

Catechol-*O*-Methyltransferase Val¹⁵⁸Met Polymorphism and Antisaccade Eye Movements in Schizophrenia

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The catechol-*O*-methyltransferase (COMT) enzyme catabolizes dopamine. The val¹⁵⁸met single nucleotide polymorphism (rs4680) in the COMT gene has received considerable attention as a candidate gene for schizophrenia as well as for frontally mediated cognitive functions. Antisaccade performance is a good measure of frontal lobe integrity. Deficits on the task are considered a trait marker for schizophrenia. The aim of this study was to investigate the association of COMT val¹⁵⁸met polymorphism with antisaccade eye movements in schizophrenia patients and healthy controls. Schizophrenia patients (N = 105) and healthy controls (N = 95) underwent infrared oculographic assessment of antisaccades. Subjects were genotyped for COMT val¹⁵⁸met and divided into 3 groups according to genotype (val/val, val/met, and met/met). Patients displayed significantly more reflexive errors, longer and more variable latency, and lower amplitude gain than controls (all $P < 0.02$). A greater number of val¹⁵⁸ alleles was associated with shorter ($P = 0.045$) and less variable ($P = 0.028$) antisaccade latency and, nonsignificantly, with lower reflexive error rate ($P = 0.056$). None of these variables showed a group-by-genotype interaction ($P > 0.1$). There were no significant associations of genotype with measures of amplitude gain or spatial error ($P > 0.2$). The results suggest that COMT val¹⁵⁸ carrier status is associated with better performance on the antisaccade task. Possible explanations of this finding are discussed.

Key words: COMT val¹⁵⁸met polymorphism/dopamine/oculomotor/antisaccade/schizophrenia/endophenotype

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Introduction

There is substantial evidence for the role of genetic factors in the etiology of schizophrenia, and recent molecular genetic studies suggest that several genes may be associated with the disorder.¹ However, no allelic variants with clear causative links to schizophrenia have yet been found for any gene.

Catechol-*O*-methyltransferase (COMT) is an enzyme involved in metabolic inactivation of dopamine,² a neurotransmitter known to play an important role in prefrontal cognitive functions.^{3,4} Because of the large body of evidence for abnormal prefrontal cortex function in schizophrenia⁵ and the role of dopamine in the treatment of schizophrenia,⁶ the COMT gene, located on chromosome 22q, is being intensively investigated as a potential susceptibility gene for schizophrenia.⁷ A codominant functional single nucleotide polymorphism in the COMT gene has attracted considerable attention. This mutation causes a substitution of methionine (met) for valine (val) at codon 158 of the membrane-bound isoform of the enzyme. The met¹⁵⁸ variant is 3–4 times less active than the val¹⁵⁸ variant. Therefore, met¹⁵⁸ homozygotes have less efficient COMT degradation than val¹⁵⁸ homozygotes and heterozygotes have intermediate enzyme activity.⁸

Investigations of humans have shown association between val¹⁵⁸met polymorphism (rs4680) and neuropsychological measures of prefrontal cortex function.^{9,10} Studies of associations with schizophrenia remain inconsistent. Although some have found the val¹⁵⁸ allele to be a risk factor for schizophrenia,^{11,12} others have not,^{13–15} and a recent meta-analysis did not support a significant association.¹⁶

The antisaccade task is a well-studied trait marker for schizophrenia.^{17–19} An antisaccade is a rapid eye movement to a location opposite of a peripheral visual stimulus. Patients with schizophrenia and their relatives make more frequent reflexive errors than controls.^{19,20} Studies have also found prolonged latency^{21–25} and decreased amplitude gain in patients and their relatives.^{21,22,26} Human lesion,^{27,28} animal electrophysiology,^{29,30} and human functional imaging studies^{31–33} demonstrate that frontal brain areas play an important role in antisaccade performance. The molecular genetic factors underlying antisaccade deficits in schizophrenia are unknown. A linkage

study of multigenerational families with schizophrenia showed linkage of a composite antisaccade and P50 suppression endophenotype to chromosome 22q,³⁴ but a study of COMT val¹⁵⁸met and antisaccades in young males did not find a significant association.³⁵

Based on the putative role of dopaminergic and frontal brain dysfunction in schizophrenia and the observation of frontally mediated antisaccade deficits in this condition,³¹ the present study aimed to investigate, for the first time, the relationship between COMT val¹⁵⁸met and antisaccade eye movements in schizophrenia patients and healthy controls.

Materials and Methods

Subjects

Subjects were drawn from a large study of eye movements in schizophrenia as presented elsewhere.³⁶ The sample consisted of 112 schizophrenia patients (mean age 41.0 years [SD = 9.9], 72.3% male) and 97 healthy controls (mean age 40.6 years [SD = 9.3], 63.9% male). Patients were recruited from the Division of Psychiatry at the Landspítali University Hospital in Reykjavik. The diagnosis was confirmed by an experienced psychiatrist according to research diagnostic criteria³⁷ using the Schedule of Affective Disorders and Schizophrenia—Lifetime Version.³⁸ Patients' symptom levels were assessed using the Positive and Negative Syndrome Scale (PANSS).³⁹ Almost 95% of patients were on stable treatment (>6 mo) with antipsychotic medications. The majority of patients were smokers (73.3%). Controls were recruited from the local community and were screened for history of axis I psychiatric disorder using the Mini-International Neuropsychiatric Interview.⁴⁰ Those with first- or second-degree relatives with psychotic illnesses were excluded. Twenty-one percent of controls were smokers. Subjects with history of neurological illness (eg, seizures, stroke, Parkinson's disease, neuro-ophthalmological abnormalities, head injury (causing loss of consciousness), and substance abuse/dependence in the past 12 months were excluded. All participants were Icelandic, between 18 and 55 years old, and provided written informed consent. The study protocol was approved by the Icelandic Scientific Ethics Committee.

COMT Val¹⁵⁸Met Genotyping

DNA was isolated from whole blood or lymphoblastoid cell lines using an extraction column method (Qiagen Inc., Valencia, California). Genotyping of the COMT val¹⁵⁸met polymorphism was carried out using the Centaurus platform (Nanogen Inc., San Diego, California).

Eye Movements

Eye movements were recorded from the left eye using infrared oculography (IRIS 6500; Skalar Medical BV,

Delft, The Netherlands) sampled at 500 Hz. Subjects were seated 57 cm from a 17-inch monitor. A white circular target (0.3°) was presented on a black background. Head movements were minimized using a chin rest.

Following a 3-point calibration trial (0°, ±12°) the antisaccade task began with the target in the central location (0°) for a random duration of 1000–2000 ms. The target then stepped to 1 of 4 peripheral locations (±6°, ±12°), where it remained for 1000 ms. Participants were instructed to look at the target while in the central position and redirect their gaze to the exact mirror image location of the target as soon as it moved to the side. Each peripheral location was used 15 times, resulting in a total of 60 trials presented in random order. Four practice trials were run prior to the task and could be repeated if needed.

Eye movements were analyzed with Eyemap 2.1 (AMTech GmbH, Weinheim, Germany). All data were scored blind to group status by 2 raters (M.H. and U.E.). Inter- and intrarater reliabilities were high ($r = 0.95–0.99$) for all antisaccade variables. It was not possible to analyze antisaccade data from 7 patients and 2 controls because of difficulties the subjects had in performing the task or due to excessive head movements and eye blinking during the task. Saccades were automatically detected on minimum amplitude (1°), velocity (30°/s), and latency (100 ms) criteria and individually categorized by a rater.

A correct antisaccade trial occurred when the participant performed a primary saccade in the direction opposite to the peripheral target. A reflexive error was counted when the participant performed a primary saccade toward the peripheral target. A corrective saccade was counted when an error was followed by a saccade in the opposite direction.

The following dependent variables were obtained: (1) Antisaccade reflexive error rate reflects the percentage of error trials over the total number of valid trials. (2) Latency of correct antisaccades was defined as the time (millisecond) from target appearance to saccade initiation. For each subject, the mean latency of all valid antisaccade trials was calculated. Additionally, we calculated the individual SD over these trials as a measure of intraindividual variability. (3) Amplitude gain of antisaccades (mean and SD) was calculated as the primary saccade amplitude divided by target amplitude multiplied by 100. (4) Spatial error (mean and SD) was obtained by calculating, for each saccade the percentage of residual error. Subtracting the target amplitude from the saccade amplitude and dividing the result by the target amplitude calculates residual error. The absolute value of this term reflects the residual error and is then averaged across all saccades and multiplied by 100.

Statistical Analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 11

Table 1: Demographic and Clinical Variables by Group and Genotype

Variable	Patients			Controls		
	val/val	val/met	met/met	val/val	val/met	met/met
n (%)	19 (18)	50 (48)	36 (34)	13 (14)	52 (55)	30 (31)
Gender ratio (male %)	84	68	72	85	65	53
Mean age (SD)	39 (10.1)	43 (9.3)	40 (10.4)	39 (7.1)	42 (8.8)	39 (10.9)
PANSS negative symptoms (mean [SD])	19.6 (6.9)	20.1 (6.4)	21.6 (8.5)			
PANSS positive symptoms (mean [SD])	14.2 (4.6)	14.9 (5.3)	15.5 (6.8)			
PANSS general (mean [SD])	36.3 (10.9)	37.9 (9.8)	39.3 (11.9)			
PANSS total (mean [SD])	70.0 (21.2)	72.9 (18.0)	76.3 (23.5)			

PANSS, Positive and Negative Syndrome Scale.

(SPSS Inc., Chicago, Illinois). Level of significance was set to $P < 0.05$. Outliers in the eye movement data were identified using box plots and all extreme values (more than 3 box lengths from edge of box) were removed. Distributions of antisaccade variables were assessed for normality using the skewness index. If positively (>1) or negatively (<1) skewed, variables were transformed using square root or square transformations, respectively.

The COMT allele distribution in the sample did not differ significantly from a distribution expected under Hardy-Weinberg equilibrium ($\chi^2 = 0.23$, $P = 0.89$).

Associations of group (patient, control) and genotype (val/val, val/met, met/met) with antisaccade performance were analyzed using multiple regression. Given previous evidence of the relationship between COMT val¹⁵⁸met allele dosage and cognitive function,^{9,41} genotype was entered as a linear predictor.

Chi-square tests were used to analyze the association between genotype (val/val, val/met, met/met) and gender (male, female) and between genotype and group (patient, control). The relationship between PANSS scores and genotype was investigated using regression and the association between age and genotype was assessed with 1-way analysis of variance.

Results

Genotype and Demographic Data

Genotype and eye movement data were obtained from 105 schizophrenia patients and 95 controls. In the patient group, there were 19 (18%) val¹⁵⁸ homozygotes, 50 (48%) val¹⁵⁸met heterozygotes, and 36 (34%) met¹⁵⁸ homozygotes. The control group included 13 (14%) val¹⁵⁸ homozygotes, 52 (55%) val¹⁵⁸met heterozygotes, and 30 (31%) met¹⁵⁸ homozygotes. Demographic statistics are summarized in table 1. The genotype frequencies did not differ significantly between the patient and control groups ($\chi^2 = 1.21$, $df = 2$, $P = 0.54$). No gender difference was found between genotype groups among patients, controls, or the combined

subject sample (all $P > 0.1$). No genotype association was found with age ($F(2,199) = 2.22$, $P = 0.11$) and there was no group-by-genotype interaction ($F(2,199) = 0.26$, $P = 0.77$). No associations were found between genotype and total PANSS score ($R^2 = 0.01$, $\beta = -3.21$, $P = 0.25$) or the individual PANSS subscores (all $P > 0.4$).

Antisaccade Eye Movements

Extreme value (outliers) antisaccade eye movement variables were removed from the data set for 4 subjects. For 2 patients, antisaccade latency was removed: for one control antisaccade gain and for the other control antisaccade spatial error. The following eye movement variables were skewed (skewness index): antisaccade latency SD (1.48) and antisaccade spatial error SD (1.75). Inferential statistical analyses were done on transformed variables, whereas the descriptive statistics in table 2 represents untransformed data.

A regression analysis demonstrated a significant effect of group on antisaccade error rate, amplitude gain, spatial error, latency, and the variability of latency (all $P < 0.02$). Schizophrenia patients had significantly higher error rate, lower amplitude gain, higher spatial error, and longer and more variable latency than controls.

The number of val¹⁵⁸ alleles was significantly related to antisaccade latency ($R^2 = 0.10$, $\beta = -1.14$, $P = 0.045$) and the variability of antisaccade latency ($R^2 = 0.10$, $\beta = -0.15$, $P = 0.028$) but there were no group-by-genotype interactions (all $P > 0.3$). Antisaccade latency and the variability of latency decreased with increasing number of val¹⁵⁸ alleles. The relationship between reflexive error rate and number of val¹⁵⁸ alleles fell marginally short of being significant ($R^2 = 0.36$, $\beta = -0.11$, $P = 0.056$) and there was no group-by-genotype interaction ($P = 0.11$). More val¹⁵⁸ alleles were nonsignificantly related to lower reflexive error rate. Figure 1 shows the COMT val¹⁵⁸met effects on antisaccade error rate antisaccade latency and latency variability.

There were no significant effects of genotype or genotype-by-group interactions for antisaccade gain,

Table 2. Antisaccade Variables by Group and Genotype

	Patients			Controls		
	val/val	val/met	met/met	val/val	val/met	met/met
Reflexive errors (%)	62.3 (24.4)	57.8 (20.2)	63.0 (22.1)	19.1 (11.2)	28.9 (17.1)	35.9 (24.4)
Latency (ms)	312.0 (66.0)	330.9 (79.2)	341.2 (80.3)	288.4 (45.5)	285.9 (42.5)	307.7 (43.1)
Variability of latency	58.5 (23.9)	76.9 (42.2)	79.5 (34.8)	56.8 (26.3)	52.7 (15.6)	60.3 (21.2)
Amplitude gain (%)	96.3 (35.5)	93.7 (29.8)	89.7 (25.5)	106.7 (19.6)	108.5 (27.6)	104.1 (26.4)
Variability of amplitude gain	48.1 (20.0)	47.0 (20.2)	45.4 (18.2)	46.2 (12.6)	46.6 (18.5)	48.9 (19.5)
Spatial error (%)	43.4 (15.5)	44.4 (12.9)	43.4 (12.7)	37.1 (10.4)	39.2 (13.7)	40.5 (12.6)
Variability of spatial error	5.5 (1.2)	5.4 (1.2)	5.2 (1.1)	5.4 (0.9)	5.2 (0.9)	5.5 (1.3)

Note: Data represent means (SDs) of antisaccade variables by group (patient, control) and catechol-*O*-methyltransferase genotype (val/val, val/met, met/met).

antisaccade spatial error, or the variability of these variables (all $P > 0.2$).

Discussion

In this study, we investigated the association between COMT val¹⁵⁸met polymorphism and performance on the antisaccade eye movement task. We found that a greater number of val¹⁵⁸ alleles were significantly associated with shorter and less variable antisaccade latency and it fell just short of being significantly related to lower number of reflexive errors. There were no significant group-by-genotype interactions for any antisaccade variable. The frequencies of val/val, val/met, and met/met carriers did not differ between schizophrenia patients and healthy controls. As in all previous studies, antisaccade performance was significantly impaired in schizophrenia patients compared with controls.¹⁹ See also Haraldsson *et al*³⁶ for a detailed discussion of psychometric properties of the patients' antisaccade performance in this sample.

The antisaccade task is an extensively studied trait marker for schizophrenia. Antisaccade performance has been shown to be more frequently impaired not only in schizophrenia patients but also in healthy relatives of patients,⁴² individuals at ultrahigh risk for psychosis⁴³ and individuals with schizotypal personality traits.³² Lesion,²⁸ functional imaging,^{31,33} and neuropsychological^{22,44} studies suggest that frontal areas such as dorsolateral prefrontal cortex, frontal and supplementary eye fields, and intraparietal sulcus are involved in antisaccade performance.

This is the first study investigating effects of COMT val¹⁵⁸met polymorphism on antisaccade eye movements in schizophrenia. We are only aware of 2 previously published studies on COMT val¹⁵⁸met and antisaccades in healthy subjects.^{35,45} Neither of them found a significant association between COMT val¹⁵⁸met carrier status and antisaccade task performance, although one reported a trend toward an association of higher error rates with the val¹⁵⁸ allele.³⁵

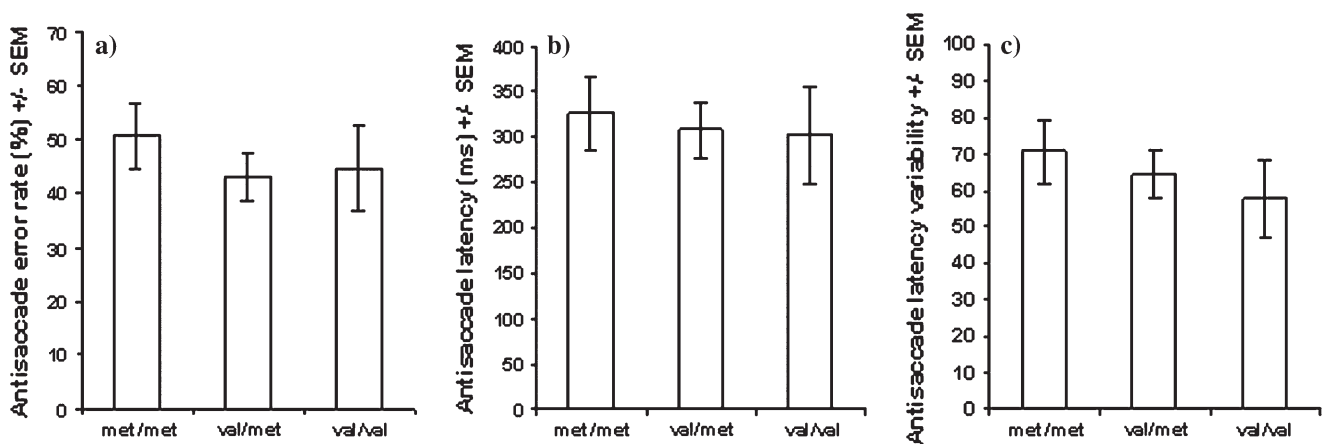


Fig. 1. Antisaccade Performance by catechol-*O*-methyltransferase (COMT) Val¹⁵⁸met Genotype. Error bars indicate ± 1 standard error of the mean. Figure shows mean antisaccade error rate (a), latency (b), and latency variability (c) by COMT val¹⁵⁸met genotype (met/met, val/met, val/val).

The finding of better antisaccade performance in val¹⁵⁸ carriers may be understood in terms of a number of different explanations. First, the results may be reconciled with a recent theory suggesting that the COMT val¹⁵⁸ allele is associated with better performance on tasks involving cognitive plasticity while the met¹⁵⁸ allele is hypothesized to be beneficial on tasks requiring cognitive stability.⁴⁶ The theory proposes that the high activity val¹⁵⁸ allele is associated with decreased tonic and increased phasic dopamine subcortically and decreased dopamine cortically and the opposite is thought to be true for the low activity met¹⁵⁸ allele. Cognitive stability is needed in tasks involving sustained attention, whereas cognitive plasticity is necessary in tasks consisting of, eg, shifts in rules, updating of working memory as well as monitoring and correction of response errors.⁴⁶ The antisaccade task can be conceptualized as a measure of cognitive plasticity such as inhibition of inappropriate responses, online monitoring of errors, and rapid generation of corrections. Additionally, antisaccade performance is sensitive to reward incentives,^{47,48} in line with the hypothesized properties of plasticity tasks.⁴⁶ However, like most complex cognitive tasks, the antisaccade task also entails elements of cognitive stability because constant alertness and sustained attention is necessary for adequate performance.

A second potential explanation for better antisaccade performance with a greater number of val¹⁵⁸ alleles may be the potential role of the met¹⁵⁸ allele in anxiety and anxiety-related traits as well as risk for other psychopathologies. There have been reports of met¹⁵⁸ being associated with increased anxiety^{49,50} and obsessive-compulsive disorder.⁵¹ Met¹⁵⁸ has also been associated with other psychiatric disorders such as bipolar disorder,^{52,53} attention deficit hyperactivity disorder (ADHD) traits,⁵⁴ and depression.⁵⁵ State-dependent anxiety,⁵⁶ obsessive-compulsive disorder^{57,58} and affective disorders^{59,60} have been associated with impaired antisaccade performance. It is possible that anxiety may have impaired the performance of the met¹⁵⁸ carriers on the antisaccade task. Measures of anxiety, affective, or ADHD symptoms or traits were not obtained in this study; therefore, this hypothesis would need to be tested in future studies.

Alternatively, the findings may be explained by alterations in prefrontal dopamine levels caused by interactions between the antisaccade task and COMT activity. There is evidence for prefrontal cognitive function having an inverted U-shaped relationship with dopamine levels.^{61,62} This means that prefrontal cognitive function is optimal at intermediate dopamine levels but impaired in hypo- and hyperdopaminergic states. It is possible that the antisaccade task procedure may have some arousing effects on the frontal cortex pushing the dopamine level too far to the right on the inverted U curve. The more active COMT val¹⁵⁸ may then counterbalance this effect better than the less efficient COMT

met¹⁵⁸ and bring the dopamine level closer to what is optimal for antisaccade performance.

Finally, there are indications that genotype-phenotype relationships in single gene association studies may be complicated by factors such as undetected copy number variations,⁶³ epigenetic phenomena,⁶⁴ and epistasis between several genes. For example, in a recent study, inefficient prefrontal working memory was found to be predicted by an epistatic interaction between the val¹⁵⁸met variation and 2 other single nucleotide pairs (SNPs) in the COMT gene.⁶⁵

A recent functional magnetic resonance imaging study may provide a neurobiological explanation for the present finding of an association of better antisaccade performance with a greater number of val¹⁵⁸ alleles. Ettinger et al⁴⁵ found that val¹⁵⁸ carriers showed deactivations of medial frontal brain areas during the antisaccade task, whereas noncarriers did not. It has been shown that deactivation of medial frontal areas is associated with better performance on the antisaccade task⁶⁶ and more efficient stimulus processing on a selective-attention task.⁶⁷

No statistically significant group-by-genotype interactions were found in the present study, suggesting that COMT val¹⁵⁸met polymorphism is associated with task performance irrespective of whether the subject has schizophrenia or not. However, for antisaccade error rate, inspection of table 2 suggests that the statistically nonsignificant effect is driven by performance in the controls but not the schizophrenia patients.

The COMT val¹⁵⁸met genotype status did not significantly relate to antisaccade amplitude gain and spatial error. These performance parameters are measures of the ability to match saccade amplitude to target amplitude. They are heavily dependent on the dorsal (magnocellular) visual stream, which is specialized for processing information on spatial orientation and transforming this signal into a motor output.⁶⁸ Previous studies have found decreased antisaccade amplitude gain in schizophrenia patients^{22,69} and their relatives.^{21,26} The present findings suggest that antisaccade amplitude gain and spatial error may be influenced by genotypes other than COMT val¹⁵⁸met.

The present study did not find COMT genotype effects on clinical symptoms of schizophrenia as determined by the PANSS. This finding is in line with a recent study, which also did not find any relationship between COMT val¹⁵⁸met polymorphism and PANSS scores in schizophrenia patients.⁷⁰ Another recent study did not observe any association between deficit/nondeficit symptoms of schizophrenia and val¹⁵⁸met.⁷¹ However, in 2 studies, associations were observed between the low activity met¹⁵⁸ allele and aggressive⁷² and suicidal behavior in schizophrenia patients.

We also did not find an association between COMT val¹⁵⁸met polymorphism and schizophrenia. While some studies have shown association with the met¹⁵⁸ allele,⁷³ others have found association with the val¹⁵⁸ allele¹² but most studies have not reported any association.^{13,74}

Two recent meta-analyses did not find support for a strong association between COMT val¹⁵⁸met polymorphism and schizophrenia.^{16,75}

It is highly unlikely that a potential relationship between COMT and schizophrenia is limited to a main effect of the val¹⁵⁸met polymorphism on the risk for schizophrenia. Therefore, investigators have studied the possibility that COMT val¹⁵⁸met interacts with other potential genetic and environmental risk factors for schizophrenia. Interestingly, a recent study found that val¹⁵⁸ carriers had an increased risk of developing schizophrenia if they used cannabis⁷⁶ and another study observed an association between several SNPs in the COMT gene (including rs4680) and SNPs in other potential schizophrenia risk genes.⁷⁷ These findings, and the role of COMT in dopamine regulation in the brain, suggest that the COMT gene might still represent a minor candidate gene for schizophrenia.⁷⁸

In conclusion, we observed a significant association between the number of COMT val¹⁵⁸ alleles and performance on the antisaccade task. No association was found between COMT genotype and symptoms of schizophrenia. Further research is needed to replicate these findings, preferably in larger and equally homogeneous samples and in individuals drawn from schizophrenia spectrum populations, such as biological relatives of patients.

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