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

Hasan Mervan Aytac, MD, Yasemin Oyaci, MS, Pinar Cetinay Aydin, MD, Mustafa Pehlivan, MD, Sacide Pehlivan, PhD.

OBJECTIVE: 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% CI: 1.272-5.698; p=0.008) and Met allele frequencies (OR: 1.716; 95% CI: 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% CI: 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.

Abstract

The COMT Val158Met polymorphism is associated with ecstasy (MDMA)-induced psychotic symptoms in the Turkish population. Hasen Mervan Aytac, MD, Yasemin Oyaci, MS, Pinar Cetinay Aydin, MD, Mustafa Pehlivan, MD, Sacide Pehlivan, PhD.

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% CI: 1.272-5.698; p=0.008) and Met allele frequencies (OR: 1.716; 95% CI: 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% CI: 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.

Journal of Neuroscience 2022; Vol. 27 (1): 24-30
doi: 10.17712/jsj.2022.1.20210045

From the Department of Psychiatry (Aytac), Basaksehir Cam and Sakura City Hospital, Department of Medical Biology (Oyaci, Pehlivan), Istanbul Faculty of Medicine, Istanbul University, and from the Department of Psychiatry (Cetinay Aydin), Bakirkoy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, Psychiatry Clinic, University of Health Sciences, Istanbul, and from the Department of Hematology (Pehlivan), Gaziantep University, Faculty of Medicine, Gaziantep, Turkey

Received 13th April 2021. Accepted 14th September 2021

Address correspondence and reprint request to: Dr. Hasan M. Aytac, Department of Psychiatry, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey. E-mail: hasanmervan.aytac@saglik.gov.tr

ORCID ID: https://orcid.org/0000-0002-1053-6808
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-methylenedioxymethamphetamine (MDA) and 3,4-methylenedioxyamphetamine (MDE), are named phenylethylamines and characterized by a mixture of hallucinogenic and psychostimulant effects. 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. Therefore, MDMA-related psychopathologies may be related to excitotoxicity, mitochondrial dysfunction, or oxidative stress in serotonergic and dopaminergic systems. Short-term neuropsychiatric consequences of MDMA can be counted as increased self-acceptance, self-confidence, reduced inhibitions, and heightened sexual sensitivity. 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. 

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. 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. 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. 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. Again, although some reports indicate a positive association between COMT polymorphisms and addiction, most studies have not detected a link between them. 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.

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). 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.

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′-CCTTTTCCAGGTCTGACAA-3′ were used as a primer to determine COMT Val158Met polymorphism.

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.

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.
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 |            |
|--------------------------|----------------------------|------------|
|                          | 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% CI: 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% CI: 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 (Table 3). 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,
COMT Val158Met polymorphism in MDMA use disorder ... Aytac et al

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=101 (%)  | n=82 (%)   |      |               |         |
| 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*  |

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=45 (%)   | 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                     | 36 (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; ‘n= 45; OR, odds ratio; CI, confidence interval; *Pearson chi-square
COMT Val158Met polymorphism in MDMA use disorder ... Aytaç et al

psychotic symptoms were reported related to stimulant use disorders.\textsuperscript{35} Stimulant usage can precipitate existing subclinical psychotic symptoms or relapse among SCZ patients.\textsuperscript{35} 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.\textsuperscript{14} In the Turkish population, Duman et al\textsuperscript{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.\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{25,27} The COMT is particularly critical in coordinating dopaminergic transmission in the prefrontal cortex, where it estimates approximately 60% of the catabolism of dopamine released.\textsuperscript{8} Furthermore, Val has a 40% higher enzyme activity in the brain, causing lower synaptic dopamine levels compared to Met.\textsuperscript{6} Especially, if Val158 carrier participants had used cannabis in adolescence, they showed an increased risk of presenting psychotic symptoms and developing schizophreniform disorder.\textsuperscript{28} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
COMT Val158Met polymorphism in MDMA use disorder ... Aytac et al

References

1. Karlsen SN, Spigset O, Slordal L. The dark side of ecstasy: neuropsychiatric symptoms after exposure to 3, 4-methylenedioxyamphetamine. 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. Currres 2018; 10: e-c3058.

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. Hosak 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 promoter and DRD2 gene in cannabinoid or synthetic cannabinoid use disorder regarding gene variants and clinical parameters. J Addict Dis 2021; 1-9.

10. Pehlivan S, Aydin PÇ, Aytac 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. Anatoinal 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 (rs6480), 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, Daryo 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. Hosak 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, Cuyás 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 psychotic 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. Intercideisp Inventif 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-methyltransferase 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 Ectasy. *Cureus* 2018; 10: e3058.

35. Duman B, Sedes N, Baskak B. Additive Effects of Former Methyleneoxyamphetamine 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 methylenedioxyamphetamine (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.

Illustrations, Figures, Photographs

All figures or photographs should be submitted in a high resolution (minimum 300 DPI) electronic version saved in jpeg or tiff format. Original hard copies of all figures may be requested when necessary. Photographs will be accepted at the discretion of the Editorial Board. All lettering, arrows, or other artwork must be done by an artist or draftsman. If arrows are used please ensure they appear in a different color to the background color, preferably black with a white border, or white with a black border. If arrows distinguish different items on the figure then different arrow styles should be used ie. long, short, wide, narrow. Written informed consent for publication must accompany any photograph in which the subject can be identified. Written copyright permission, from the publishers, must accompany any illustration that has been previously published.