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Association of the *COMT* Val108/158Met genotype with professional career and education: The Val-allele is more frequent in managers and in enterprising occupations

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ABSTRACT

Catechol-*O*-methyl transferase (COMT) is a key player in neurotransmission by catecholamines, and the functional *COMT* Val108/158Met polymorphism is strongly related to prefrontal reactivity and to dopamine levels. As dopamine is a critically important neurotransmitter in cognition, emotion and motivation, we addressed the potential impact of this genotype on life course by examining its association with being in enterprising professions. The parents ($n = 1410$) of the target subjects in the Estonian Children Personality Behaviour and Health Study reported their current occupation, and those classified as enterprising ($n = 197$; 18%) were compared with the remaining group. Additionally, the subjects self-classified themselves according to the International Standard Classification of Occupations and the group of managers (6.2%) was compared to other groups. We found that the *COMT* Val108/158Met Val/Val homozygotes were overrepresented among enterprising occupations and the Val-allele carriers among self-classified managers. While several measures associated with the Val/Val homozygosity were also associated with enterprising occupation, no simple path from the genotype to enterprising occupations emerged from structural equation models, suggesting that the *COMT* Val108/158Met genotype contributes to choices of profession via multiple interactive features. We also reproduced a previous finding that the *COMT* genotype is associated with educational attainment in a gender-dependent manner.

1. Introduction

Catechol-*O*-methyl transferase (COMT) is an enzyme of major importance in the metabolism of such neurotransmitters as noradrenaline and dopamine. COMT plays a particularly important role with regard to inactivation of dopamine in the prefrontal cortex (Karoum, Chrapusta, & Egan, 1994). A single nucleotide polymorphism in exon 4 of the *COMT* gene results in replacement of valine with methionine in the COMT protein, and this leads to lower activity of the encoded enzyme (Lotta et al., 1995). Because of higher COMT activity, Val/Val homozygotes have 3–4-fold lower presynaptic dopamine levels as compared to the Met/Met homozygotes, and heterozygotes have midway values. Numerous investigations have associated this genetic variation with differences in prefrontal function (e.g., Egan et al., 2001; Mier, Kirsch, & Meyer-Lindenberg, 2010). Dopaminergic neurotransmission is a major regulator of motivation, personality, and behaviour (Depue & Collins, 1999; Ikemoto & Panksepp, 1999) and hence a genetic variation that causes significant differences in dopamine function would be expected to produce major impacts on personal life course. Because both alleles of the *COMT* polymorphism are common, it is likely that the form of expression of their association with major behavioural variables depends strongly on the environment and these factors hinder the detection of any significant associations in small groups or pooled convenience samples (Harro, 2010; Harro & Oreland, 2016). Nevertheless, in unbiased, population-representative samples of sufficient size such associations should become manifest.

We have previously reported that the *COMT* Val108/158Met genotype was associated with educational attainment in a population representative sample of young adults, while this association was strongly dependent on gender (Lehto, Akkermann, Parik, Veidebaum, & Harro, 2013). Herewith we have addressed the question of whether or not the dopamine-related *COMT* Val108/158Met genotype is associated with enterprising occupations in middle-age population. Having found

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a significant association of the genotype with enterprising professions, we next addressed the question of mediating mechanisms, with focus on factors previously shown to be associated with the *COMT* Val108/158Met genotype.

2. Methods

2.1. Study population

We used the data of parents ($n = 1410$; mothers, $n = 831$ and fathers, $n = 579$) of the target subjects of the original Estonian sample of the European Youth Heart Study (1998/99), which was subsequently incorporated into the longitudinal Estonian Children Personality Behaviour and Health Study (ECPBHS). The rationale and procedure of the formation of the target sample have been described elsewhere (Harro et al., 2001). In brief, all schools of Tartu County, Estonia, that agreed to participate (54 of the total of 56) were included into the sampling using the probability proportional to the number of students of the respective age groups in the school, and 25 schools were selected. In 1998/99, all children from grades 3 (younger cohort) and 9 (older cohort) were invited to participate. A written informed consent was received from 79.1% ($n = 1176$) of the invited subjects and their parents. Sixty-two additional subjects joined the study in 2001 during the first follow-up. Parents of the ECPBHS children were invited to become participants themselves and were assessed in 2011–2013. Of the eligible subjects, 68% of the mothers ($n = 831$; mean age 52 years) and 47% of the fathers ($n = 579$; mean age 54 years) participated in the study. Using the national registry we became aware that 4% of the mothers ($n = 51$) and 11% of the fathers ($n = 139$) were dead by the time of sampling. The rest of individuals either were not possible to locate, were living far away, had too serious health problems, served a sentence in prison or refused to participate. This study was approved by the Tartu University Ethics Review Committee on Human Research.

2.2. Classification of occupations

Subjects were asked to classify themselves within 9 groups of occupations according to the International Standard Classification of Occupations (ISCO 08) and Holland RIASEC model (http://www.ilo.org/public/english/bureau/stat/isco/isco08/index.htm). Of those who were employed, the distribution of professions was as follows: Managers (6.2%), Professionals (13.3%), Technicians and Associate Professionals (26.1%), Clerical Support Workers (7.0%), Services and Sales Workers (17.1%), Skilled Agricultural, Forestry and Fishery Workers (2.1%), Craft and Related Trades Workers (12.0%), Plant and Machine Operators and Assemblers (5.0%), Elementary Occupations (11.2%). Participants were also asked to name their occupation, and a researcher experienced in use of ISCO classified them into enterprising occupations (sales managers, managers, chairmen, headteachers, foremen, shopwalkers, store managers etc.; 18%, $n = 197$) and non-enterprising occupations according to Holland Occupational Themes (Holland, 1992), and also according to ISCO into managers and non-managers. Self-classifications were received from 1089 subjects and occupation was reported by 1084 subjects; 196 were not employed, 79 were retired and 3 reported full-time engagement in studies. Comparison of self-classifications and the researcher classification revealed that 14 subjects (5 males, 9 females) were self-classified but not researcher-classified as managers, and 119 subjects (63 males, 56 females) were researcher-classified but not self-classified as managers. It is obvious that the information available for classification was different for the participants themselves and for us, so this mismatch in about 12% of subjects could have been expected. Having learned from this comparison that self-classifications into managerial jobs were not likely to reflect self-enhancement, we used the more conservative self-classification in further analysis, because the subjects themselves, possessing more information, were in a better position for judgement.

2.3. Level of education

The participants were asked to report their current level of education as (1) primary; (2) secondary; (3) vocational; (4) incomplete higher or (5) higher education.

2.4. Psychometric instruments

We examined a variety of measures for their potential to serve as mediators in the association of *COMT* genotype and occupation. The five-factor model of personality was measured by using the EPIP-NEO questionnaire that is a semantically simplified version of the NEO-PI-R (Mõttus, Pullmann, & Allik, 2006). For the measurement of perceived relationships with parents, participants filled out the Estonian-language version (Tulviste & Rohner, 2010) of the Parental Acceptance-Rejection/Control Questionnaire (Adult PARQ/Control (Short Form); Rohner, 2005) about perceptions of behaviours of their mothers and fathers separately. General satisfaction with work was assessed with the relevant questions from the Copenhagen Psychosocial Questionnaire (COPSOQ II; Kristensen, Hannerz, Høgh, & Borg, 2005). The participants were asked how pleased in general they are with (a) their work prospects, (b) the physical working conditions, (c) the way their abilities are used, and (d) their job as a whole, everything taken into consideration. Response scale included the options “very satisfied”, “satisfied”, “un-satisfied” and “very un-satisfied” and responses to each of the four items formed the total sore.

2.5. Genotyping

COMT Val108/158Met genotyping was carried out as previously described (Lehto et al., 2013). All participants who provided a DNA sample (mothers, $n = 829$, fathers, $n = 572$) were successfully genotyped, and genotypes were in the Hardy-Weinberg equilibrium. Genotype frequencies are shown in Table 1.

2.6. Statistical analysis

The chi-square test was used to assess distribution of occupations and education levels genotype-wise. PARQ scores in subjects with different genotypes were analyzed with the Mann-Whitney *U* test, and personality scores with one-way ANOVA and post hoc comparisons by Fisher's LSD tests. Correlations were assessed by the Spearman method. Multiple analysis of variance (MANOVA) was carried out to detect possible two-way interactions between genotype and occupation in regard to satisfaction with occupation, with subsequent Mann-Whitney *U* tests. For fitting of the path model we used the AMOS package of structural equation modeling (SEM), with the ADF (asymptotically distribution free) estimation with simple covariances for SEM. Genotype was entered into the SEM model as dichotomous variable: Val/Val homozygotes vs. Met-allele carriers. For validation of the model we used Bayesian model by MCMC (Markov chain Monte Carlo) method with probit model for binary variables. The results appeared to be very similar to the AMOS ADF model. We also conducted multigroup structural equation modeling including gender, and found that there was acceptable configural invariance (similarity of effect pattern) of female and male models, but structural weights, covariances and residuals were not identical. Hence we decided to present the same conceptual model estimated separately for males and females.

Table 1
COMT Val158Met genotype frequencies in mothers and fathers of the ECPBHS children, in total and separately in both birth cohorts. In parentheses, the number of subjects.

	Met/Met	Val/Met	Val/Val
Mothers	30% (251)	48% (398)	22% (180)
Fathers	29% (168)	49% (278)	22% (126)

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