.

When the literature about *COMT* Val158Met gene polymorphism related to stimulants induced psychosis is reviewed, it can be seen that stimulants may cause adverse outcomes over the psychotic disorder's spectrum and some psychotic attacks with the use of cannabinoids.[31] Many temporary and dose-dependent

psychotic symptoms were reported related to stimulant use disorders.[32] Stimulant usage can precipitate existing subclinical psychotic symptoms or relapse among SCZ patients.[33] It was also published that the use of a single dose of ecstasy could induce persistent psychotic symptoms (delusions), and these symptoms may not be quickly reversible after cessation of use.[34] In the Turkish population, Duman et al[35] showed that a former use of ecstasy and cannabis is connected to the significant increase in the severity of subclinical psychotic symptoms. It was thought that besides acute psychotic attacks due to the MDMA usage, dopaminergic and serotonergic toxicity associated with chronic usage might increase the risk of psychosis.[1]

In the present cross-sectional study, there was a significant difference between the *COMT* Val158Met genotype distributions of the MUD patient groups due to psychotic symptoms. The participants carrying the Val/Val genotype had a lower risk of developing psychotic symptoms in MUD patients in our study. Our results were compatible with Suzuki et al's[28] research that reported the percentages of Met allele of the *COMT* were associated with methamphetamine psychosis and spontaneous relapse.In contrast to the current study, Hosak et al[36] found the psychotic symptoms induced by methamphetamine more frequent in Val carriers than Met/Met homozygotes.

The *COMT* Val158Met might be one of the essential candidate genes for examining stimulant-induced psychotic symptoms since it encodes for the *COMT*, which is a crucial enzyme for catabolizing dopamine, norepinephrine, and catechol estrogens.[25,37] The *COMT* is particularly critical in coordinating dopaminergic transmission in the prefrontal cortex, where it estimates approximately 60% of the catabolism of dopamine released.[8] Furthermore, Val has a 40% higher enzyme activity in the brain, causing lower synaptic dopamine levels compared to Met.[6] Especially, if Val158 carrier participants had used cannabis in adolescence, they showed an increased risk of presenting psychotic symptoms and developing schizophreniform disorder.[38] This outcome may be associated with the relatively enhanced midbrain dopamine function connected to the Val158 allele since cannabis induces dopamine release in the nucleus accumbens. This effect might be magnified in Val158 homozygotes, probably developing psychosis.[39] For our study, there may be several reasons why having the Met carrier *COMT* genomes (Val/Met and Met/Met) were found to be associated with MDMA-induced psychotic symptoms different from SCZ and cannabis-induced psychosis. First, *COMT* is involved in the MDMA's breakdown pathways, and slow degradation of MDMA likely enhances toxicity.[22] Second, MDMA may induce persistent damage to serotonergic neurons in the human brain by binding to presynaptic monoamine transporters (SERT), causing the quick release and subsequent consumption of serotonin and dopamine from presynaptic terminals.[40] Therefore the Met carrier *COMT* genomes may be included in the MDMA-induced serotonin toxicity and psychotic symptoms. Moreover, higher levels of extracellular dopamine are associated with hyperthermia, which can also generate serotonergic damage.[41]

Our study's strength is the first study that showed the relationship between *COMT* Val158Met polymorphism and MDMA-induced psychotic symptoms. Secondly, because MUD patients and healthy participants were selected from the same location in Istanbul (the European side), our study's findings seem more critical. However, besides the strengths of the present research, there are also several limitations. The first limitation was the small sample size, which can restrict the statistical power. A second limitation of our research is that only polymorphism in *COMT* was investigated, but it was impossible to determine other mutations in CYP2D6 gene polymorphism that is also responsible for the degradation of MDMA. Third, there was no control over the amount and purity of MDMA in the ecstasy tablets. Finally, we can not examine a dose-response relationship since the MDMA dosages information was not given by the participants clearly in our research.

To sum up, *COMT* Val158Met polymorphism was found to be related to both MUD itself and MDMA-induced psychotic symptoms. Although it is likely not possible within most clinical settings to assess the Val/Val polymorphism presence, one of the characteristics associated with this polymorphism could be evaluated as lower risk for MDMA-induced psychotic symptoms. Early identification of patients at risk for MDMA-induced psychotic symptoms is a critical step for individuals at heightened risk for transitioning from MUD to psychosis. Confirming these findings with different ethnicities will better examine the relationship between *COMT* Val158Met polymorphism and MUD. Future researches are required to investigate further the function of *COMT* polymorphisms in MDMA-induced neurotoxicity and its outcomes.

Acknowledgement. *The authors gratefully acknowledge Cambridge Proofreading LLC for native English editing.*

References

1. Karlsen SN, Spigset O, Slørdal L. The dark side of ecstasy: neuropsychiatric symptoms after exposure to 3, 4–methylenedioxymethamphetamine. ***Basic & clinical pharmacology & toxicology*** 2008; 102: 15-24.
2. Han DD, Gu HH. Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. ***BMC pharmacology*** 2006; 6: 1-7.
3. Quinton MS, Yamamoto BK. Causes and consequences of methamphetamine and MDMA toxicity. ***AAPS J*** 2006; 8: E337-E347.
4. Virani S, Daya GN, Brainch N, Kotapati VP, Zaveri D, Ahmed S. Persistent Psychosis due to Single Dose of Ecstasy. ***Cureus*** 2018; 10: e3058.
5. Potash MN, Gordon KA, Conrad KL. Persistent psychosis and medical complications after a single ingestion of MDMA "Ecstasy": a case report and review of the literature. ***Psychiatry (Edgmont)*** 2009; 6: 40-44.
6. Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. ***Am J Hum Genet*** 2004; 75: 807-821.
7. Lachman HM. Does COMT val158met affect behavioral phenotypes: yes, no, maybe? ***Neuropsychopharmacology*** 2008; 33: 3027-3029.
8. Hosák L. Role of the COMT gene Val158Met polymorphism in mental disorders: a review. ***Eur Psychiatry*** 2007; 22: 276-281.
9. Oyaci Y, Aytac HM, Pasin O, Cetinay Aydin P, Pehlivan S. Detection of altered methylation of MB-COMT promotor and DRD2 gene in cannabinoid or synthetic cannabinoid use disorder regarding gene variants and clinical parameters. ***J Addict Dis*** 2021; 1-19.
10. Pehlivan S, Aydin PÇ, Aytaç HM, Uysal MA, Sever Ü, Pehlivan M. Investigation of Catechol-O-Methyltransferase and Cannabinoid Receptor 2 gene variants in tobacco use disorder or tobacco use disorder and schizophrenia comorbidity. ***Anatolian Journal of Psychiatry*** 2020; 21: 572-578.
11. Kirov G, Murphy K, Arranz M, Jones I, McCandles F, Kunugi H, et al. Low activity allele of catechol-O-methyltransferase gene associated with rapid cycling bipolar disorder. ***Mol Psychiatry*** 1998; 3: 342-345.
12. Strous RD, Nolan KA, Lapidus R, Diaz L, Saito T, Lachman HM. Aggressive behavior in schizophrenia is associated with the low enzyme activity COMT polymorphism: a replication study. ***Am J Med Genet B Neuropsychiatr Genet*** 2003; 120B: 29-34.
13. Pehlivan S, Aytac HM, Kurnaz S, Pehlivan M, Cetinay Aydin P. Evaluation of COMT (rs4680), CNR2 (rs2501432), CNR2 (rs2229579), UCP2 (rs659366), and IL-17 (rs763780) gene variants in synthetic cannabinoid use disorder patients. ***Journal of Addictive Diseases*** 2020: 1-11.
14. Tammimäki AE, Männistö PT. Are genetic variants of COMT associated with addiction? ***Pharmacogenet Genomics*** 2010; 20: 717-741.
15. Jugurnauth SK, Chen CK, Barnes MR, Li T, Lin SK, Liu HC, et al. A COMT gene haplotype associated with methamphetamine abuse. ***Pharmacogenet Genomics*** 2011; 21: 731-740.
16. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. ***JAMA*** 2013; 310: 2191-2194.
17. Baclig MO, Predicala RZ, Mapua CA, Lozano-Kühne JP, Daroy MLG, Natividad FF, et al. Allelic and genotype frequencies of catechol-O-methyltransferase (Val158Met) and CYP2D6* 10 (Pro34Ser) single nucleotide polymorphisms in the Philippines. ***Int J Mol Epidemiol Genet*** 2012; 3: 115-121.
18. Lee W-C, Wang L-Y. Simple formulas for gauging the potential impacts of population stratification bias. ***Am J Epidemiol*** 2008; 167: 86-89.
19. Lohoff FW, Weller AE, Bloch PJ, Nall AH, Ferraro TN, Kampman KM, et al. Association between the catechol-O-methyltransferase Val158Met polymorphism and cocaine dependence. ***Neuropsychopharmacology*** 2008; 33: 3078-3084.
20. Mizuno Y, Jung M, Fujisawa TX, Takiguchi S, Shimada K, Saito DN, et al. Catechol-O-methyltransferase polymorphism is associated with the cortico-cerebellar functional connectivity of executive function in children with attention-deficit/hyperactivity disorder. ***Sci Rep*** 2017; 7: 4850.
21. Hosák L. Role of the COMT gene Val158Met polymorphism in mental disorders: a review. ***Eur Psychiatry*** 2007; 22: 276-281.
22. Schilt T, Koeter MW, de Win MM, Zinkstok JR, van Amelsvoort TA, Schmand B, et al. The effect of Ecstasy on memory is moderated by a functional polymorphism in the cathechol-O-methyltransferase (COMT) gene. ***Eur Neuropsychopharmacol*** 2009; 19: 116-124.
23. Fagundo AB, Cuyàs E, Verdejo-Garcia A, Khymenets O, Langohr K, Martín-Santos R, et al. The influence of 5-HTT and COMT genotypes on verbal fluency in ecstasy users. ***J Psychopharmacol*** 2010; 24: 1381-1393.
24. Li T, Chen Ck, Hu X, Ball D, Lin SK, Chen W, et al. Association analysis of the DRD4 and COMT genes in methamphetamine abuse. ***Am J Med Genet B Neuropsychiatr Genet*** 2004; 129B: 120-124.
25. Taylor S. Association between COMT Val158Met and psychiatric disorders: A comprehensive meta-analysis. ***Am J Med Genet B Neuropsychiatr Genet*** 2018; 177: 199-210.
26. Hosak L, Libiger J, Cizek L, Beranek M, Cermakova E. The COMT Val158Met polymorphism is associated with novelty seeking in Czech methamphetamine abusers: preliminary results. ***Neuro Endocrinol Lett*** 2006; 27: 799-802.
27. Bousman C, Cherner M, Atkinson J, Heaton R, Grant I, Everall I, et al. COMT Val158Met polymorphism, executive dysfunction, and sexual risk behavior in the context of HIV infection and methamphetamine dependence. ***Interdiscip Perspect Infect Dis*** 2010; 2010: 678648.
28. Suzuki A, Nakamura K, Sekine Y, Minabe Y, Takei N, Suzuki K, et al. An association study between catechol-O-methyl transferase gene polymorphism and methamphetamine psychotic disorder. ***Psychiatr Genet*** 2006; 16: 133-138.
29. 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 U S A*** 2001; 98: 6917-6922.
30. Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. ***Proc Natl Acad Sci U S A*** 2003; 100: 6186-6191.
31. Sara GE, Large MM, Matheson SL, Burgess PM, Malhi GS, Whiteford HA, et al. Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation. ***Aust N Z J Psychiatry*** 2015; 49: 106-117.

32. McKetin R, McLaren J, Lubman DI, Hides L. The prevalence of psychotic symptoms among methamphetamine users. ***Addiction*** 2006; 101: 1473-1478.
33. Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. ***Br J Psychiatry*** 2004; 185: 196-204.
34. Virani S, Daya GN, Brainch N, Kotapati VP, Zaveri D, Ahmed S. Persistent Psychosis due to Single Dose of Ecstasy. ***Cureus*** 2018; 10: e3058.
35. Duman B, Sedes N, Baskak B. Additive Effects of Former Methylenedioxymethamphetamine and Cannabis Use on Subclinical Psychotic Symptoms. ***Noro Psikiyatr Ars*** 2017; 54: 38-42.
36. Hosák L, Serý O, Beranek M, Alda M. Lack of association between the Val158Met catechol-O-methyltransferase gene polymorphism and methamphetamine dependence. ***Neuro Endocrinol Lett*** 2011; 32: 469-474.
37. Zumárraga M, Arrúe A, Basterreche N, Macías I, Catalán A, Madrazo A, et al. COMT haplotypes, catecholamine metabolites in plasma and clinical response in schizophrenic and bipolar patients. ***Pharmacogenomics*** 2016; 17: 837-851.
38. Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, et al. Midbrain dopamine and prefrontal function in humans: interaction and modulation by COMT genotype. ***Nat Neurosci*** 2005; 8: 594-596.
39. Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. ***Biol Psychiatry*** 2006; 60: 141-151.
40. Gouzoulis-Mayfrank E, Daumann J. Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage? ***Addiction*** 2006; 101: 348-361.
41. Kanthasamy A, Sprague J, Shotwell J, Nichols D. Unilateral infusion of a dopamine transporter antisense into the substantia nigra protects against MDMA-induced serotonergic deficits in the ipsilateral striatum. ***Neuroscience*** 2002; 114: 917-924.

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