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Association between Novelty Seeking of opiate-dependent patients and the catechol-*O*-methyltransferase Val^{158}Met polymorphism

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Abstract

Background: Candidate genes of the dopaminergic system have been reported as key elements in shaping human temperament. Catechol-*O*-methyltransferase (COMT) plays a vital role in dopamine inactivation, and the Val^{158}Met single nucleotide polymorphism (rs4680) in its gene has been recently associated with the Novelty Seeking (NS) temperament scale of the Temperament and Character Inventory in studies of healthy adults, as well as methamphetamine abusers.
Method: Our goal was to examine the association between temperament dimensions of the Temperament and Character Inventory and the COMT Val^{158}Met variation in a Hungarian sample of 117 heroin-dependent patients and 124 nondependent controls.
Results: Case-control analysis did not show any significant difference in allele or genotype distributions. However, dimensional approach revealed an association between the COMT Val^{158}Met and NS (P = .01): both controls and opiate users with Met/Met genotypes showed higher NS scores compared to those with the Val allele. The NS scores are also significantly higher among opiate users; however, no interaction was found between group status and COMT genotype.
Conclusion: Association of the COMT polymorphism and NS temperament scale has been shown for heroin-dependent patients and controls regardless of group status.

1. Introduction

Twin and adoption studies demonstrate substantial heritability of personality (h^2 for Temperament and Character Inventory [TCI] temperament scales range from 0.3 to 0.4 based on a large Australian twin study [1]). However, these studies do not provide information about candidate polymorphisms responsible for individual variability. The initial ground breaking results in the field of candidate gene studies of personality were published in 1996 by three groups [2-4], independently demonstrating statistically significant association between dimensions measured by personality questionnaires and candidate gene polymorphisms. In good agreement with the psychobiological personality model of Cloninger and his colleagues [5], genetic variants of the dopamine D4 receptor (DRD4) were related to the Novelty Seeking (NS) dimension of the Temperament and Personality Questionnaire (TPQ) [3]. Applying the Five-Factor Model of personality, Benjamin and his colleagues [2] found concordant results with Ebstein et al [3], demonstrating the association between the DRD4 gene and the extraversion dimension of the revised NEO Personality Inventory. Lesch and colleagues [4] revealed an association of the serotonin transporter variants and anxiety-related personality traits. Our earlier results indicated a higher NS score on TCI questionnaire for females with the DRD4-521 CC genotype [6], but no association between the DRD4 variable number of tandem repeats (VNTR) and NS [7] in agreement with the meta-analysis of Munafo and colleagues [8]. On the other hand, we demonstrated that male individuals with the 7-

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repeat allele of DRD4 VNTR exhibited significantly lower Persistence [7], a distinct fourth dimension of personality.

Among numerous mechanisms controlling synaptic dopamine levels, degradation of dopamine by the enzyme catechol-*O*-methyltransferase (COMT) is of critical importance. A widely studied variation of the COMT gene is a single nucleotide polymorphism (SNP, rs4680) in the fourth exon generating an amino acid substitution (Val^{158}-Met) in the expressed protein. This amino acid change has a functional effect [9]: degradation of catecholamines, such as dopamine, is 3 to 4 times faster by the Val variant (high activity form) compared to the Met variant (low activity form). Though the Val^{158}Met polymorphism is the most studied genetic variation, the COMT gene has several further polymorphisms [10] which may also influence enzyme activity.

The role of the COMT polymorphisms in psychiatric disorders has been widely investigated, but results are contradictory (see the recent review of Hosak [11]). As diagnostic categories involve a diverse and extremely complex phenotype, dimensional analyses of psychiatric phenotypes might result in better understanding of the genetic background. Studies of schizophrenic patients demonstrated an association between presence of the COMT low activity variant (Met allele) and homicidal behavior [12] or impulsive aggression [13]. These results have been reinforced in non-schizophrenic samples demonstrating that COMT low-activity homozygotes (Met-Met) were overrepresented among violent suicide attempters [14]. Based on these results, the low activity form of COMT resulting in higher dopamine concentration in the prefrontal cortex seems to be related to impulsive-aggressive behavior.

A recent report showed that subjects with the Met/Met genotype of the COMT gene had higher NS than carriers of the Val/Val and Val/Met genotypes, although this association was seen only in women [15]. An association between the COMT Val^{158}Met genotypes and the TCI NS scores has been recently reported by Hosak and colleagues [16] in a sample of 38 methamphetamine dependent subjects. Results showed an increased TCI NS score in the presence of the Met allele. Here we present results supporting association between the COMT Val^{158}Met genotype and NS using a sample of 117 heroin-dependent subjects and 124 controls.

2. Subjects and methods

2.1. Patients

The heroin user sample met the criteria of opiate dependence (F11.22 and F11.24 according to the *International Statistical Classification of Diseases, 10th Revision* [17]) and were recruited from the methadone substitution program of Nyírő Gyula Hospital Drug Outpatient Center, Budapest, Hungary. Of the 200 patients maintained on methadone at the outpatient center 117 agreed to participate in the study. Participants were maintained on a daily dose of 50 to 150 mg of methadone and none of them showed any withdrawal symptoms at the time of assessment.

Control subjects were healthy Hungarian university students recruited at the Institute of Psychology, Eötvös Loránd University on a voluntary basis. They had no lifetime history of diagnosis or treatment for psychiatric disease, but those individuals with a history of experimental or recreational drug use were not excluded from the study.

2.2. Population homogeneity

To address the issue of population stratification, the participation was restricted to subjects of Caucasian (Hungarian) origin, thus creating an ethnically homogenous population. Selection criteria including age range (18-35 years) and valid TCI questionnaire data (all items answered and at least three of the five TCI validity items indicate appropriate responses) were applied for both groups, resulting in a total of 117 opiate-dependent patients and 124 controls with valid results. Mean age for the dependent group was 27.4 (±3.7); which is significantly higher $t_{239} = 8.1$ ($P < .001$) than that of the control group: 23.2 (±4.4). As an anticipated result of the random sampling method sex ratio in the 2 groups was reversed: there were 70.1% men and 29.9% women in the dependent group, whereas 26.6% men and 73.4% women in the control group $\chi^2(1,241) = 45.6$, ($P < .001$). Owing to these differences, sex and age were used as covariates in all association analysis. Study protocols were approved by the Hungarian National Ethical Committee (ETT-TUKEB); all participants provided written informed consent.

2.3. Phenotyping

Temperament profiles of NS, Harm Avoidance (HA), Reward Dependence (RD) and, Persistence (P) were assessed by the Hungarian version [18] of the TCI [19]. Internal consistency of the scales was assessed by calculating Cronbach's α values and was found satisfactory (NS: 0.756, HA: 0.827, RD: 0.713, P: 0.691).

2.4. Genotyping

Noninvasive DNA sampling (buccal epithelial cells) and genotyping of the COMT Val^{158}Met polymorphism was described earlier [20]. Two independent DNA samples per person were amplified in separate polymerase chain

Table 1
COMT *Val*^{158}*Met* genotype frequencies

	Heroin dependents			Controls		
	Male (n = 82)	Female (n = 35)	Total (n = 117)	Male (n = 33)	Female (n = 91)	Total (n = 124)
Val/Val	26.8%	37.1%	29.9%	24.2%	26.4%	25.8%
Val/Met	48.8%	45.7%	47.9%	39.4%	51.6%	48.4%
Met/Met	24.4%	17.2%	22.2%	36.4%	22.0%	25.8%

Not significant.

Table 2
TCI mean raw scores of heroin dependent subjects and controls

	Heroin dependents	Controls	t_{239} =
	n = 117	n = 124	
NS	25.5 (±6.1)	21.3 (±6.0)	5.296*
Harm avoidance	17.7 (±8.0)	13.0 (±6.2)	5.176*
Reward dependence	14.2 (±3.5)	15.7 (±3.9)	-3.181*
Persistence	3.5 (±2.0)	4.4 (±2.2)	-3.305*

* $P < .001$.

reactions for higher reliability of genotypes. No significant deviation from the Hardy-Weinberg equilibrium was found in either sample (see Table 1). Further testing within the dependent and the control group confirmed no significant differences between males and females in genotype frequencies.

2.5. Statistical analysis

The SPSS program for Windows (17.0 version; SPSS, Chicago, Ill) was used. χ^2 analysis was carried out for assessment of allele and genotype frequencies. Independent-samples *t* test and Pearson correlation were used to assess the relationships between the TCI scores and sex or age, respectively. Genetic association analyses were carried out by univariate analysis of variance (2-way analysis of covariance [ANCOVA]) separately for each of the four TCI temperament scales as dependent variables and the group status (heroin dependents vs. controls), and genotypes as grouping factors with sex and age were used as covariates. The following statistical values are reported with the F values of each analysis: level of significance, effect size (η^2) and observed power.

3. Results

3.1. Case-control association analysis

COMT Val^{158}Met genotype was determined for 117 opiate dependents and 124 controls with valid TCI results. Table 1 presents genotype frequencies of the case and the control group. Distribution of the COMT Val^{158}Met genotype frequencies did not show any significant difference between opiate dependents and the control group either for the whole sample or for the male and female subsamples.

3.2. TCI temperament scores in the sample of opiate dependents and controls

Mean TCI raw scores of the dependent group differed from controls: NS and HA scores were significantly higher, while RD and P scores were significantly lower in opiate dependents as compared to controls (Table 2).

Sex and age effects on the TCI scales were also assessed within each sample. In opiate dependents sex appeared to effect two TCI scales: RD and HA. Men showed a significantly lower average score (13.6 ± 3.3) on RD as compared to women (15.7 ± 3.3) $t_{115} = -3.22$ ($P = .002$). Average HA scores of males was also lower (16.8 ± 8.0) than those of females (19.8 ± 7.7); however, this difference did not reach the level of significance $t_{115} = -1.85$, $P = .067$. Similar sex differences were observed in the control sample: RD of males was significantly lower (14.5 ± 3.9) than that of females (16.2 ± 3.9) $t_{122} = -2.08$, $P = .04$; HA scores of males were also lower (12.5 ± 7.0) as compared to females (13.2 ± 5.9), but these differences were statistically not significant. Age showed a tendentious correlation with NS ($r = 0.17$, $P = .075$) and with RD ($r = 0.16$, $P = .083$) in the opiate-dependent sample and also showed a significant correlation with HA ($r = -0.20$, $P = .028$) and with RD ($r = -0.26$, $P = .003$) in controls. For these reasons, sex and age were entered as covariates in all subsequent analyses of variance testing genetic effects.

3.3. Association analysis between TCI temperament scales and the COMT genotypes

To explore psychogenetic association of the COMT polymorphism and the TCI temperament phenotypes, we used a dimensional approach (Table 3). Univariate analysis (2-way ANCOVA) of the NS temperament scale showed a significant main effect of the COMT Val^{158}Met SNP genotypes $F_{1,233} = 3.365$, $P = .036$, $\eta^2 = 0.028$,

Table 3
Effect of COMT *Val^{158}Met* genotypes on TCI temperament dimensions

	Heroin dependents			Controls			Association analysis (2-way ANCOVA)		
	Val/Val (n = 35)	Val/Met (n = 56)	Met/Met (n = 26)	Val/Val (n = 32)	Val/Met (n = 60)	Met/Met (n = 32)	Genotype main effect	Group main effect	Interaction
NS	25.1 (±6.2)	24.5 (±6.2)	28.0 (±5.4)	20.9 (±6.2)	21.0 (±5.9)	22.3 (±6.0)	$F_{2,233} = 3.37$ ($P < .036$)	$F_{1,233} = 22.4$ ($P < .001$)	NS
Harm avoidance	17.5 (±7.8)	17.9 (±8.5)	17.7 (±7.5)	13.1 (±6.7)	13.5 (±6.3)	11.9 (±5.4)	NS	$F_{1,233} = 29.9$ ($P < .001$)	NS
Reward dependence	14.5 (±3.5)	14.0 (±3.4)	14.4 (±3.7)	16.4 (±4.0)	15.1 (±3.9)	16.2 (±3.8)	NS	NS	NS
Persistence	3.7 (±2.1)	3.5 (±2.1)	3.5 (±1.6)	4.9 (±2.2)	4.5 (±2.2)	3.9 (±2.2)	NS	$F_{1,233} = 4.3$ ($P < .04$)	NS

Mean raw scores and standard deviations (in brackets) are presented.

power = 0.631. Novelty Seeking scores were higher for individuals with the Met/Met genotype in both the dependent and the control groups. Main effect of group status was also significant on NS: $F_{1,233} = 22.442$, $P < .001$, $\eta^2 = 0.088$, power = 0.997. Novelty Seeking scores were higher in the dependent group as compared to controls. The interaction effect of group status and genotypes was not significant. Sex and age covariates had no significant effect. Univariate analyses for the three other TCI scales revealed no significant COMT Val^{158}Met SNP genotype effects. The main effects for group status were significant for HA: $F_{1,233} = 29\,939$, $P < .001$, $\eta^2 = 0.114$, power = 1.000, and P: $F_{1,233} = 4.282$, $P = .040$, $\eta^2 = 0.018$, power = 0.540. Dependents report higher levels of Harm avoidance and lower levels of Persistence. The main effect of the sex covariate was significant for RD only: $F_{1,233} = 13.036$, $P < .001$, $\eta^2 = 0.053$, power = 0.949; the age covariate had no significant effect.

The COMT Val/Val and Val/Met genotype groups showed similar mean raw scores for NS within the dependent as well as the control groups. Thus, Val/Val homozygotes were grouped with the Val/Met heterozygotes to test the effect of "Val present" vs. "Val absent" genotype categories on the TCI NS scale (Fig. 1). Significant main effect of the Val-allele present vs. absent COMT genotypes was observed for the NS scale: $F_{1,235} = 6.703$, $P = .010$, $\eta^2 = 0.028$, power = 0.732. Main effect of group status on NS was also significant: $F_{1,235} = 21.321$, $P < .001$, $\eta^2 = 0.083$, power = 0.996). Interaction effect of group status and genotypes was not significant (effect size was minimal: $\eta^2 = 0.005$). Mean raw NS scores are higher in the dependent group as compared to controls, and NS scores are also higher in the Met/Met genotype group in both opiate dependents and controls. Novelty seeking scores were highest for the 26 dependents with the Met/Met (Val absent) genotype 28.04(±5.37).

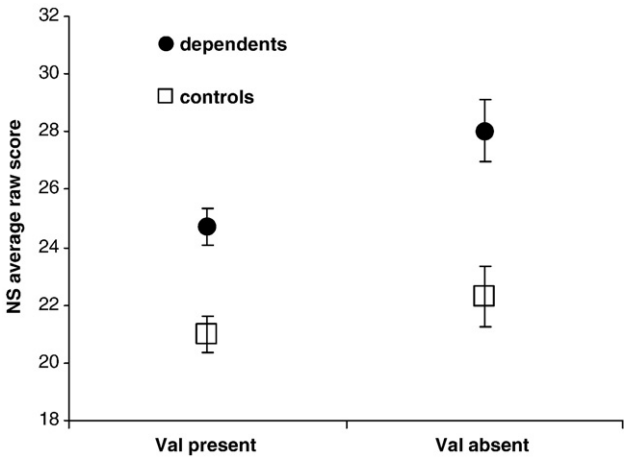

Fig. 1. Effect of group status and the COMT polymorphism on TCI NS scores. Novelty Seeking mean raw scores are presented according to group status vs the COMT grouped genotypes ($P < .001$). The Y-error bars represent ± SE.

4. Discussion

Association between genetic variations of COMT and the risk of drug abuse has been studied by several groups using case control setup, comparing genotype frequencies of the case and control groups. Early results reported association; however, attempts to reproduce these findings in other populations have often failed. Vandenbergh and colleagues [21] showed a higher presence of the Val allele among polysubstance abusers, and Li et al also demonstrated higher frequency of the Val allele among methamphetamine abusers [22]. Horowitz and colleagues [23] showed an increased frequency of the Val allele on a small sample of opiate dependent subjects using a family-based haplotype relative risk strategy; however, they failed to replicate these results on a larger case-control sample possibly due to population stratification. Recently, Oosterhuis and colleagues [24] found an association with opiate dependence, but only in women and the results ceased to be significant after correction for multiple testing. These data suggested the possible role of the Val variant (high activity form resulting in lower synaptic dopamine concentrations), as a genetic risk factor for drug abuse in accordance with the theory of reward deficiency syndrome. This theory assumes that the hypofunction of the mesolimbic dopaminergic system results in a deficiency of the reward mechanism, which, in turn leads to drug seeking behavior, as drugs are activators of dopamine release in the nucleus accumbens [25].

On the other hand, Lohoff et al [26] found an increased frequency of the Met allele (low activity form) in cocaine users. In the present study, results from a case-control analysis is reported (Table 1) with no differences in Val/Met genotype frequencies of the opiate dependent and control group. These conflicting results might derive from the heterogeneous nature of the cases, as well as from the diverse effects of the mesolimbic reward system on dopaminergic functions. It is also important to point out that the effect of a single candidate gene variant is usually very small and it is in interaction with other genetic and environmental factors when shaping behavior [27]. Therefore, the rough distinction of dependent subjects vs. controls and allele present vs. absent might not be refined enough to portray the effect of a single candidate gene. In the present study, we applied a dimensional approach to better understand genetic effects forming temperament dimensions, especially NS, as a main feature of addictive behavior.

In accordance with published results, here we demonstrate that NS score is elevated in the presence of drug-using behavior. Bardo et al [28] suggest that exposure to novelty partly activates the same neural substrate that mediates the rewarding effects of drugs of abuse. Parallel to this assumption, studies have unequivocally shown that the NS dimension of TPQ is one, if not the strongest, predictor of psychoactive substance use, the early onset of substance use, and the intensity of use as well. Wills et al [29] have

proven the role of NS on the onset of substance use, although they also point out that NS leads to substance use by means of other mediating factors [30]. Studies on opiate dependent patients have also confirmed the role of NS in opiate dependence, as subjects addicted to opiates were characterized with higher NS than anorectic men or controls [31]. Opiate-dependent subjects maintained on methadone also scored higher NS than controls according to the results of Cohen et al [32]. Others found a significant increase only in the NS scores among the temperament scales, regardless of the presence of a comorbid personality disorder in a large sample (N = 180) of opiate abusers [33]. In another study [34], opiate dependent patients scored higher on NS than alcoholics or a random population. All these convergent results suggest the dysfunction of the dopaminergic system in case of opiate dependence, supposing that the NS dimension is related to this system, as suggested by Cloninger [35] and others [36].

As one of the main determinants of the dopamine level in the brain is the activity of COMT, especially in the prefrontal cortex, numerous association studies have been performed between the high and low activity COMT genotypes and NS on healthy population; however, results are highly contradictory. Golimbet et al [15] found an association between NS and COMT genotype in a sample of healthy volunteers; however, Tsai et al found the same effect in the opposite direction in a sample of 120 healthy young Chinese females [37], i.e., the highest NS scores were seen among the Val/Val homozygotes. Reuter & Hennig [38], and Hashimoto et al [39] found no association between COMT Val/Met polymorphism and NS in a healthy Japanese sample of 137 persons. Based on results from the present study, NS scores of both control subjects and opiate dependents with the Val allele were lower than scores of those without this allele. As seen on Fig. 1, this difference is more pronounced for dependents. Based on the above results, the COMT effect on personality dimensions might be smaller for healthy people as various compensatory mechanisms may correct the genetic influence. Interpretation of results with respect to healthy controls is further complicated by the fact that studies were carried out on ethnically diverse samples with large differences on the prevalence of the COMT Val allele [40].

On the other hand, Hosak et al [16] recently demonstrated a significant effect of the COMT genotype on NS on a small sample of methamphetamine users (N = 37). Based on our results presented here, we confirmed these findings using a larger sample of opiate dependent patients (N = 117), demonstrating that the effect of COMT on NS is not drug specific. In accordance with previous findings, cases were characterized by higher NS than controls regardless of their genotypes. However, the COMT Val/Met polymorphism also had a significant main effect on NS scores: those individuals without the Val allele (Met/Met homozygous) showed a significantly higher NS score. This difference was more pronounced for opiate users than controls; however, interaction between group status and the COMT Val/Met genotypes was not significant.

Dreher and colleagues [41] have recently pointed out that Met/Met homozygotes show an elevated prefrontal cortical activity during anticipation of uncertain rewards, which can be considered as a neurobiological basis for elevated NS level of opiate users. Here, we hypothesized that, in the presence of Met allele, higher dopamine concentration in the prefrontal cortex [42] overactivates dopamine D1 receptors, which in turn suppress the dopamine release in the nucleus accumbens [43,44]. As NS behavior may enhance dopaminergic neurotransmission in the nucleus accumbens, this might be a compensation for the genetic effects. A similar compensatory mechanism was found in our former study investigating efficiency of methylphenidate treatment in attention deficit hyperactivity disorder (ADHD), demonstrating an association between the Val/Val genotype and good drug response [20].

In conclusion, results of the present study indicate an association between the COMT genotypes and NS in both controls and drug abusers.

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