Variation in Catechol-O-Methyltransferase val\textsuperscript{158} met Genotype Associated with Schizotypy but Not Cognition: A Population Study in 543 Young Men

Nicholas C. Stefanis, Jim Van Os, Dimitrios Avramopoulos, Nikolaos Smyrnis, Ioannis Evdokimidis, Ioanna Hantoumi, and Costas N. Stefanis

Background: Increased catechol-O-methyltransferase activity associated with variation in catechol-O-methyltransferase valine\textsuperscript{158} methionine genotypes may result in reduced dopamine neurotransmission in the prefrontal cortex and thus contribute to the poor performance of frontally mediated cognitive tasks and the occurrence of associated negative symptoms observed in patients with schizophrenia; however, reported associations between catechol-O-methyltransferase valine\textsuperscript{158} methionine genotypes and measures of cognition have not been consistent.

Methods: Catechol-O-methyltransferase genotyping, measures of schizotypy, cognitive measures of memory and attention, as well as the antisaccade eye movement task, a measure sensitive to prefrontal cortical function, were obtained in a sample of 543 young men representative for that age group (mean age 21 years).

Results: None of the cognitive measures was associated with catechol-O-methyltransferase valine\textsuperscript{158} methionine genotypes; however, there was an effect of high-activity allele loading on schizotypy, in particular the negative and disorganization dimensions.

Conclusions: Previously reported inconsistencies in the relationship between catechol-O-methyltransferase valine\textsuperscript{158} methionine genotypes and cognition were not resolved; however, catechol-O-methyltransferase genotype may affect expression of negative schizotypy by direct or indirect effects on central dopamine neurotransmitter signaling.

Key Words: Catechol-O-methyltransferase, cognition, genetics, negative symptoms, schizophrenia

There has long been speculation that a familial factor affecting the function of the enzyme catechol-O-methyltransferase (COMT), involved in catecholamine degradation, may contribute to the susceptibility for schizophrenia (Baron et al 1984; Dunham et al 1992; Eberhard et al 1989; Wei et al 1996), and many studies, reporting inconsistent findings, have been investigating brain COMT activity in patients with schizophrenia (Crow et al 1979; Walker et al 1976; Wise et al 1974). The gene encoding for COMT is located on chromosome 22q11, which a recent meta-analysis of genome-wide linkage scans identified as one of three loci that had the highest likelihood of harboring schizophrenia-risk genes (Badner and Gerstein 2002). Another meta-analysis concluded that in schizophrenia there is evidence for an association with variants of the COMT gene in case-control and, in particular, in family-based studies of European samples (Glatt et al 2003; Li et al 1996).

There may be biological plausibility for a causal link with COMT through its possible link with dopamine-mediated cognitive function. Gasparini et al (1997) observed that administration of tolcapone, a reversible, selective inhibitor of COMT, substantially improved cognitive function in patients with advanced Parkinson disease. Catechol-O-methyltransferase activity has been found to display a pattern of variability characterized by a trimodal distribution of low, intermediate, and high levels of activity. A G-to-A transition at codon 158 of the COMT gene, resulting in a valine (val) to methionine (met) substitution yielding different val\textsuperscript{158} met genotypes, has been associated with differential COMT activity. The val allele results in a thermolabile protein with a threefold to fourfold increase in enzymatic activity (Mannisto and Kaakkola 1999; Scanlon et al 1979) compared with the met allele. Increased COMT activity may result in reduced dopamine neurotransmission in the prefrontal cortex and thus contribute to the poorer performance of frontally mediated cognitive tasks and the occurrence of associated negative symptoms observed in patients with schizophrenia.

Consistent with the hypothesis of genetically determined variation in prefrontal dopamine signaling, Egan et al (2001) showed that the load of the low-activity met allele was related in allele dosage fashion to enhanced performance on the Wisconsin Card Sorting Test (WCST) of executive cognition, which was replicated in sample of 73 healthy volunteers (Malhotra et al 2002) but not in a community sample of 120 young females (Tsai et al 2003). One report found an association between WCST performance and COMT genotype in patients but not in healthy controls (Joobert et al 2002), and another found an association in healthy siblings but not in their patient siblings (Rosa et al 2004).

In an extension of the Egan et al (2001) sample, an effect of allelic load on executive cognition and working memory was demonstrated with a different neuropsychological task, the N-back, with val/val individuals again showing the lowest N-back performance; no effect of COMT genotype was seen on measures of attention using the Continuous Performance Test (Goldberg et al 2003). Bilder et al (2002), however, reported that the met allele was associated with better performance in the processing speed and attention domain but not with other domain scores measuring executive and visuoperceptual functions, declarative verbal learning and memory, simple motor ability, or global neurocognitive function. The relative inconsistencies in the findings so far may result from the fact, as argued by Nolan et al (2004), that neuropsychological tests such as the WCST and N-back require
both cognitive stability and cognitive flexibility, whereas recent evidence supports the notion that level of met loading is associated with better cognitive stability but at the same time with poorer cognitive flexibility.

The negative symptoms of schizophrenia are consistently associated with indices of cognitive impairment (van Os and Verdoux 2003), and a deficit of dopamine transmission in the prefrontal cortex (PFC) has been hypothesized to underlie their occurrence (Weinberger 1987). A recent study showed that the COMT val/158 met polymorphism is involved in the regulation of emotional response to stressful stimuli. In an experiment involving response to sustained pain, individuals homozygous for the met allele showed higher sensory and affective ratings of pain and a more negative internal affective state, whereas opposite effects were observed in val/158 homozygotes (Zubieta et al 2003). In view of their reduced affective response, val/val individuals may be more liable to develop negative symptoms. In healthy control subjects, there is accumulating evidence from genetic association studies (Blum et al 1997; Jonsson et al 2003; Rosmond et al 2001) and positron-emission tomography (PET) studies (Breier et al 1998; Laakso et al 2000) that low dopaminergic neurotransmission is associated with the personality trait detachment, a trait resembling negative symptoms in patients with schizophrenia, although this was not replicated in studies using instruments that differed from the detachment subscale of the Karolinska Scales of Personality (Kessler et al 2000).

Schizotypy has a strong familial relationship with schizophrenia (Kendler et al 1993) and is similarly characterized by dimensions of positive, negative, disorganization, and possibly paranoid experiences (Stefanis et al 2004). It has been shown that negative schizotypy is moderately heritable (Linney et al 2003) and that the negative symptoms in patients with schizophrenia are expressed as negative schizotypy in their first degree relatives (Fanous et al 2001), indicating that negative symptoms occur on an etiologic continuum with their personality-based counterparts. Negative schizotypy has a distribution in the population (Stefanis et al 2002), and a plausible hypothesis, therefore, is that COMT genotype contributes to population variation in negative schizotypy similar to the hypothesized relationship between COMT genotype and population variation in cognition.

In a previous general population study of 379 healthy 18- to 24-year-old men (Avramopoulos et al 2002), a positive association was demonstrated between val allele loading and total score of the Schizotypal Personality Questionnaire (SPQ) (Raine 1991). In the current study, a very large sample of over 500 young men, representing an extension of the sample in our previous study (Avramopoulos et al 2002), was used to address the following issues: 1) in view of the relative contradictory results of the association between COMT genotype and cognitive measures of attention on the one hand and executive function and memory on the other, associations between COMT genotype and these cognitive measures was examined; and 2) the hypothesis was tested that associations between COMT genotype and schizotypy should be apparent for the negative dimension rather than the other dimensions of schizotypy.

Methods and Materials

Sample

The Athens Study of Psychosis Proneness and Incidence of Schizophrenia (ASPIS) (Avramopoulos et al 2002; Ekdokimidis et al 2002; Smyrnis et al 2002; Stefanis et al 2004) examined, in eight separate waves between January 1999 and March 2000, 2243 randomly selected young male conscripts aged 18 to 24 years from the Greek Air Force in their first 2 weeks of admission to the National Basic Air Force Training Center. This sample was specifically chosen, as there is consistent evidence that individuals at this age are most likely to display the clinical and subclinical experiences of psychosis (Peters et al 1999; van Os et al 2000; Verdoux et al 1998), thus increasing statistical power. Military service is compulsory in Greece and all healthy males are recruited and assigned to the different army corps by random assignment. All conscripts had already received a standardized screening interview by a team of army medical doctors of different specialties and had been evaluated as not suffering from a medical condition. Conscripts underwent an extensive interview of computerized neurocognitive abilities and a self-rated psychometric evaluation. After obtaining informed consent, DNA was extracted from mouthwash samples. The study was approved by The Bioethics and Medical Deontology Committee of the University Mental Health Research Institute.

Subjects

Out of 1355 conscripts who had reliably completed the SPQ (see below) and who had undergone a neurocognitive assessment, 603 were randomly selected for COMT genotyping according to the last digit of an alphabetically assigned identification number. Sixty samples were excluded due to unobservable COMT genotyping results, leaving 543 conscripts for analysis. There were no large or significant differences between the 60 excluded and the 543 included subjects on any of the cognitive, schizotypy, or eye movement measures, with the exception of a small difference in positive schizotypy (excluded: .24, SD = .12; included: .20, SD = .11, p = .014). Our goals and procedures were explained to the subjects and written informed consent was acquired.

Questionnaires

The SPQ (Raine 1991) is a 74 “dichotomous” item (yes/no) questionnaire that assesses all nine aspects of DSM-III-R schizotypal personality disorder. It can be used as a screening instrument in the general population for the identification of individuals with broad schizotypal traits, and may serve as a measure of individual differences in schizotypal personality.

The SPQ was translated into Greek by two independent bilingual translators and back-translated by two other bilingual translators. The back translation was communicated to the author of the questionnaire for review and was accepted as accurate. To verify the degree of collaboration with the self-report scales, we used the four validity items of the Temperament and Character Inventory (Cloninger et al 1993). Only individuals found to respond reliably to these items were included in the analysis.

In a previous publication, we demonstrated by employing a confirmatory factor analytic approach that a four-factor model of schizotypy (cognitive/perceptual, paranoid, negative, and disorganization schizotypal dimensions) provided the best fit to the conscript data (Stefanis et al 2004).

Cognitive Assessments

Each conscript underwent a computerized neurocognitive battery and an assessment of eye movements. For the purposes of this article, tasks that had been the subject of previous reports of associations with COMT genotype were included. Thus, verbal and spatial memory were assessed with the verbal and spatial N-back test, which engages the working memory system in maintaining and updating information over short delays (Gevins et al 1996). In the N-back analyses, the hit rate for the verbal and spatial 2-back task was used (Goldberg et al 2003). Attention was assessed with the Continuous Performance Test (Cornblatt et al 1988, 1989) and the d-prime index was used in the analyses.
et al. 1988), and deficits in the performance of executive tasks (Kashima et al. 1994), frontal ventricular enlargement (Fukushima et al. 1997) point to the importance of frontal areas in the performance of executive functions such as the Wisconsin Card Sorting test (Rosse et al. 1993).

DNA Extraction
The DNA was extracted from mouthwash as follows: 15 mL of sterile saline solution was supplied and the subjects were instructed to perform a rigorous mouthwash for approximately 20 seconds. The sample was centrifuged at 14,000g for 15 minutes at 4°C. The pellet was resuspended in 2 mL Lysis buffer (2% SDS, 0.1 mol/L sodium chloride [NaCl], 0.05 mol/L tris hydrochloride [HCl] (pH 8.0), 1 mmol/L ethylenediaminetetraacetic acid [EDTA]) and incubated at 37°C for 16 hours with 2 mg of Proteinase K. Proteins were precipitated and removed with the addition of 1 mL of 6 mol/L NaCl and centrifugation at 21,000g for 20 minutes at 4°C. The DNA was precipitated from the supernatant with ethanol. Mouthwash was chosen to obtain a better procedure acceptance rate and to avoid possible denials related to psychological profile (e.g., fear of the needle). It has been shown in large samples that there are no genotyping discrepancies between DNA obtained from blood and mouthwash (de Vries et al. 1996).

COMT Typing
Typing was performed by PCR amplification and digestion with the restriction enzyme NlaIII and 3% agarose electrophoresis as described by Kirov et al. (1998). Agarose gels were scored independently by two researchers (DA and IH) blind to the schizotypy scores of the subjects. Alleles were assigned as L (low activity, NlaIII site present) and H (high activity, NlaIII site absent).

Data Analysis
The subjects were assigned to three groups according to their genotype (val/val, val/met, or met/met), and linear effects of val allelic loading were tested using multiple regression in STATA, with the mean loading (values 0, 1, and 2) indicates an additive effect of .25 SD in the outcome variable with each unit change in val loading. Alpha was set at 5%. To normalize the distribution, an arc sin transformation of N-back hit rate and antisaccade error rate scores was performed.

In view of indications that a correlation may exist between depressive items and the met/met allele (Ohara et al. 1998) and because experience of depression accompanies experience of positive and negative symptoms of psychosis not only in clinical samples but also in the general population (Stefanis et al. 2002), an adjustment was made for depressive symptoms measured with the depression subscale of the Symptom Checklist-90R (SCL-90R) (Derogatis 1977). Other a priori confounders included age, intelligence quotient (IQ) assessed with Raven's Progressive Matrix test (Raven 1982), and number of years of schooling (range: 6–17 years). To assess independence of any associations between COMT genotypes and cognitive measures and schizotypy measures, a second adjustment was made for cognitive measures in the schizotypy analyses and for schizotypy dimensions in the cognitive measure analyses.

For the correlated schizotypy dimensions, cross-equation analyses were carried out by Wald test to compare associations between val loading and different schizotypy dimensions.

Sample Heterogeneity
As we had reported before on an association between SPQ total score and COMT genotype in 379 individuals (Avramopoulos et al. 2002) of whom 369 were again included in the current sample of 543, we investigated whether there was heterogeneity of effects of COMT val allelic loading in the subsamples of 369 “old” and the 174 “new” subjects by fitting sample x val allelic loading in models of SPQ total score, positive, negative, paranoid, and disorganization schizotypy. As there was no evidence of large or significant interactions, the samples were jointly analyzed.

Results
The mean age was 21.0 years (SD = 1.9) and mean number of years of schooling was 13.0 years (SD = 2.0). Alleles of val and met were present at overall frequencies of 56.4% and 43.6%, respectively. The three genotype frequencies were met/met: 20.5% (112/543), met/val: 46% (250/543), and val/val: 33.5% (181/543), not deviant from that expected for genotypes in Hardy-Weinberg equilibrium. No large or significant differences were observed between allelic loading and age (B = -0.07, \( \chi^2 = 1.5, df = 1, p = .22 \)) or years of schooling (B = -0.09, \( \chi^2 = 2.1, df = 1, p = .15 \)). Mean measures of schizotypy and cognitive measures by COMT genotype are depicted in Table 1.

<table>
<thead>
<tr>
<th>COMT Genotype</th>
<th>Paranoid SPQ Mean (SD)</th>
<th>Positive SPQ Mean (SD)</th>
<th>Negative SPQ Mean (SD)</th>
<th>Disorganized SPQ Mean (SD)</th>
<th>Verbal Working Memory Hit Rate Mean (SD)</th>
<th>Spatial Working Memory Hit Rate Mean (SD)</th>
<th>CPT d-prime Mean (SD)</th>
<th>Antisaccade Error Rate Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met/Met</td>
<td>.43 (.20)</td>
<td>.20 (.12)</td>
<td>.15 (.11)</td>
<td>.39 (.21)</td>
<td>2.62 (.85)</td>
<td>2.77 (.98)</td>
<td>1.86 (.90)</td>
<td>0.45 (.21)</td>
</tr>
<tr>
<td>Met/Val</td>
<td>.44 (.18)</td>
<td>.19 (.10)</td>
<td>.19 (.12)</td>
<td>.41 (.20)</td>
<td>2.65 (.83)</td>
<td>2.91 (1.01)</td>
<td>1.87 (.87)</td>
<td>0.46 (.19)</td>
</tr>
<tr>
<td>Val/Val</td>
<td>.46 (.16)</td>
<td>.21 (.11)</td>
<td>.20 (.12)</td>
<td>.45 (.18)</td>
<td>2.65 (.91)</td>
<td>2.74 (1.03)</td>
<td>1.77 (.90)</td>
<td>0.50 (.20)</td>
</tr>
</tbody>
</table>

COMT, catechol-O-methyltransferase; SPQ, Schizotypal Personality Questionnaire; CPT, Continuous Performance Test; Met, methionine; Val, valine.

Table 1. Mean Values of Schizotypy and Cognition Variables by COMT Genotype

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was significantly greater than the association between disorganization schizotypy and positive schizotypy: the associations were not significantly greater than those with positive schizotypy were not significantly greater than those with positive schizotypy. Significant in showing associations with COMT genotypes, they were not entirely specific, as associations between COMT genotypes and negative and disorganization schizotypy measures were more sensitive in showing associations with COMT genotypes, they were not entirely specific, as associations between COMT genotypes and paranoid and positive schizotypy were not significantly greater than those with positive and paranoid schizotypy, with the exception of the comparison between disorganization schizotypy and positive schizotypy: the association between \( val \) loading and disorganization schizotypy was significantly greater than the association between \( val \) loading and positive schizotypy: \( F = 6.96, df = 1, p = .0086 \). The proportion of the schizotypy variance explained by \( val \) loading was negative schizotypy: 1.4%, disorganization schizotypy: 1.1%, paranoid schizotypy: .7%, and positive schizotypy: .3%.

### COMT Genotyping and Cognitive Measures

A total of 519 conscripts (95.9%) completed the antisaccade task, 528 conscripts (97.4%) completed the CPT vigilance task, and 458 conscripts (84.4%) completed the N-back tasks. In all, 80% of the 543 conscripts completed all four neurocognitive tasks. Controlling for vigilance, the partial correlation between antisaccade error rate and N-back hit rate performance revealed small correlations (verbal N-back \( r = -.16 \), spatial N-back \( r = -.17 \), both \( p < .001 \)) indicating that the antisaccade and N-back tasks, which are both dependent on the integrity of the prefrontal cortex, engage different aspects of working memory processes.

There was no association between COMT \( val \) loading and any of the cognitive variables, the largest association with antisaccade error rate remaining statistically inconclusive (\( B = .12, \chi^2 = 3.8, df = 1, p = .052 \)), also after adjustment for schizotypy measures (\( B = .12, \chi^2 = 3.6, df = 1, p = .057 \) (Table 3).

### Discussion

Catechol-O-methyltransferase \( val^{158} \) met genotypes were associated with schizotypy measured with the SPQ, thus replicating our original finding in a larger sample (Avramopoulos et al 2002). In addition, it was shown that conscripts with the high activity \( val \) allele exhibited, independent of measures of cognition, a significant increase with allelic load in the negative and disorganization schizotypy factor scores but not in the paranoid and positive schizotypy factor scores. It should be noted, however, that although negative and disorganization schizotypy measures were more sensitive in showing associations with COMT genotypes, they were not entirely specific, as associations between COMT genotypes and paranoid and positive schizotypy were mostly not significantly greater than associations between COMT genotypes and paranoid and positive schizotypy.

Reported inconsistencies in associations between COMT

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**Table 2. Associations Between COMT and Schizotypy and Effect of Adjusting for Various Confounders**

<table>
<thead>
<tr>
<th>COMT Genotype</th>
<th>Paranoid SPQ</th>
<th>Positive SPQ</th>
<th>Negative SPQ</th>
<th>Disorganized SPQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( B^a )</td>
<td>( P )</td>
<td>( B^a )</td>
<td>( P )</td>
</tr>
<tr>
<td>Met/Met</td>
<td>0.00</td>
<td>.96</td>
<td>0.00</td>
<td>.91</td>
</tr>
<tr>
<td>Met/Val</td>
<td>.07</td>
<td>.52</td>
<td>.09</td>
<td>.44</td>
</tr>
<tr>
<td>Val/Val</td>
<td>.22</td>
<td>.07</td>
<td>.13</td>
<td>.29</td>
</tr>
<tr>
<td>Effect Linear Trend Unadjusted</td>
<td>.11</td>
<td>.054</td>
<td>.08</td>
<td>.17</td>
</tr>
<tr>
<td>Effect Linear Trend Adjusted</td>
<td>.11</td>
<td>.049</td>
<td>.07</td>
<td>.20</td>
</tr>
<tr>
<td>Effect Linear Trend Adjusted 1°</td>
<td>.12</td>
<td>.067</td>
<td>.08</td>
<td>.18</td>
</tr>
</tbody>
</table>

**Table 3. Associations Between COMT Genotype and Cognitive Variables**

<table>
<thead>
<tr>
<th>COMT Genotype</th>
<th>Verbal Working Memory Hit Rate</th>
<th>Spatial Working Memory Hit Rate</th>
<th>CPT d-prime</th>
<th>Antisaccade Error Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( B^a )</td>
<td>( P )</td>
<td>( B^a )</td>
<td>( P )</td>
</tr>
<tr>
<td>Met/Met</td>
<td>0.00</td>
<td>.96</td>
<td>0.00</td>
<td>.91</td>
</tr>
<tr>
<td>Met/Val</td>
<td>.02</td>
<td>.86</td>
<td>.13</td>
<td>.28</td>
</tr>
<tr>
<td>Val/Val</td>
<td>.007</td>
<td>.96</td>
<td>-.03</td>
<td>.82</td>
</tr>
<tr>
<td>Effect Linear Trend Unadjusted</td>
<td>.01</td>
<td>.85</td>
<td>-.03</td>
<td>.64</td>
</tr>
<tr>
<td>Effect Linear Trend Adjusted 1°</td>
<td>.02</td>
<td>.78</td>
<td>-.03</td>
<td>.57</td>
</tr>
<tr>
<td>Effect Linear Trend Adjusted 2°</td>
<td>.02</td>
<td>.73</td>
<td>-.03</td>
<td>.58</td>
</tr>
</tbody>
</table>

**Note:**

- COMT, catechol-O-methyltransferase; CPT, Continuous Performance Test; Met, methionine; Val, valine; IQ, intelligence quotient.
- *Regression coefficient from multiple regression procedure.
- Reference category.
- The increase in the schizotypy variable with one unit increase in \( val \) loading (values: 0, 1, and 2).
- Adjusted for age, IQ, education, and depression.
- Adjusted as above and additionally for N-back, CPT, and antisaccade.

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= .17, \( \chi^2 = 7.9, df = 1, p = .005 \) and disorganization (\( B = .14, \chi^2 = 5.7, df = 1, p = .017 \)) but not with positive (\( B = .08, \chi^2 = 1.86, df = 1, p = .17 \)) and paranoid schizotypy (\( B = .11, \chi^2 = 3.7, df = 1, p = .054 \)) (Table 2). Adjustment for confounding and for cognitive variables did not affect the pattern of results (Table 2). Comparative cross-equation analyses revealed that the associations between \( val \) loading and negative and disorganization schizotypy were not significantly greater than those with positive and paranoid schizotypy, with the exception of the comparison between disorganization schizotypy and positive schizotypy: the association between \( val \) loading and disorganization schizotypy was significantly greater than the association between \( val \) loading and positive schizotypy: \( F = 6.96, df = 1, p = .0086 \). The proportion of the schizotypy variance explained by \( val \) loading was negative schizotypy: 1.4%, disorganization schizotypy: 1.1%, paranoid schizotypy: .7%, and positive schizotypy: .3%.

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- Adjusted as above and additionally for N-back, CPT, and antisaccade.
val<sup>158</sup> met genotypes and measures of cognition were not resolved, as associations with measures of both memory and attention that in previous work had shown both positive and negative associations (Bilder et al. 2002; Egan et al. 2001; Goldberg et al. 2003; Malhotra et al. 2002; Tsai et al. 2005) were inconclusive. In addition, COMT val<sup>158</sup> met genotypes did not appear to be associated with a differential pattern of performance on an eye movement task surveyed by the integrity of the prefrontal cortex, although it should be noted that the results were of marginal statistical significance and therefore can be seen to provide some support to previous findings relating measures of executive function to COMT val<sup>158</sup> met genotypes (Egan et al. 2001; Joober et al. 2002; Rosa et al. 2004).

Clearly, the SPQ results need replication, as they are at risk of showing the same inconsistencies between studies as the findings relating COMT val<sup>158</sup> met genotypes with cognitive measures; however, if replicated, the results may indicate that possible relative hypodopaminergia occasioned by the high activity variant of COMT may have behavioral implications with relevance to the psychosis phenotype. Cognitive outcomes may be much less sensitive to reduced dopamine signaling, which could go some way toward explaining the discrepancy in reported results on cognition and COMT val<sup>158</sup> met genotypes. An alternative explanation for the current dissociation between cognitive and behavioral findings, however, is the suggestion by Nolan et al. (2004) that commonly used cognitive tests such as WCST and N-back may not have optimal sensitivity, as they require both cognitive stability and cognitive flexibility, whereas COMT val<sup>158</sup> met genotypes may have opposite effects on both.

These results should be interpreted in the light of several limitations. First, we relied on self-report data, which in the case of schizotypy may be less sensitive to genetic effects than interview measures (Kendler et al. 1996). This, however, would have biased any genetic results to the null rather than create spurious results. Secondly, motivation in recruits may have been low, resulting in poor discrimination on cognitive test results. Although we cannot exclude this possibility, recruits were in general motivated, as participation in the research exercise was provided by Intrasoft Co. We thank the following colleagues, Ministry of Development. The technical support for this project was provided by Intrasoft Co. We thank the following colleagues, among others: Ioannis Gionzalis, Georgios Kastrinakis, Emanuel Katooulas, Catherine Paximidis, and Christos Theleritis.


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