

To: **Personality and Individual Differences**

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

Authors:

Triin Kurrikoff [a](#), Katrin Kaarma [b,c](#), Liina-Mai Tooding [a](#), Mariliis Vaht [b](#), Tiia Tulviste [d](#),
Toomas Veidebaume [e](#), Jaanus Harro [b,*](#)

[a](#) Institute of Social Studies, University of Tartu, Lossi 36, 51003 Tartu, Estonia

[b](#) Division of Neuropsychopharmacology, Department of Psychology, University of Tartu, Ravila 19A, 50411 Tartu, Estonia

[c](#) Psychiatry Clinic, North Estonia Medical Centre, Paldiski 52, 10614 Tallinn, Estonia

[d](#) Division of Developmental Psychology, Department of Psychology, University of Tartu, Näituse 2, 50409 Tartu, Estonia

[e](#) National Institute for Health Development, Hiiu 42, 11619 Tallinn, Estonia

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.

Keywords

Dopamine; *COMT*; Val158Met genotype; Enterprising occupation; Education; Family relations; Personality; Job satisfaction

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 and 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, Vidgren, Tilgmann, Ulmanen, Melén, Julkunen and Taskinen, 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, Goldberg, Kolachana, Callicott, Mazzanti, Straub, Goldman and Weinberger, 2001; Mier, Kirsch and Meyer-Lindenberg, 2010). Dopaminergic neurotransmission is a major regulator of motivation, personality, and behaviour (Depue and Collins, 1999; Ikemoto and 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 and Orelund, 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 and 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 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, Eensoo, Kiive, Merenäkk, Alep, Orelund and Harro, 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 (Möttus, Pullmann and Allik, 2006). For the measurement of perceived relationships with parents, participants filled out the Estonian-language version (Tulviste and 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 and 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”, “unsatisfied” and “very unsatisfied” and responses to each of the four items formed the total score.

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.

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) |

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.

3. Results

According to the Holland classification, a significantly higher proportion of Val/Val homozygotes were in an enterprising occupation as compared to the Met-allele carriers (22.4%, n=55 vs. 16.8%, n=139; $\chi^2=3.94$; df=1; p=0.047). This difference was mostly derived from the male subjects (31.4% vs. 22.4%), as the difference between proportions in females (15.5% vs. 13.4%) was minor. Regarding self-classification according to ISCO, a higher proportion of Val-allele carriers as compared to the Met/Met homozygotes had reported themselves as managers (7.3%, n=55 vs. 3.4%, n=11; $\chi^2=5.92$; df=1; p=0.015). While there were more male managers, proportionally the difference was similar in males and females (males, 12.1% vs. 5.8%; females, 4.0% vs. 2.0%). No other genotype difference between self-classified occupations was found. After these results were obtained we also examined the genotype prevalence in the occupationally least active group of participants, the retired subjects and those not currently employed, added together. While the numbers were small, a trend toward genotype effect was found among males for the Val/Val homozygotes to be the least frequently out of the job market (Val/Val, 16.4%, Val/Met, 23.2%, Met/Met, 27.3% of those with the respective genotype; $\chi^2=4.72$; df=2; p=0.094).

We next attempted to identify the mediating mechanisms that could facilitate higher proportion of Val/Val homozygotes undertaking an enterprising occupation. In this sample the *COMT* Val108/158Met genotype was not associated with five-factor personality, although a non-significant trend was found for Met-allele homozygotes to have lower neuroticism (data not shown). Nevertheless, because subjects in enterprising occupations had higher scores of extraversion, openness to experience and agreeableness (data not shown), these personality traits were added to the structural equation model. While extraversion contributed to working in enterprising occupation directly in the final model (Figure 1), and openness to experience through higher education, none of the personality traits appeared to mediate the significant association between the *COMT* genotype and enterprising occupation.

While the *COMT* Val108/158Met genotype did not interact with enterprising occupation in relation to recalled relationships with either mother or father, subjects in enterprising positions had enjoyed significantly better relationship both with their mothers and fathers in childhood (Table 2). Somewhat similarly, subjects who worked as managers had had better relationships with their mothers and a trend toward better relationships with fathers. In males, *COMT* Val/Val homozygotes had had better relationship with their mother than the Met-allele carriers, while in females the Met/Met homozygotes had had better relationship (Figure 2). Better relationship with mothers in the past was positively associated with being in an enterprising position, mostly in males, but it was not mediating the *COMT* genotype effect (Figure 1).

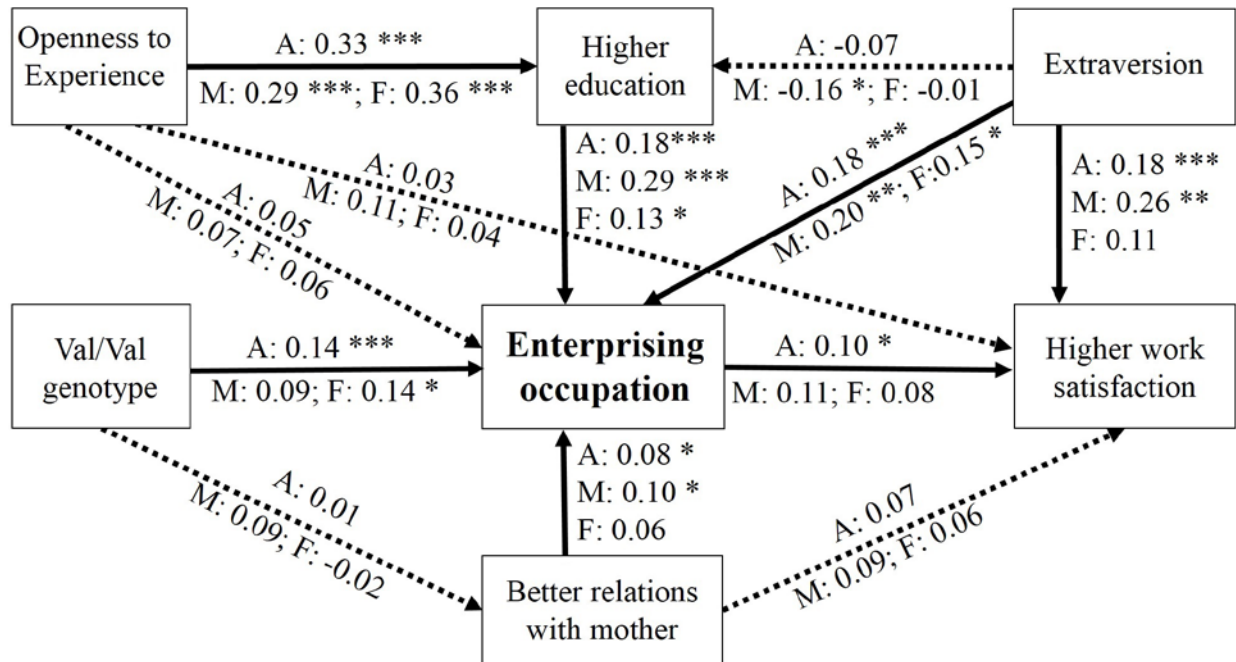


Figure 1. A structural equation model of the relationship between COMT Val108/158Met genotype and enterprising occupation, and a number of additional variables. Results are given separately for males (M) and females (F) and all subjects (A) as standardized direct effects * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Bold arrows present significant standardized direct effects for all subjects. The value of root mean square error of approximation (RMSEA) was smaller than 0.06 for all groups and the comparative fit index (CFI) was 0.94 or higher.

Table 2. Relationship with mother and father, being in enterprising or managerial occupation, and satisfaction with work.

| | All subjects | Males | Females |
|--|----------------------------------|----------------------------------|---------------------------------|
| Relationship with mother | | | |
| Enterprising occupation vs. other occupations | 105.1 (15.9) vs. 99.1 (20.0) *** | 106.8 (14.4) vs. 100.6 (18.6) ** | 103.0 (17.6) vs. 98.3 (20.6) |
| Managers vs. other positions | 108.6 (11.6) vs. 99.8 (19.6) ** | 109.9 (8.4) vs. 101.4 (18.4) * | 106.2 (15.9) vs. 98.8 (20.1) |
| Relationship with father | | | |
| Enterprising occupation vs. other occupations | 103.3 (16.5) vs. 99.1 (19.0) * | 102.8 (13.7) vs. 98.9 (17.1) | 103.9 (19.3) vs. 99.3 (19.9) * |
| Managers vs. other positions | 105.9 (12.2) vs. 100.0 (18.7) | 104.1 (12.1) vs. 99.7 (16.8) | 110.1 (11.7) vs. 100.2 (19.7) * |
| Correlation of work satisfaction with relationship with parents | | | |
| Relationship with father | $r = 0.17$ * | $r = 0.10$ | $r = 0.21$ * |
| Relationship with mother | $r = 0.11$ * | $r = 0.13$ * | $r = 0.09$ * |

Mean and Standard Deviation of the PARQ scores in parentheses; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ with Mann-Whitney U-Test or Spearman correlation analysis.

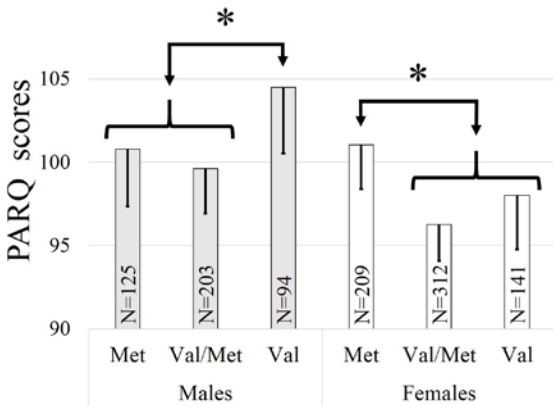


Figure 2. Relationship with mothers by gender and COMT Val108/158Met genotype. * $p < 0.05$, Mann-Whitney U-test.

Subjects, who worked in an enterprising occupation or as a manager were more satisfied with their work (12.1 ± 2.0 vs. 11.4 ± 2.0 ; $p < 0.0001$ and 12.4 ± 1.9 vs. 11.5 ± 2.0 ; $p < 0.001$, respectively, Mann-Whitney U-tests). Satisfaction with work was in positive correlation with relations with parents (Table 2), whereas relationship with fathers appeared more important for females. Next we examined the general satisfaction with their work in subjects in enterprising and in all other occupations in association with the COMT genotype. Subjects in enterprising occupation were significantly more satisfied with their work [$F(1,862)=19.0$; $p < 0.001$]. While ANOVA for an overall genotype effect missed the conventional level of significance [$F(1,862)=3.71$; $p=0.055$], separate analysis of males suggested that male Val/Val homozygotes in enterprising occupations were more satisfied with their work than Met-allele carriers, while in Met-allele carriers being in enterprising occupation was not associated with higher work satisfaction [genotype and occupation interaction $F(1,330)=4.61$; $p=0.032$; Figure 3]. This interaction between genotype and occupation was not present in females.

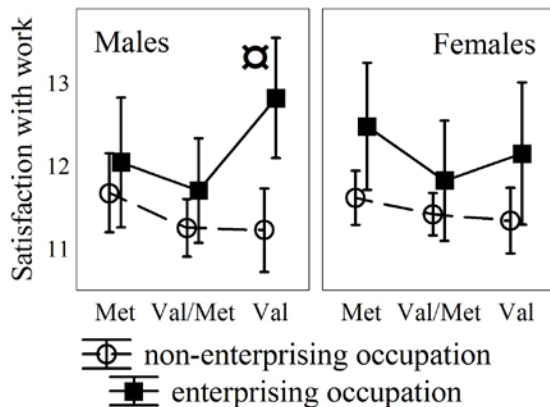


Figure 3. Work satisfaction by COMT Val108/158Met genotype and gender. COMT Val/Val homozygous males, who working in enterprising occupations had the highest satisfaction with their work. $\alpha p < 0.05$ different from all male Met-allele carriers in enterprising occupations.

Educational attainment was not significantly different between the total genotype groups, but there was a difference between male and female *COMT* Val/Met heterozygotes with regard to prevalence of higher education: While male Val/Met heterozygotes had attained higher education, either completed or incomplete, with the lowest frequency, the opposite was true for the female Val/Met heterozygotes (Table 3).

Table 3. Attainment of higher education by *COMT* Val158Met genotype and gender. In parentheses, the number of subjects.

| | Met/Met | Val/Met | Val/Val |
|--|----------------|-------------------|----------------|
| Higher (including incomplete higher) education | | | |
| Total | 42% (172) | 41% (269) | 40% (121) |
| Males | 39% (65) | 36% (98)* | 41% (51) |
| Females | 43% (107) | 44% (171) | 40% (70) |
| Complete higher education | | | |
| Total | 36% (149) | 36% (238) | 34% (101) |
| Males | 31% (51) | 31% (84) † | 35% (44) |
| Females | 40% (98) | 40% (154) | 33% (57) |

* Chi-square = 4.44, df=1, p=0.04 different from heterozygous females with higher (including incomplete higher) education;

† Chi-square = 5.54, df=1, p=0.02 different from heterozygous females with complete higher education.

4. Discussion

The main novel finding in the reported analysis is that in general population, the *COMT* Val108/158Met genotype is associated with enterprising occupations: The Val/Val homozygotes, with presumably the highest activity of dopaminergic neurotransmission, were more often in professions considered enterprising, and Val-allele carriers self-reported themselves as in managerial position more frequently. This finding suggests that the *COMT* genotype is a critically important factor in choice of work area, and this association appears independent of several potentially contributing factors, including education, while we reproduced in a new sample our earlier finding that *COMT* Val108/158Met genotype is associated with educational attainment.

We had the hypothesis that because dopaminergic neurotransmission is positively associated with active behaviours, the *COMT* Val108/158Met Val-allele carriers, and in particular the Val/Val homozygotes could be more frequently found in managerial and enterprising

occupations. This was indeed the case in this sample that fairly well represents general population of a geographic region. As the numbers of self-categorized managers were low in the sample, in further analysis we focused on the group of enterprising occupations categorized as suggested by Holland (1992). Several variables hypothetically related to the *COMT* genotype and working in enterprising occupation were examined and found to be significantly associated with either or both, but none appeared to significantly mediate the genotype effect alone or in the given combination.

We had previously reported that in the older birth cohort of the ECPBHS the *COMT* Val108/158Met genotype was associated with neuroticism in a gender-dependent manner, the Val/Val homozygous females developing higher neuroticism by young adulthood (Lehto et al., 2013). It is conceivable that people select jobs appropriate for their personalities (Kristof, 1996), and entrepreneurship is a more appropriate occupation for some personalities than for others (Baron and Markman, 2004; Zhao, Seibert and Lumpkin, 2010). In this adult sample of the parents of the ECPBHS subjects no significant association between the genotype and personality was found. This is hardly surprising given that across many samples the *COMT* Val108/158Met genotype has not been in consistent association with personality, including Extraversion (Balestri, Calati, Serretti and De Ronchi, 2014; Montag and Reuter, 2014). However, in some studies using the Multidimensional Personality Questionnaire (Hamidovic, Dlugos, Palmer and de Wit, 2010) or NEO-FFI (Hoth, Paul, Williams, Dobson-Stone, Todd, Schofield, Gunstad, Cohen and Gordon, 2006), the *COMT* Val/Val homozygotes have been reported as more extravert, and the reasons why this association differs across samples is worth of closer examination in future.

The meta-analysis of Zhao et al. (2010) concluded that extraversion and openness to experience have an association with entrepreneurial performance and we could observe an association of these traits with being in enterprising occupation, while these occupational traits are far from overlapping. Nevertheless, personality traits were not found to mediate the association between the *COMT* Val108/158Met genotype and the occupation. It has been reported that *COMT* Val/Val homozygotes have higher scores specifically in the agency component of extraversion – the one including social dominance, assertiveness, activity, being exhibitionistic, and having a sense of accomplishing goals (Wacker, Mueller, Hennig and Stemmler, 2012). Nevertheless, in our sample the *COMT* Val108/158Met genotype was not associated with similar traits covered as subscales of Extraversion, that is Activity, Assertiveness and Positive emotion (data not shown).

Parental warmth was reported to facilitate the performance of the *COMT* Val/Val homozygotes in the Iowa Gambling Task (He, Xue, Chen, Lu, Chen, Lei, Liu, Li, Zhu, Moyzis, Dong and Bechara, 2012). In our sample the *COMT* genotype was associated with relationship with mothers in a gender-specific manner. Perceived better relationship with mother was predictive of enterprising occupation, especially for males, and in males there was a tendency for contribution to mediation of the genotype effect that should be further explored in other

samples. Male Val/Val homozygotes in enterprising occupations was the group with the highest work satisfaction, but this association could not be shown to explain the genotype effect on occupation. Recent research suggesting a critical role for dopamine in social attachment (Feldman, 2017) opens another avenue for understanding the mechanisms how could the *COMT* genotype shape life choices but addressing this would require additional information that we do not possess at present.

Hence, while we could find evidence supporting our hypothesis that the Val-allele of the *COMT* Val108/158Met genotype promotes engagement in enterprising occupations, the mediating mechanisms remain to be elucidated. It is conceivable that the genotype, via its impact of dopaminergic neurotransmission, contributes to and interacts with a number of different variables that predict enterprising occupation, and these combinations of factors, while leading to a similar outcome, are multiple and co-vary with the individual's environment(s) (Harro and Kiive, 2011). This would make it necessary to explore alternative hypotheses and to use hierarchical and dynamic modeling to detect the genotype effect on any coping strategy.

We have previously found the *COMT* genotype associated with obtaining university education in the ECPBHS but dependent on gender (Lehto et al., 2013): The male and female Val/Met heterozygotes had large differences by age 25 in their level with education, the Val/Met females having most frequently of all groups completed university education, while in Val/Met males this was the least frequent. Education did not mediate the *COMT* genotype association with enterprising occupation but it was directly contributing to it, and interestingly more so in males. It was also found in this middle-age sample that *COMT* Val/Met heterozygous females had higher education than other females, and male heterozygotes had the least experience of university. Because the heterozygotes have intermediate dopaminergic activity that could be thought of the optimal middle ground for survival strategies, the possibility might be considered that in the socio-cultural circumstances characteristic to Estonia, and possibly to the CCEE as a whole, a preferred strategy for females has been to strive toward university education but for males to pursue other career options. It may be worth of attention that while in females extraversion did not play a role in obtaining university education, it was a negatively associated factor for males. In any case, the genotypic pattern in higher education is present for at least two generations in this geographic area, a finding that may have implications to the understanding of the gender aspect of gene-environment interaction.

A limitation of the presented approach is that the category of enterprising occupations is obviously fairly heterogenous. Nevertheless, if association of this occupational category with the biological variable is related to the essence of the construct, certain degree of heterogeneity may be an advantage when re-examining the association in samples with different nature and facilitate reproduction of the finding. This however remains to be attempted.

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