Epistasis between COMT Val\textsuperscript{158}Met and DRD3 Ser\textsuperscript{9}Gly polymorphisms and cognitive function in schizophrenia: genetic influence on dopamine transmission

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Objective: To assess the relationship between cognitive function, a proposed schizophrenia endophenotype, and two genetic polymorphisms related to dopamine function, catechol-O-methyl transferase (COMT) Val\textsuperscript{158}Met and dopamine receptor 3 (DRD3) Ser\textsuperscript{9}Gly.

Methods: Fifty-eight outpatients with schizophrenia/schizoaffective disorder and 88 healthy controls underwent neurocognitive testing and genotyping. Analyses of covariance (ANCOVAs) using age, sex, and years of education as covariates compared cognitive performance for the proposed genotypes in patients and controls. ANCOVAs also tested for the epistatic effect of COMT and DRD3 genotype combinations on cognitive performance.

Results: For executive functioning, COMT Val/Val patients performed in a similar range as controls (30.70-33.26 vs. 35.53-35.67), but as COMT Met allele frequency increased, executive functioning worsened. COMT Met/Met patients carrying the DRD3 Ser/Ser genotype performed poorest (16.184 vs. 27.388-31.824). Scores of carriers of this COMT/DRD3 combination significantly differed from all DRD3 Gly/Gly combinations (p < 0.05), from COMT Val/Met DRD3 Ser/Gly (p = 0.02), and from COMT Val/Val DRD3 Ser/Ser (p = 0.01) in patients. It also differed significantly from all control scores (p < 0.001).

Conclusion: Combined genetic polymorphisms related to dopamine neurotransmission might influence executive function in schizophrenia. Looking at the effects of multiple genes on a single disease trait (epistasis) provides a comprehensive and more reliable way to determine genetic effects on endophenotypes.

Keywords: Endophenotype; psychosis; genetics; dopamine; executive function

Introduction

The intricate etiopathogenetic mechanisms underlying the clinical manifestations of schizophrenia greatly hamper the search for gene-illness associations.\textsuperscript{1} Since psychotic symptoms represent an array of biological, psychological, and behavioral phenomena,\textsuperscript{2} an alternative to understanding this complex array has been to study gene-environment interactions.\textsuperscript{3} However, such studies must evaluate large samples and control for a multitude of confounding factors. Consequently, an operative definition of the exact role of genes in schizophrenia has yet to be achieved.\textsuperscript{4} One strategy to overcome these difficulties relies on the identification of endophenotypes, which are stable across the life span, usually related to fewer but more specific genes, and less susceptible to the effects of environmental factors.\textsuperscript{5} The occurrence of cognitive impairment in schizophrenia has been widely studied, and there is robust evidence supporting it as one of the better-described endophenotypes of the disorder.\textsuperscript{5}

Cognitive impairment has been suggested by some as one of the core manifestations of schizophrenia.\textsuperscript{6} Cognitive deficits are pervasive, usually starting years before the onset of psychosis\textsuperscript{7} and progressing with the disease course.\textsuperscript{8} Cognitive deficits are also present among non-affected relatives of persons with schizophrenia, further strengthening the role of these deficits as endophenotypes.\textsuperscript{9} Moreover, the dopaminergic system – which plays a central role in the pathophysiology of psychotic symptoms\textsuperscript{10} – has been implicated in the workings of several cognitive functions.\textsuperscript{11}

Thus, researchers have focused their efforts in determining the link between genes related to dopamine function and cognitive endophenotypes. One important target is the gene that encodes the catechol-O-methyltransferase (COMT) Val\textsuperscript{158}Met and dopamine receptor 3 (DRD3) Ser\textsuperscript{9}Gly.
transferase (COMT) enzyme. COMT degrades catecholamines, including dopamine, in the synaptic cleft; it is expressed throughout the brain, but especially in the prefrontal cortex and striatum. A functional polymorphism at codon 158 (COMT Val<sup>158</sup>Met) results in its loss of function: Met/Met carriers hold 25% of Val/Val wild-type activity, while heterozygotes display intermediate enzymatic activity. Several studies have implicated COMT polymorphisms in both cognitive function and schizophrenia. Dopamine receptors are another potential target for the investigation of genetic determinants of cognitive endophenotypes. Five different dopamine receptors have been well studied so far. They are classified into two groups according to structural similarity: D1/D5 receptors and D2/D3/D4 receptors. D1 and D2 receptors have been most extensively researched, with several studies supporting their association with cognition. Regarding the D3 receptor, a genetic polymorphism characterized by a substitution of serine by glycine at codon 9 (DRD<sub>3</sub> Ser<sup>9</sup>Gly) has been hypothesized to be associated with susceptibility to development of schizophrenia. However, few studies have addressed the association of this polymorphism with cognitive deficits in schizophrenia. The aim of the present study was to investigate the influence of the COMT Val<sup>158</sup>Met and DRD<sub>3</sub> Ser<sup>9</sup>Gly polymorphisms on various neurocognitive functions of individuals with schizophrenia and healthy controls. Since both polymorphisms affect dopamine neurotransmission, and since recent studies have addressed the effect of genotype × genotype interactions, we also tested for a possible epistatic effect of these genes on cognition.

Method

Participants

Outpatients with schizophrenia or schizoaffective disorder (diagnosed per DSM-IV criteria) were recruited from the Institute of Psychiatry, Universidade de São Paulo, SP, Brazil. Neurological disorders, mental retardation, and unstable medical conditions affecting brain functioning constituted our exclusion criteria. Controls had no current or past history of psychiatric disorder according to an evaluation conducted by trained psychiatrists using the Mini International Neuropsychiatric Interview (MINI), and no family history (first-degree relatives) of mood or psychotic disorders.

The study was approved by the local ethics committee, and all subjects provided written consent to participate in the study after being fully oriented about its procedures.

Clinical and neurocognitive assessments

All clinical assessments were conducted by experienced and trained psychiatrists (AAL, MTB, RTS, LTV, MVZ) and a psychologist (DSB). Psychiatric diagnosis was established with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Symptom severity was assessed using the Positive and Negative Symptom Scale (PANSS).

Neurocognitive assessment was carried out by one of the investigators (DSB), an experienced psychologist trained in standardized neuropsychological testing. A 2-hour test battery was administered in fixed order, assessing the following domains: a) attention: Wechsler Adult Intelligence Scale III (WAIS-III) subtest Digit Span (WAIS-DS), Trail Making Test – Part A (TMT-A), Stroop Color-Word Test (SCWT); b) verbal memory: Wechsler Memory Scale subtest – Logical Memory (WMS-LM), immediate (1) and delayed (2); c) visual memory: Rey-Osterrieth Complex Figure Test (RCFT) delayed recall; d) visuospatial function: WAIS-III – Block Design (WAIS-BD), RCFT copy; e) language: Controlled Oral Word Association Test (FAS), WAIS-III Vocabulary subtest (WAIS-V); f) psychomotor speed: TMT-A; g) executive function: WAIS-III Letter-Number Sequence (WAIS-LNS), WAIS-DS, SCWT, TMT-B, WAIS Similarities (WAIS-S), Matrix Reasoning (WAIS-MR), RCFT copy, Wisconsin Card Sorting Test (WCST) Conceptual Level Responses (WCST-CONC), Perseverative Responses (WCST-PR), Failure to Maintain Set (WCST-FMS), Corrected Categories (WCST-CC), Errors (WCST-E), Non-Perseverative Errors (WCST-NP), Perseverative Errors (WCST-P); h) intelligence: WAIS – Total Intelligence Quotient (IQ), Estimated IQ (EIQ), Execution IQ (EIXIQ), and Verbal IQ (VIQ). In the majority of these tests, better performance is indicated by higher scores, with the exception of the SCWT and TMT (scores measured in seconds).

Genotyping

DNA was extracted from peripheral blood according to the salting-out protocol and then genotyped for COMT rs4680 (Val<sup>158</sup>Met) and DRD<sub>3</sub> rs6280 (Ser<sup>9</sup>Gly). Polymorphisms were determined by real-time polymerase chain reaction (PCR) allelic discrimination with TaqMan<sup>®</sup> SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA) according to the manufacturer’s instructions. Amplification and allelic discrimination were carried out using a 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Thermal cycling consisted of initial denaturation for 10 min at 95 °C, followed by 40 cycles of denaturation at 95 °C for 15 s and annealing at 60 °C for 1 min. The allele-detection process and allelic discrimination were performed for 1 min at 60 °C.

Statistical analysis

The allele frequencies of both patients and healthy controls were tested for Hardy-Weinberg equilibrium (HWE). Estimation of allele and genotype frequencies was performed by the gene counting method. Afterwards, chi-square statistics were calculated to compare allele and genotype frequencies between patient and control groups.

Since neurocognitive measures were the dependent variables, the data was tested for normality using a Q-Q plot with their transformed residuals and the standard normal distribution.

After observing a normal distribution, analyses of covariance (ANCOVAs) were used to compare neuropsychological performance between the various genotypes of
Gly/Gly and DRD3 and controls. Since only one subject had the combination of differences between each DRD3/COMT combination in patients and controls. Since only one subject had the combination of DRD3 Gly/Gly and COMT Val/Val, this individual’s performance was pooled with DRD3 Ser/Ser COMT Val/Val for the pairwise comparison. The results of this single subject on the RCFT (copy and recall) were very similar to those of DRD3 Ser/Ser COMT Val/Val subjects, allowing us to proceed with this merger and thus enabling statistical analyses. SPSS version 18.0 was used for all analyses.

Results

The sample comprised 58 patients who agreed to participate in the study and completed the study protocol (40 men, 18 women; mean age 37.2 ± 10.6 years). Four participants (7%) had received a diagnosis of schizoaffective disorder, and the remaining patients were diagnosed as having schizophrenia (93%). Overall, 40 patients (70.2%) were white, and the mean educational attainment was 10.2 ± 2.6 years. At the time of evaluation, 51 (88%) were on antipsychotics, 9 (16%) were on typical antipsychotics, 12 (21%) were on a mood stabilizer, 24 (41%) were on antidepressants, and 12 (21%) were on benzodiazepines. Ethnicity was self-reported according to the Brazilian Institute of Geography and Statistics (IBGE) classification. Our control sample comprised 88 healthy individuals recruited through local advertisements from the Universidade de São Paulo. The mean age of controls was 24-2.4 years. At the time of evaluation, 51 (88%) were white, and the mean educational attainment was 13.8 ± 2.4 years.

Allele frequencies in patients and healthy controls showed that both samples were in HWE (data not shown). Table 1 shows DRD3 Ser^2Gly and COMT Val^158Met genotype frequencies in patients and healthy controls. Regarding DRD3 Ser^2Gly, while Ser/Gly variant frequencies were nearly identical between both groups (48.2% vs. 50.6% for patients and controls, respectively), patients had significantly more Gly/Gly (26.8 vs. 8.0%) and less Ser/Ser (25.0 vs. 41.4%) relative to healthy controls (chi-square = 10.43, p = 0.005). For COMT Val^158Met polymorphisms, heterozygosity was significantly more frequent in patients than in healthy controls (Val/Met = 57.1 vs. 26.1%; chi-square = 14.14, p = 0.001).

Table 2 shows cognitive performance according to DRD3 Ser^2Gly and COMT Val^158Met genotypes for patients and healthy controls. Concerning DRD3 Ser^2Gly genotypes, while there was no effect of genotype on any of the cognitive measures in patients, the Ser/Gly genotype was associated with poorer executive function performance in healthy controls, as measured by TMT-B (p = 0.04). For COMT Val^158Met genotypes, only in the patient group was the Val/Val variant significantly related to poorer performance on attention measures (WAIS-DS; p = 0.02). The Met/Met genotype was associated with poorer performance on executive function tests in both patients and healthy controls. However, this was detected by means of the WCST-FMS in patients (p = 0.02), whereas in controls, the TMT-B showed a statistically significant difference (p = 0.01). Results from the other cognitive tests are provided in supplementary tables.

In healthy controls, all combinations between the two genotypes had the same effect on executive functioning as measured by the RCFT copy (all p > 0.05) (Figure 1). In the patient group, COMT Val/Val individuals also performed equally to controls (30.70-33.26 vs. 35.53-35.67), regardless of DRD3 genotype. However, as COMT Met allele frequency increased, cognitive functioning worsened for patients. For the COMT Val/Met genotype, this effect was most pronounced for DRD3 Ser/Ser subjects (25.903 for Ser/Ser vs. 29.642-30.304 for other DRD3 genotypes), whereas for COMT Met/Met genotypes, the DRD3 Ser/Ser genotype was associated with the poorest performance on executive functioning (16.184 vs. 27.388-31.824).

Pairwise comparisons showed that this specific COMT/DRD3 combination significantly differed from all DRD3 Gly/Gly combinations (p < 0.05), from COMT Val/Met DRD3 Ser/Ser (p = 0.02), and from COMT Val/Val DRD3 Ser/Ser (p = 0.01) in patients. It also significantly differed from all control scores (p < 0.001). Patients’ scores significantly differed from those of controls, except for those with the COMT Val/Val and COMT Met/Met DRD3 Gly/Gly genotypes.

When executive functioning and visual memory were assessed with the RCFT recall (Figure 2), all combinations

| Table 1 DRD3 Ser^2Gly and COMT Val^158Met genotype frequencies among patients and controls |
|-----------------|-----------------|-----------------|----------------|
|                 | Patients        | Controls        | p-value       |
| DRD3 Ser^2Gly   |                 |                 |               |
| Gly/Gly         | 15 (26.8)       | 7 (8.0)         |               |
| Ser/Gly         | 27 (48.2)       | 44 (50.6)       |               |
| Ser/Ser         | 14 (25.0)       | 36 (41.4)       | 10.43         |
|                 |                 |                 | 0.005         |
| COMT Val^158Met |                 |                 |               |
| Met/Met         | 11 (19.6)       | 26 (29.5)       |               |
| Val/Met         | 32 (57.1)       | 23 (26.1)       |               |
| Val/Val         | 13 (23.2)       | 39 (44.3)       | 14.14         |
|                 |                 |                 | 0.001         |

Data expressed as n (%). COMT = catechol-O-methyl transferase; DRD3 = dopamine receptor 3.
between the two genotypes had the same effect on cognitive functioning in controls and in patients. The only exceptions were COMT Val/Val carriers heterozygous for DRD3 Ser9Gly; their scores were significantly different from all other patient scores (19.739 vs. 1.28-10.833, p < 0.01), and this was the only genotype combination that showed performance comparable to that of controls (19.739 for patients and 18.943-28.77 for controls, p < 0.05).

**Discussion**

To our knowledge, this is the first study to evaluate the effects of epistasis between COMT Val<sup>158</sup>Met and DRD3 Ser<sup>9</sup>Gly polymorphisms on the cognitive functioning of patients with schizophrenia and healthy controls.

Our results showed that the DRD3 Ser<sup>9</sup>Gly Gly/Gly and COMT Val<sup>158</sup>Met heterozygote genotypes were significantly more frequent in patients than controls. Control heterozygotes for DRD3 Ser<sup>9</sup>Gly and both patients and controls carrying COMT Val<sup>158</sup>Met Met/Met showed poorer performance on executive function tests compared to the other groups. Patients carrying COMT Val<sup>158</sup>Met Val/Val performed poorly on attention tasks. Epistasis between DRD3 Ser<sup>9</sup>Gly Ser/Ser and COMT Val<sup>158</sup>Met Met/Met significantly worsened executive functioning in patients relative to healthy controls.

**Table 2** Analysis of variance (ANOVA) between neurocognitive performance, DRD3 Ser<sup>9</sup>Gly and COMT Val<sup>158</sup>Met genotypes

<table>
<thead>
<tr>
<th>Polymorphism/ cognitive domain/test</th>
<th>Patients</th>
<th>p-value</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD3 Ser&lt;sup&gt;9&lt;/sup&gt;Gly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive function TMT-B</td>
<td>144.88±96.98</td>
<td>135.65±55.58</td>
<td>149.00±96.47</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>48.00±29.58</td>
<td>66.15±41.45</td>
<td>50.05±20.99</td>
<td>0.04</td>
</tr>
<tr>
<td>COMT Val&lt;sup&gt;158&lt;/sup&gt;Met</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention WAIS-DS</td>
<td>7.27±1.55</td>
<td>7.39±1.98</td>
<td>6.67±1.72</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>10.83±2.95</td>
<td>10.62±2.21</td>
<td>10.25±2.06</td>
<td>0.25</td>
</tr>
<tr>
<td>Executive function WCST-FMS</td>
<td>1.18±0.87</td>
<td>0.48±0.71</td>
<td>0.42±0.67</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>0.21±0.77</td>
<td>0.42±1.10</td>
<td>0.33±0.73</td>
<td>0.66</td>
</tr>
<tr>
<td>TMT-B</td>
<td>137.18±62.42</td>
<td>154.48±93.11</td>
<td>110.33±78.76</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>72.34±47.11</td>
<td>53.31±24.55</td>
<td>53.08±25.95</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data expressed as mean ± standard deviation.
COMT = catechol-O-methyl transferase; DRD3 = dopamine receptor 3; TMT-B = Trail Making Test – Part B; WAIS-DS = Wechsler Adult Intelligence Scale – Digit Span subtest; WCST-FMS = Wisconsin Card Sorting Test – Failure to Maintain Set.

Data in bold indicate poorest performance.

**Figure 1** Analysis of covariance (ANCOVA) between executive function performance (Rey-Osterrieth Complex Figure Test – copy) and combinations of COMT rs4680 and DRD3 Ser<sup>9</sup>Gly genotypes. COMT = catechol-O-methyl transferase; DRD3 = dopamine receptor 3.
Genotype frequencies in patients with schizophrenia versus healthy controls

Differing from our finding of a higher frequency of DRD3 Ser9Gly Gly/Gly in patients, a number of previous studies reported no association between DRD3 Ser9Gly polymorphisms and schizophrenia.25 The synergistic effects of the DRD3 gene on susceptibility to schizophrenia and the possibility that this association might only be found in certain racial or clinical subgroups have been proposed as possible explanations for this absence of a relationship. Nevertheless, consistent with our results, more recent findings suggest an association between the Gly/Gly variant and schizophrenia.26-28 The Gly allele frequency reported herein is similar to that described in these studies, which provides further evidence supporting the hypothesis that this allele is under the influence of natural selection, being more frequent in Asian and Latin American regions.28

Regarding the relationship between the COMT Val158Met polymorphism and schizophrenia, although we found a higher frequency of heterozygosity among patients, there is no consensus in the literature about this issue. A meta-analysis conducted by Glatt et al.29 indicated that the Val158 allele might be a weak risk factor for the development of schizophrenia. However Costas et al.14 suggested that heterozygosity possesses a small but significant protective effect for the development of the disorder. Given the variety of findings,30,31 it is increasingly clear that such relationships are more complex than simple allele-disorder associations.32

Interactions between genotypes and cognitive measures

Few studies have evaluated the impact of DRD3 Ser9Gly polymorphisms on cognition. Our results corroborate the findings of Lane et al.,33 who observed poorer executive functioning performance in healthy volunteers heterozygous for the DRD3 Ser9Gly polymorphism. We also found that this polymorphism had no effect on the executive functioning of schizophrenic patients, similarly to the findings of Rybakowski et al.16 One group has reported results contrary to these findings,2 but the authors acknowledged that the different cognitive paradigm they studied possibly accounted for this contrary effect.

Regarding the effect of COMT Val158Met polymorphisms on cognition, our patients with schizophrenia carrying the Val/Val allele performed poorly in attention tests, a finding similar to those reported by previous studies34 on a normal population. However, when executive function was tested, Met/Met patients performed poorly compared to healthy controls. The effects of different COMT genotypes on cognition have been extensively studied, but great heterogeneity of results has been observed.35 Some studies found individuals with schizophrenia carrying the Val158 allele to present better cognitive performance,36 whereas others reported better performance of Met158 allele carriers37 or negative findings.38 Savitz et al.39 argued that differences in the specific cognitive domain assessed might, at least partly, account for these discrepancies. They hypothesized that hyperdopaminergic states would be associated with perseverative errors and thus with executive functioning deficits, while hypodopaminergic states would be more related to attention deficits. The fact...
that Met<sup>158</sup> carriers display lower enzymatic activity, thus contributing to a hyperdopaminergic state, while the presence of a Val<sup>158</sup> allele produces the opposite effect, corroborates our findings. We can thus hypothesize that patients with schizophrenia can be classified into two major groups according to the COMT genotype versus cognition interaction: individuals with schizophrenia carrying COMT Val/Val will have more genetically determined dopaminergic hypoactivity and attention deficits, while COMT Met/Met carriers will have more genetically determined dopaminergic hyperactivity and executive dysfunction. This could possibly explain, at least in part, why results simply relating COMT polymorphisms to the disorder fail to lead to a consensus.

Epistatic genetic interactions on cognition

Combining the effects of DRD3 Ser<sup>9</sup>Gly and COMT Val<sup>158</sup>Met genotypes, schizophrenia patients with a COMT Val/Val genotype performed similarly to healthy controls in executive functioning. Interestingly, schizophrenia patients carrying the COMT Met<sup>158</sup> allele showed poorer executive function performance relative to controls. Resuming what was stated previously and further discussing the issue, poor performance on cognitive tasks with a greater cognitive integration requirement, such as executive function tests, have been associated with hyperdopaminergic states and with the presence of the Met<sup>158</sup> allele. According to Howes & Kapur, cognitive dysfunction (and other schizophrenia symptoms) would be a result of a dopamine imbalance, mainly due to depletion of dopamine in the prefrontal cortex, leading to uncontrolled dopaminergic firing in other brain areas. As with executive functioning, demand for cognitive integration would also decrease in this case, and the lack of dopaminergic control inherent to schizophrenia would make Met<sup>158</sup> carriers more vulnerable to poorer cognitive performance. Resembling Savitz's theory, this might result from disordered and increased firing of dopaminergic neurons.

According to our results, if considered separately, DRD3 genotypes had no effect on patients’ cognition. However, when epistatic effects under high dopamine availability (COMT Met/Met) were weighed in the analyses, we found results similar to those of Szekeres et al., who also reported an association between DRD3 Ser/Ser genotype and poorer executive function performance in schizophrenic individuals.

Thus, the effect of the DRD3 polymorphism on cognition could only be unveiled when it was analyzed in combination with the COMT polymorphism; DRD3 Ser/Ser potentiated the poor cognitive performance effect of the COMT Met<sup>158</sup> allele. Similar findings were observed by Lee et al. when studying the same epistatic interaction in patients with bipolar disorder: the authors found that the same combination of polymorphisms was associated with type I bipolar disorder.

When visual memory was added to the cognitive paradigm through the RCFT recall subtest, the epistatic effects of the DRD3 Ser<sup>9</sup>Gly and COMT Val<sup>158</sup>Met polymorphisms on cognitive performance were amplified. Among patients with COMT Val<sup>158</sup>Met Val/Val, only those heterozygous for DRD3 rs6280 persisted, performing similar to controls. For all other genotype combinations, patients performed comparably worse than healthy controls. This suggests that, under a greater cognitive load, deficits in patients became more apparent, and that the above combination was the only one to confer “protection” against low cognitive performance.

Several methodological limitations should be considered in the interpretation of our results. First, the relatively modest sample size increases the risk of both type I and type II statistical errors. For instance, we contextualized our results with the findings of Lee et al., who investigated the same genotype combination and found similar data. However, their paradigm related diagnosis to genotype, while our paradigm related genotype to cognition within the diagnosis. Taking into account that Bombin et al. also found positive results for DRD3 but in the other direction (though pooling patients and controls in their results), our results should be approached with caution due to the possibility of type I error. Furthermore, sample size did not allow us to control our results for current use of medication, and obligated us to combine two genetic polymorphisms for pairwise comparisons. Even though these limitations were present, as cited above, our data are consistent with the international literature and provide some important contributions for future research. Thus, replication of the present findings in larger samples is warranted.

In conclusion, it is important to consider the epistasis of multiple genetic polymorphisms related to a neurotransmitter system. Our study confirmed the importance of dopaminergic neurotransmission in the pathophysiology of psychosis, especially in determining endophenotypic characteristics such as cognitive performance. More studies with larger samples should further analyze epistatic phenomena in an attempt to replicate these findings. Finally, this genetic paradigm could be tested in individuals at risk for psychosis, to determine whether it influences conversion rates or predicts a clinical course with poor cognitive performance.

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Disclosure

The authors report no conflicts of interest.

References

1 Lakhán SE, Vieira KF. Schizophrenia pathophysiology: are we any closer to a complete model? Ann Gen Psychiatry. 2009;8:12-12.


Genetic influence on dopamine transmission

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