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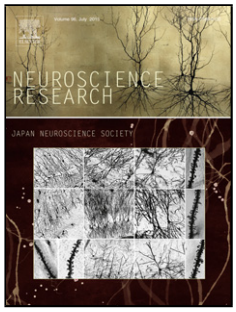


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# *Sex Moderates the Association Between the COMT Val158Met Single-Nucleotide Polymorphism and Disorderliness Facet of Novelty Seeking*

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## Highlights

- The *COMT* Val[158]Met polymorphism is significantly associated with the disorderliness facet of novelty seeking (NS4)
- Sex is a moderator of the association between COMT enzyme activity and NS4 scores
- Females scoring high on the NS4 show lower COMT enzyme activity and persistence scores, and greater attention abilities
- Males scoring high on the NS4 show higher absorption and lower persistence scores
- *COMT* genotype has no effect on measures of attention and hypnotic suggestibility

## Summary

Polymorphisms in dopamine system genes are associated with personality traits and cognitive performance; however, inconsistent results were provided on the involvement of Val[158]Met polymorphism of the catechol-O-methyltransferase gene. In the present study, the following tests were administered to a group of Italian university students: the Temperament/Character Inventory–Revised, the Differential/Attention Processes Inventory, the Tellegen Absorption Scale, and the Waterloo–Stanford-Group Scale of Hypnotic Susceptibility. While the *COMT* Val[158]Met polymorphism was significantly associated with the disorderliness facet of novelty seeking, in a

gender-dependent manner, no association with attention and/or hypnotic suggestibility measures was found. These results provide additional evidence of a gender-specific influence on the gene–behaviour association.

**Keywords:** *COMT*; gene polymorphism; dopamine; personality traits; novelty seeking; attentional characteristics; hypnotic suggestibility.

Polymorphism variants of the dopaminergic system are involved in various aspects of cognition and personality traits. The functional Val$^{158}$Met polymorphism of the *catechol-O-methyltransferase* (*COMT*) gene plays a key role in determining *COMT* and dopamine activity in the prefrontal cortex (PFC). This polymorphism results in fourfold *COMT* activity and the lowest extracellular dopamine levels in the PFC among homozygous, Val allele carriers, compared to Met allele carriers (Dickinson & Elvevåg, 2009). Accordingly, it could be predicted that the *COMT* gene polymorphism influences multifaceted personality dimensions, reflecting individuals' tendencies concerning rewards, approach-related behaviours, and various components of high-order cognitive processes (DeYoung, 2013).

This research was conceived to study the associations between dopaminergic activity in the PFC (as estimated by the level of *COMT* activity) and personality traits, using a multivariate approach and hypothesising that sex may play an important role in modulating personality traits and gene associations (e.g., Chen et al., 2011; Harrison & Tunbridge, 2008). Cloninger's model posits that personality traits are complex and have multiple dimensions and that dopaminergic activity specifically modulates novelty seeking (NS) behaviours (Cloninger & Przybeck, 1993); moreover, high sensation seekers have a greater focused attention ability compared to low sensation seekers (e.g., Ball & Zuckerman, 1992), suggesting that the former may have lower *COMT* enzyme activity. In light of this, we investigated which of the NS behavioural (i.e., exploratory excitability, impulsiveness, extravagance, and disorderliness) and attentional characteristics (i.e., hypnotic suggestibility, absorption, extremely focused attention, moderately focused attention, dual attention

cognitive–cognitive, and dual attention physical–cognitive) are influenced by *COMT* activity. Via separate exploratory multivariate regression analyses on the whole sample and on male/female groups, the researchers also sought to determine the predictive value of personality traits and attentional characteristics on the NS facet that is significantly associated with *COMT* activity.

In the present study, participants consisted of 199 genetically unrelated Caucasian university student volunteers of Italian origin (117 females; $M_{age}$ = 21.21, *SD* = 4.28; 82 males: $M_{age}$ = 22.79, *SD* = 2.91) who had no history of psychiatric or neurological disorders and were medication-free.

Participants were tested in groups of five to ten individuals by administering the following questionnaires in a counterbalanced order:

- *Temperament and Character Inventory-Revised test* (TCI-R; Cloninger, 1999), measuring four dimensions of temperament: Persistence (PS), Novelty Seeking (NS), Reward Dependence (RD), and Harm Avoidance (HA). We specifically examined the following NS facets: Exploratory Excitability (NS1), Impulsivity (NS2), Extravagance (NS3), and Disorderliness (NS4). In this study, NS, PS, RD, and HA exhibit a strong internal consistency (Cronbach's α = 0.80, 0.91, 0.85, 0.89, respectively).
- *Differential Attention Processes Inventory* (DAPI; Crawford et al., 1993), assessing individual differences in focused and dual attention such as Extremely (DAPI1) and moderately (DAPI2) Focused Attention; Dual Attention Cognitive-Cognitive (DAPI3); Dual Attention Physical-Cognitive (DAPI4). In this study, DAPI1, DAPI2, DAPI3, and DAPI4 exhibit a good internal consistency (Cronbach's α = 0.81, 0.86, 0.83, and 0.72, respectively).
- *Tellegen Absorption Scale* (TAS) reduced version, measuring the personality/cognitive construct of absorption (Tellegen & Atkinson, 1974). In the present study, we used a reduced version of the TAS, which is comprised of the first 7 items reported in the original paper (Tellegen & Atkinson, 1974). We choose to use this version of the TAS based on the results of our previous studies. Indeed, while we did not find a significant association between the original version of the TAS and hypnotic suggestibility (e.g., Scacchia & De Pascalis, 2020), the

association resulted significant when the 7-item version of the TAS was used (e.g., De Pascalis, Ray, Tranquillo, & D'Amico, 1998). In this study, the TAS exhibits a good internal consistency (Cronbach's α = 0.71).

Afterwards, the participants were administered the *Waterloo–Stanford Group Scale of Hypnotic Susceptibility, Form C* (WSGC; Bowers, 1993), with which they self-rated their responses to hypnotic suggestions. In this study, the WSGC exhibits a good internal consistency (Cronbach's α = 0.66).

*COMT* genotype frequencies within female (27 Met/Met, 53 Val/Met, 37 Val/Val) and male (16 Met/Met, 41 Val/Met, 25 Val/Val) groups (Mione et al., 2015) fell within the Hardy–Weinberg equilibrium (females: $\chi^2 = 0.89$, $p = 0.34$; males: $\chi^2 = 0.01$, $p = 0.91$). No sex differences in genotype distribution were observed ($\chi^2 = 0.53$, $p = 0.77$). Males were significantly older than females ($t = 2.51$, $p = 0.01$, 95% CI [0.28, 2.39]). To estimate the minimum detectable effect size with $N = 199$, $\alpha = 0.05$ and $1\text{-}\beta = 0.80$, the researchers performed a power analysis using the G*Power 3 software (Faul et al., 2007). For a two-way analysis of variance (ANOVA) (i.e., Sex [Male, Female] * *COMT* [Met/Met, Val/Met, Val/Val]), the minimum effect size for detecting a reliable main *COMT* effect and *COMT*-by-sex interaction effect on the attention/personality measures was $d = 0.44$.

Separate two-way analyses of variance (ANOVAs) were used to test the main and interaction effects of sex and COMT on the attention/personality measures. To control for Type I error, the permutation test (9999 random replicates) was computed to estimate p-values for each ANOVA (e.g., Camargo et al., 2008). Indeed, this method resamples the total number of observations for certain times (in this study, 9999 times) to estimate the regression coefficient in each shuffled sample and the probability of the estimated regression coefficients being greater than the observed regression coefficient (i.e., permutation p). Thus, the adjusted p-values < 0.05 were considered statistically significant. Post-hoc permutation t-test was computed to better specify the results. In addition, we performed Cohen's d effect size using the Hedges' g correction (Hedges & Olkin, 1985), which produces an unbiased effect size estimate.

Descriptive statistics and separate two-way ANOVAs evaluating the effects of sex, *COMT*, and their interaction on the attention/personality measures are displayed in Table 1.

**Table 1**

*Descriptive Statistics and Separate Two-Way Analyses of Variance (ANOVAs) on Attention/Personality Measures.*

| Attention/Personality Measures | Sex | Met/Met *M* (*SD*) | Val/Met *M* (*SD*) | Val/Val *M* (*SD*) | Sex Effect *F* | *COMT* Effect *F* | *COMT* *Sex *F* |
|---|---|---|---|---|---|---|---|
| **WSGC** | Female | 5.33 (2.15) | 5.42 (2.45) | 5.50 (2.60) | 1.40 | 0.17 | 0.33 |
| | Male | 6.25 (1.81) | 5.60 (2.63) | 5.96 (2.26) | | | |
| **TAS** | Female | 14.77 (5.08) | 13.11 (4.41) | 13.38 (4.54) | 0.36 | 0.93 | 3.56 |
| | Male | 11.94 (4.72) | 14.49 (4.95) | 11.84 (3.94) | | | |
| **DAPI1** | Female | 47.15 (10.88) | 43.51 (8.27) | 45.38 (11.41) | **6.29*** | 1.87 | 0.51 |
| | Male | 44.44 (6.80) | 41.15 (10.46) | 39.84 (9.65) | | | |
| **DAPI2** | Female | 33.33 (8.60) | 34.43 (7.40) | 33.03 (9.80) | 0.35 | 0.72 | 0.09 |
| | Male | 33.44 (8.55) | 33.66 (8.06) | 31.72 (7.56) | | | |
| **DAPI3** | Female | 10.52 (4.64) | 11.17 (4.29) | 10.70 (4.92) | 0.45 | 1.22 | 0.47 |
| | Male | 10.19 (4.29) | 11.22 (4.29) | 9.36 (3.43) | | | |
| **DAPI4** | Female | 27.48 (3.96) | 26.36 (3.64) | 26.32 (4.78) | 2.48 | 0.51 | 0.82 |
| | Male | 25.25 (4.54) | 26.15 (4.86) | 24.96 (4.77) | | | |
| **PS** | Female | 120 (17.60) | 121.30 (14.88) | 118.19 (17.30) | **5.19*** | 0.08 | 0.89 |
| | Male | 111.62 (24.94) | 113.22 (20.12) | 117.40 (14.63) | | | |
| **NS** | Female | 108.55 (12.51) | 101.40 (12.35) | 100.62 (10.15) | 0.01 | 2.44 | 1.98 |
| | Male | 102.56 (9.74) | 102.39 (13.65) | 103.92 (8.98) | | | |
| **NS1** | Female | 32.37 (3.69) | 32.02 (5.23) | 31.16 (5.77) | 0.75 | 0.29 | 0.30 |
| | Male | 32.50 (4.55) | 32.32 (4.64) | 32.56 (3.35) | | | |
| **NS2** | Female | 24.44 (5.37) | 22.85 (4.79) | 22.59 (5.08) | 2.17 | 1.58 | 0.11 |
| | Male | 22.94 (3.71) | 21.93 (4.60) | 22 (3.45) | | | |
| **NS3** | Female | 28.59 (5.97) | 26.26 (4.67) | 27.11 (4.36) | 1.48 | 2.35 | 1.91 |
| | Male | 25.44 (4.29) | 25.27 (6.02) | 28.08 (5.57) | | | |
| **NS4** | Female | 23.37 (4.51) | 20.26 (3.17) | 19.76 (3.71) | **6.86**** | **5.89**** | **5.16*** |
| | Male | 21.69 (2.75) | 22.88 (3.55) | 21.28 (3.31) | | | |
| **RD** | Female | 100.41 (14.76) | 104.28 (12.01) | 99.43 (16.30) | 0.06 | 2.94 | 0.39 |
| | Male | 96.06 (16.57) | 104.22 (16.55) | 100 (11.49) | | | |
| **HA** | Female | 102.74 (14.84) | 102.74 (14.85) | 105.62 (17.85) | **9.57**** | 0.05 | 0.57 |
| | Male | 96.44 (13.99) | 97.41 (17.85) | 94.64 (17.18) | | | |

*Note.* WSGC = Waterloo-Stanford Group Scale of Hypnotic Susceptibility, Form C; TAS = Tellegen Absorption Scale; DAPI1 = Extremely Focused Attention; DAPI2 = Moderately Focused Attention; DAPI3 = Dual Attention Two Cognitive; DAPI4 = Dual Attention Physical and Cognitive; PS = Persistence; NS = Novelty Seeking (NS consists of the following four subscales: NS1 = Exploratory Excitability; NS2 = Impulsivity; NS3 = Extravagance; NS4 = Disorderliness); RD = Reward Dependence; HA = Harm Avoidance.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; † $p < 0.0001$ (all the $p$-values were corrected using 9999 random permutations).

For the NS4 scores, we found significant effects for sex ($\eta^2 = 0.031$, $d = 0.36$), *COMT* genotype ($\eta^2 = 0.053$, $d = 0.47$) and their interaction ($\eta^2 = 0.047$, $d = 0.44$) (**Figure 1**).

A post hoc permutation *t*-test revealed that, when participants were stratified by:

- sex, males showed higher NS4 scores than females ($t = 2.51$, $p = 0.01$, 95% CI [0.28, 2.39]; $g = 0.36$).

- *COMT* genotype, Met/Met homozygous participants showed higher NS4 scores than Val/Val individuals ($t$ = 3.17, $p$ = 0.002, 95% CI [0.89, 3.86]; $g$ = 0.63).
- Sex and *COMT*, Met/Met females showed significantly higher mean scores for NS4 compared to Val/Met ($t$ = 3.58, $p$ = 0.0005, 95% CI [1.38, 4.83]; $g$ = 0.85) and Val/Val females ($t$ = 3.51, $p$ = 0.0008, 95% CI [1.55, 5.67]; $g$ = 0.89). Heterozygous males showed significantly higher NS4 scores than heterozygous females ($t$ = 3.76, $p$ = 0.0003, 95% CI [1.23, 3.99]; $g$ = 0.78). However, no genotype effects were found among only the male subjects.

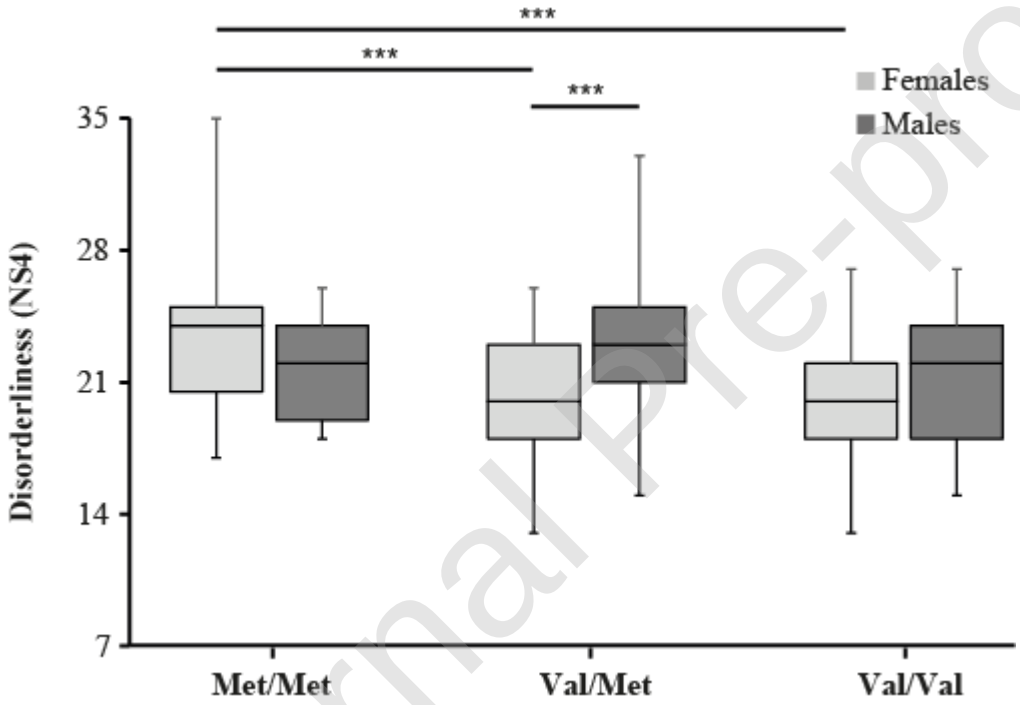


***Figure 1: Disorderliness facet of novelty seeking sum scores (NS4) are presented separately for sex and COMT Val$^{158}$Met polymorphism****. Values are represented as median (central mark of the box) and quartiles (the bottom and the top of the box represented the first and the third quartile, respectively). The whiskers are error bars. Post-hoc permutation t-test revealed that Met/Met females showed significantly higher mean scores on the NS4 compared to others female genotypes. In addition, females showed significantly lower mean scores in the Val/Met genotype compared to males. No genotype effect was found in males.*

** p < 0.05; ** p < 0.01; *** p < 0.001; † p < 0.0001 (all the p-values were corrected using 9999 random permutations).*

Our results also indicate that females had higher scores than males on the DAPI1 ($t$ = 2.50, $p$ = 0.01,

95% CI [0.75, 6.35]; $g$ = 0.36), PS ($t$ = 2.29, $p$ = 0.02, 95% CI [0.81, 10.86]; $g$ = 0.33), and HA ($t$ = 3.11, $p$ = 0.003, 95% CI [2.67, 11.87]; $g$ = 0.45). No other significant effects of *COMT* and *COMT*-by-sex interaction were found on the attention/personality measures ($p > 0.05$) (**Table 1**).

As the F-test for homogeneity of group variances for the measures between (a) male and female groups and (b) male and female participants stratified into Met/Met, Val/Met, Val/Val groups, was significant for only NS1 scores (no significant differences were found for other measures, demonstrating the homogeneity of group variances), our findings cannot be related to the different SDs between the two sexes**.**

To assess how strictly NS4 is related to the *COMT* genotype and can be predicted by other personality/attention measures, we used a set of tests to deal with the problem of multicollinearity as in Lichtenberg et al. (2004). To this aim, we first conducted a Pearson's correlation analysis between attention/personality measures (**Table 2**). The significance of these correlations was assessed by performing 9999 random permutations. Each zero-order correlation coefficient with an adjusted p-value < 0.05 was considered statistically significant.

**Table 2**

*Pearson's Correlation Coefficients Between Attention/Personality Measures for All Participants.*

| | TAS | DAPI1 | DAPI2 | DAPI3 | DAPI4 | PS | NS | NS1 | NS2 | NS3 | NS4 | RD | HA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WSGC** | **0.23**** | **0.14*** | -0.08 | -0.10 | -0.07 | -0.02 | 0.01 | -0.01 | -0.07 | 0.08 | 0.01 | 0.11 | 0.11 |
| **TAS** | - | **0.44†** | 0.05 | 0.04 | **0.27***** | 0.12 | **0.16*** | 0.12 | -0.01 | 0.05 | **0.26***** | **0.14*** | 0.06 |
| **DAPI1** | | - | 0.05 | 0.05 | 0.13 | 0.02 | 0.12 | 0.09 | 0.10 | 0.05 | 0.05 | -0.09 | **0.17*** |
| **DAPI2** | | | - | **0.62†** | **0.32†** | **0.23**** | -0.09 | 0.04 | -0.05 | **-0.18*** | -0.02 | **-0.18*** | -0.14 |
| **DAPI3** | | | | - | **0.22**** | **0.18*** | -0.13 | -0.05 | 0.01 | **-0.22**** | -0.05 | **-0.18**** | -0.04 |
| **DAPI4** | | | | | - | **0.18*** | **0.16*** | **0.26***** | 0.01 | -0.01 | **0.19**** | **0.15*** | -0.12 |
| **PS** | | | | | | - | **-0.16*** | 0.09 | **-0.15*** | -0.13 | **-0.23**** | 0.03 | **-0.31†** |
| **NS** | | | | | | | - | **0.62†** | **0.70†** | **0.70†** | **0.55†** | **0.28***** | **-0.34†** |
| **NS1** | | | | | | | | - | **0.24**** | **0.17*** | **0.15*** | **0.40†** | **-0.41†** |
| **NS2** | | | | | | | | | - | **0.32†** | **0.21**** | 0.05 | **-0.20**** |
| **NS3** | | | | | | | | | | - | **0.21**** | **0.17*** | -0.07 |
| **NS4** | | | | | | | | | | | - | 0.05 | **-0.21**** |
| **RD** | | | | | | | | | | | | - | **-0.15*** |

*Note*. WSGC = Waterloo-Stanford Group Scale of Hypnotic Susceptibility, Form C; TAS = Tellegen Absorption Scale; Differential Attention Processes Inventory: DAPI1 = Extremely Focused Attention; DAPI2 = Moderately Focused Attention; DAPI3 = Dual Attention Two Cognitive; DAPI4 = Dual Attention Physical and Cognitive. Temperament-Character Inventory, Revised: PS = Persistence; NS = Novelty Seeking (NS consists of the following four subscales: NS1 = Exploratory Excitability; NS2 = Impulsivity; NS3 = Extravagance; NS4 = Disorderliness); RD = Reward Dependence; HA = Harm Avoidance.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; † $p < 0.0001$ (all the $p$-values were corrected using 9999 random permutations).

Then, since correlated measures may affect the multiple regression analyses (Tabachnick & Fidell, 2007), we evaluated the multidimensional relationships between attention/personality measures by using standardized individual factor scores as derived by the varimax-rotated factor-loading matrix of principal component analysis. This method derives factors that are orthogonal and uncorrelated to each other (in the present study, the Pearson's correlation coefficients between factors ranged from -0.023 to 0.026). The factors were interpreted by examination of the variables with loadings above the threshold of 0.50 or below the threshold of -0.50 (**Table 3**). Specifically, Factor 1 accounted for 19.06% of the total variance: high loadings were found for the DAPI2, DAPI3, and DAPI4. Factor 2 accounted for 17.07% of the total variance: high loadings were found for the WSGC, TAS, and DAPI1. Factor 3 accounted for 16.43% of the total variance: high loadings were found for the NS, RD, and HA. Factor 4 accounted for 12.15% of the total variance: high loadings were found for the PS.

**Table 3**

*Varimax-Rotated Factor Loading Matrix for Principal Component Analysis of Attention/Personality Measures.*

| Variables | Factor 1 | Factor 2 | Factor 3 | Factor 4 |
|---|---|---|---|---|
| **WSGC** | -0.39 | **0.51** | -0.14 | 0.32 |
| **TAS** | 0.08 | **0.80** | 0.20 | 0.10 |
| **DAPI1** | 0.13 | **0.76** | -0.03 | -0.18 |
| **DAPI2** | **0.83** | 0.03 | -0.08 | 0.18 |
| **DAPI3** | **0.79** | 0.03 | -0.18 | 0.11 |
| **DAPI4** | **0.51** | 0.30 | 0.42 | 0.05 |
| **PS** | 0.23 | 0.04 | 0.01 | **0.84** |
| **NS** | -0.04 | 0.10 | **0.80** | -0.28 |
| **RD** | -0.29 | 0.09 | **0.61** | 0.20 |
| **HA** | -0.13 | 0.33 | **-0.59** | -0.45 |
| **Eigenvalues** | 1.91 | 1,71 | 1.64 | 1.21 |
| **% of Variance** | 19.06 | 17.07 | 16.43 | 12.15 |

*Note*. WSGC = Waterloo-Stanford Group Scale of Hypnotic Susceptibility, Form C; TAS = Tellegen Absorption Scale; Differential Attention Processes Inventory: DAPI1 = Extremely Focused Attention; DAPI2 = Moderately Focused Attention; DAPI3 = Dual Attention Two Cognitive; DAPI4 = Dual Attention Physical and Cognitive. Temperament-Character Inventory, Revised: PS = Persistence; NS = Novelty Seeking; RD = Reward Dependence; HA = Harm Avoidance.

Finally, the correlations and factors presented above guided us in the choice of independent variables to be included in the multiple regression models. We chose as predictors all variables that

significantly correlated with NS4 and loaded above 0.50 or below -0.50 on independent factors.

Thus, separate multivariate Least Absolute Shrinkage and Selection Operator (LASSO; Tibshirani, 1996) regression analyses were performed for the total sample and for male and female samples using the NS4 scores as the criterion and the COMT (as there was evidence of a linear trend using a regression approach, *COMT* polymorphism was coded as the number of Val alleles in the following manner: Met/Met = 0; Val/Met = 1; Val/Val = 2), TAS, DAPI4, and PS scores as predictors (**Table 4**). The Mellow's C(p) criterion and the Cross Validation (CV) criterion were used as selection and stop criterions, respectively (Judge, et al., 1985). The significance level for removing and entering effects was set at p = 0.05. We used LASSO regression because it is a good method to handle the problem of multicollinearity, in which regression coefficients associated with irrelevant or redundant variables are reduced to zero.

The *COMT*, TAS, DAPI4, and PS were selected as significant predictors for the whole sample and female group, accounting for 20% and 23% of the total variance, respectively. For the male group, TAS and PS scores significantly predicted NS4 scores, accounting for 20% of the total variance.

**Table 4**

*Results of Separate Multivariate Least Absolute Shrinkage and Selection Operator (LASSO) Regression Analyses for Total, Female, and Male Samples Using Disorderliness (NS4) as Criterion and COMT, Absorption (TAS), Dual Attention Physical and Cognitive (DAPI4), and Persistence (PS) as Predictors.*

| | | | | | |
|---|---|---|---|---|---|
| | | | ***Total Sample*** | | |
| **Criterion: *Disorderliness (NS4)*** | ***B*** | ***β*** | ***SE B*** | ***t*** | **95% CI** |
| $F(4, 194) = 12.08$†, $R^2 = 0.20$ | | | | | |
| **Intercept** | 23.33 | 0 | 2.05 | **11.39**† | 19.29, 27.37 |
| **COMT** | -0.99 | -0.19 | 0.33 | **-2.94**** | -1.65, -0.32 |
| **TAS** | 0.19 | 0.24 | 0.05 | **3.53***** | 0.08, 0.30 |
| **DAPI4** | 0.14 | 0.16 | 0.06 | **2.35*** | 0.02, 0.25 |
| **PS** | -0.06 | -0.28 | 0.01 | **-4.32**† | -0.09, -0.03 |
| | | | ***Females*** | | |
| **Criterion: *Disorderliness (NS4)*** | ***B*** | ***β*** | ***SE B*** | ***t*** | **95% CI** |
| $F(4, 112) = 8.30$†, $R^2 = 0.23$ | | | | | |
| **Intercept** | 20.36 | 0 | 3.06 | **6.66**† | 14.31, 26.44 |
| **COMT** | -1.54 | -0.29 | 0.44 | **-3.47***** | -2.42, -0.66 |
| **TAS** | 0.17 | 0.20 | 0.07 | **2.33*** | 0.03, 0.32 |
| **DAPI4** | 0.22 | 0.23 | 0.08 | **2.63**** | 0.05, 0.38 |
| **PS** | -0.05 | -0.21 | 0.02 | **-2.43*** | -0.09, -0.01 |
| | | | ***Males*** | | |
| **Criterion: *Disorderliness (NS4)*** | ***B*** | ***β*** | ***SE B*** | ***t*** | **95% CI** |
| $F(2, 79) = 9.97$†, $R^2 = 0.20$ | | | | | |
| **Intercept** | 24.94 | 0 | 2.17 | **12.01**† | 21.74, 30.37 |
| **TAS** | 0.15 | 0.22 | 0.07 | **3.28**** | 0.09, 0.37 |
| **PS** | -0.04 | -0.24 | 0.02 | **-3.55***** | -0.09, -0.03 |

*Note* . The Mellow's C(p) criterion and the Cross Validation (CV) criterion were used as selection and stop criterion, respectively (Judge et al., 1985). The significance level for removing and entering effects was set at p = 0.05 ).

*COMT* = Met/Met (0), Val/Met (1), Val/Val (2).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; † $p < 0.0001$.

Our main findings show that the *COMT* Val$^{158}$Met polymorphism is significantly associated with the disorderliness facet of novelty seeking (NS4), in a sex-dependent manner; low COMT enzyme activity is associated with high levels of NS4 for the whole sample and female group, whereas no genotype effect was found for male subjects.

These findings are consistent with several studies showing that elevate dopamine levels lead to greater NS behavior (Zald et al., 2008) and that Met/Met females exhibit higher NS scores than other

genotypes (Demetrovics et al., 2010). Two other studies have provided a positive and significant association between COMT activity and the exploratory (Reuter & Hennig, 2005) or extravagance (Glavina Jelaš, et al., 2018) facets of NS in a mixed-sex student groups.

Our results (1) highlight the importance of considering NS as a heterogeneous trait with its subscales having a different genetic background and encompassing, besides exploration behavior and impulsivity, also facets of psychoticism (Stallings et al., 1996; Zuckerman & Cloninger, 1996); (2) underlie the importance of including sex as a biological variable when studying gene-personality associations (Chen et al., 2011). Indeed, there are a number of marked sexual dimorphisms in COMT's function that are generally ascribed to estrogenic regulation (Harrison and Tunbridge, 2008).

We demonstrate that lower COMT activity, greater absorption and dual attention physical-cognitive scores, and lower persistence scores predicted higher NS4 scores for both the whole sample and the female group. In contrast, higher absorption scores and lower persistence scores predicted higher NS4 scores for the male group.

These results are in agreement with the tonic-phasic dopamine theory (Bilder *et al*., 2004) and the warrior/worrier model (Stein *et al*., 2006), suggesting Met homozygosis causes an increase in the dopamine tonic activity, which down-regulates phasic dopamine response (Floresco, et al, 2003), thus leading to greater exploratory behaviors (Golimbet *et al*., 2007); attention abilities (Egan *et al*., 2001); and to propensity for aggressive-impulsive responses to new stimuli and complex situations (Bilder *et al*., 2004).

These findings are also supported by additional evidence indicating two different types of dopaminergic neurons, value and salience coding neurons (Bromberg-Martin et al., 2010), with a key roles in exploratory behaviours (DeYoung, 2013). Specifically, value coding neurons, located predominantly in the ventromedial substantia nigra pars compacta and throughout the ventral tegmental area, are activated by unpredicted reward and inhibited by unpredicted aversive stimuli and are supported by brain systems involved in exploration for specific rewards. Conversely, salience

coding neurons, located in the dorsolateral substantia nigra pars compacta and medial ventral tegmental area, are activated by both rewarding/aversive events and provide an index of the salience of stimuli and are believed to be supported by brain systems for attentional orienting toward significant stimuli, cognitive processing, and increasing general motivation. In addition, alerting signals, i.e. events that are directly associated with rewarding and aversive experiences, activate both neuron populations (Bromberg-Martin et al., 2010).

Based on these subsets of dopaminergic neurons, DeYoung (2013) proposed that if sensation-seeking involves planning, perseverance, and assessment of risk, it may be related to the salience system, whereas if this trait refers to a more spontaneous, impulsive facet of sensation seeking, it may be related to the value system. Accordingly, since we found that individual differences in the NS4 can be partially explained by high extracellular dopamine levels, greater attention abilities, and low proneness to persevere, we speculate that COMT activity mainly affects the value coding dopaminergic system.

Finally, we found significant associations between absorption, extremely focused attention, and hypnotic suggestibility measures. Furthermore, as previously observed (e.g., Lyons & Crawford, 1997), the principal component analysis showed that these measures loaded on the same factor. These findings provide further evidence (a) of the reliability and validity of these measurements and (b) that hypnotic suggestibility is reflective of individual differences in absorptive and extremely focused attention. In line with these results, several studies have shown that high hypnotizable individuals seem to possess a greater attentional control and cognitive flexibility than the low ones, suggestive of a far more efficient dopamine-mediated fronto-limbic attentional system (e.g., De Pascalis & Scacchia, 2016; Hoeft et al., 2012). Nevertheless, we failed to find a significant association between these attention measures and COMT activity. This result confirms findings from two previous studies (Bryant *et al*., 2013; Presciuttini *et al*., 2014) and challenges the hypnotic suggestibility theory based on dopamine, at least at the cortical level. In contrast, five studies have shown a significant association between COMT gene and hypnotic suggestibility, even though the direction, magnitude, and

reliability of this association remain unclear (Katonai et al., 2017; Lichtenberg et al., 2000; Raz, 2005; Storozheva et al., 2018; Szekely et al., 2010).

Although the present study has shed new light on the impact of *COMT* Val$^{158}$Met polymorphism on personality phenotypes, it still holds several limitations. Indeed, a more comprehensive understanding of the genetic factors underlying individual differences in personality needs to consider the contribution of multiple genes as well as other neurotransmitter systems (e.g., serotoninergic system) likely interact with the *COMT* gene.

This study accords to the ethical standards of the APA and was approved by the institutional review board of the Department of Psychology, Sapienza University of Rome (Italy) according to the Helsinki Declaration.

## CONTRIBUTIONS

P.S. and V.D.P. designed the study, performed statistical analyses, and interpreted the results. P.S. carried out the experiment and wrote the paper. M.L. designed and carried out the identification of genomic DNA. S.C. supervised all phases of DNA analysis. V.D.P. supervised all phases of the study. M.T.F. contributed with advice and discussion. All authors provided critical feedback, contributed to manuscript editing, and approved the final version of the manuscript.

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