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Catechol-*O*-Methyltransferase Val[158]Met Polymorphism and Antisaccade Eye Movements in Schizophrenia

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The catechol-*O*-methyltransferase (COMT) enzyme catabolizes dopamine. The val[158]met 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 val[158]met 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 val[158]met 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 val[158] 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 val[158] carrier status is associated with better performance on the antisaccade task. Possible explanations of this finding are discussed.

Key words: COMT val[158]met polymorphism/dopamine/oculomotor/antisaccade/schizophrenia/endophenotype

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 schizophrenia[5] 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 met[158] variant is 3–4 times less active than the val[158] variant. Therefore, met[158] homozygotes have less efficient COMT degradation than val[158] homozygotes and heterozygotes have intermediate enzyme activity.[8]

Investigations of humans have shown association between val[158]met polymorphism (rs4680) and neuropsychological measures of prefrontal cortex function.[9,10] Studies of associations with schizophrenia remain inconsistent. Although some have found the val[158] 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

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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 val[158]met 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 val[158]met 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 Landspitali University Hospital in Reykjavik. The diagnosis was confirmed by an experienced psychiatrist according to research diagnostic criteria[37] 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 Val[158]Met Genotyping

DNA was isolated from whole blood or lymphoblastoid cell lines using an extraction column method (Qiagen Inc., Valencia, California). Genotyping of the COMT val[158]met 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

	Patients			Controls		
Variable	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 val[158]met 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%) val[158] homozygotes, 50 (48%) val[158]met heterozygotes, and 36 (34%) met[158] homozygotes. The control group included 13 (14%) val[158] homozygotes, 52 (55%) val[158]met heterozygotes, and 30 (31%) met[158] 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 val[158] 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 val[158] alleles. The relationship between reflexive error rate and number of val[158] 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 val[158] alleles were nonsignificantly related to lower reflexive error rate. Figure 1 shows the COMT val[158]met 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 val^{158}met polymorphism and performance on the antisaccade eye movement task. We found that a greater number of val^{158} 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 psychosis[43] 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 val^{158}met polymorphism on antisaccade eye movements in schizophrenia. We are only aware of 2 previously published studies on COMT val^{158}met and antisaccades in healthy subjects.[35,45] Neither of them found a significant association between COMT val^{158}met carrier status and antisaccade task performance, although one reported a trend toward an association of higher error rates with the val^{158} allele.[35]

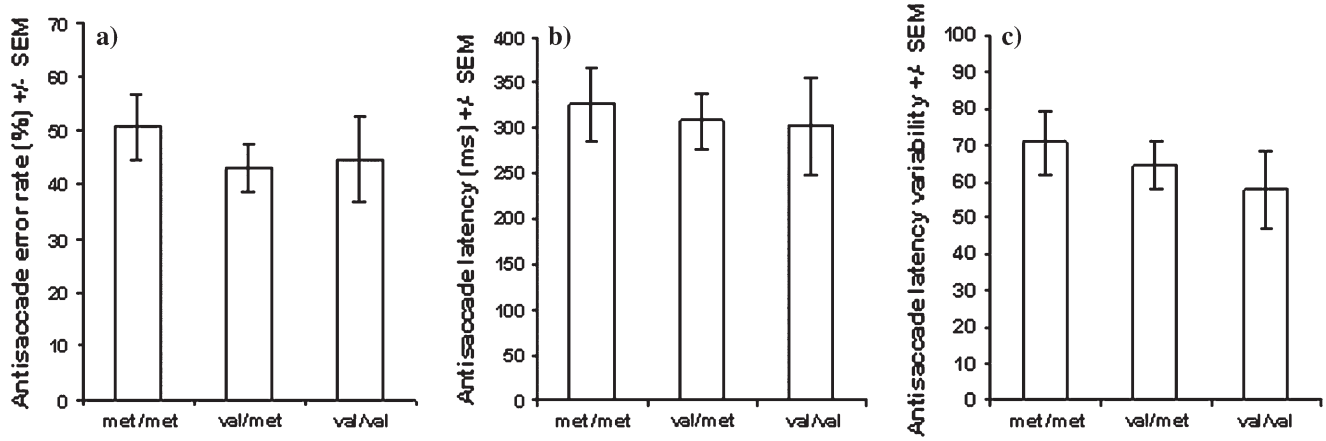

Fig. 1. Antisaccade Performance by catechol-*O*-methyltransferase (COMT) Val^{158}met Genotype. Error bars indicate ± 1 standard error of the mean. Figure shows mean antisaccade error rate (a), latency (b), and latency variability (c) by COMT val^{158}met genotype (met/met, val/met, val/val).

The finding of better antisaccade performance in val[158] 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 val[158] allele is associated with better performance on tasks involving cognitive plasticity while the met[158] allele is hypothesized to be beneficial on tasks requiring cognitive stability.[46] The theory proposes that the high activity val[158] 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 met[158] 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 val[158] alleles may be the potential role of the met[158] allele in anxiety and anxiety-related traits as well as risk for other psychopathologies. There have been reports of met[158] being associated with increased anxiety[49,50] and obsessive-compulsive disorder.[51] Met[158] 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 met[158] 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 val[158] may then counterbalance this effect better than the less efficient COMT met[158] 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 val[158]met 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 val[158] alleles. Ettinger et al[45] found that val[158] 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 task[66] 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 val[158]met 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 val[158]met 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 val[158]met.

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 val[158]met polymorphism and PANSS scores in schizophrenia patients.[70] Another recent study did not observe any association between deficit/nondeficit symptoms of schizophrenia and val[158]met.[71] However, in 2 studies, associations were observed between the low activity met[158] allele and aggressive[72] and suicidal behavior in schizophrenia patients.

We also did not find an association between COMT val[158]met polymorphism and schizophrenia. While some studies have shown association with the met[158] allele,[73] others have found association with the val[158] allele[12] but most studies have not reported any association.[13,74]

Two recent meta-analyses did not find support for a strong association between COMT val[158]met 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 val[158]met polymorphism on the risk for schizophrenia. Therefore, investigators have studied the possibility that COMT val[158]met interacts with other potential genetic and environmental risk factors for schizophrenia. Interestingly, a recent study found that val[158] carriers had an increased risk of developing schizophrenia if they used cannabis[76] 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 val[158] 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 homogenous samples and in individuals drawn from schizophrenia spectrum populations, such as biological relatives of patients.

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References

1. Riley B, Kendler KS. Molecular genetic studies of schizophrenia. *Eur J Hum Genet*. 2006;14(6):669–680.
2. Axelrod J, Tomchick R. Enzymatic O-methylation of epinephrine and other catechols. *J Biol Chem*. 1958;233(3):702–705.
3. Gasparini M, Fabrizio E, Bonifati V, Meco G. Cognitive improvement during tolcapone treatment in Parkinson's disease. *J Neural Transm*. 1997;104(8–9):887–894.
4. Sawaguchi T, Goldman-Rakic PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science*. 1991;251(4996):947–950.
5. Weinberger DR, Egan MF, Bertolino A, et al. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry*. 2001; 50(11):825–844.
6. Carlsson A. Historical aspects and future directions. In: Kapur S, ed. *Dopamine in the Pathophysiology and Treatment of Schizophrenia.* London: Taylor and Francis; 2003:1–13.
7. Craddock N, O'Donovan MC, Owen MJ. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophr Bull*. 2006;32(1):9–16.
8. Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics*. 1996;6(3):243–250.
9. Egan MF, Goldberg TE, Kolachana BS, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2001;98(12):6917–6922.
10. Goldberg TE, Egan MF, Gscheidle T, et al. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch Gen Psychiatry*. 2003;60(9):889–896.
11. Chen X, Wang X, O'Neill AF, Walsh D, Kendler KS. Variants in the catechol-o-methyltransferase (COMT) gene are associated with schizophrenia in Irish high-density families. *Mol Psychiatry*. 2004;9(10):962–967.
12. Shifman S, Bronstein M, Sternfeld M, et al. A highly significant association between a COMT haplotype and schizophrenia. *Am J Hum Genet*. 2002;71(6):1296–1302.
13. Chen CH, Lee YR, Chung MY, et al. Systematic mutation analysis of the catechol O-methyltransferase gene as a candidate gene for schizophrenia. *Am J Psychiatry*. 1999;156(8): 1273–1275.
14. Daniels JK, Williams NM, Williams J, et al. No evidence for allelic association between schizophrenia and a polymorphism determining high or low catechol O-methyltransferase activity. *Am J Psychiatry*. 1996;153(2):268–270.
15. Karayiorgou M, Gogos JA, Galke BL, et al. Identification of sequence variants and analysis of the role of the catechol-O-methyl-transferase gene in schizophrenia susceptibility. *Biol Psychiatry*. 1998;43(6):425–431.
16. Munafo MR, Bowes L, Clark TG, Flint J. Lack of association of the COMT (Val158/108 Met) gene and schizophrenia: a meta-analysis of case-control studies. *Mol Psychiatry*. 2005; 10(8):765–770.
17. Calkins ME, Iacono WG. Eye movement dysfunction in schizophrenia: a heritable characteristic for enhancing phenotype definition. *Am J Med Genet*. 2000;97(1):72–76.
18. Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. *Biol Psychiatry*. 1988; 23(7):670–677.
19. Hutton SB, Ettinger U. The antisaccade task as a research tool in psychopathology: a critical review. *Psychophysiology*. 2006;43(3):302–313.
20. Calkins ME, Curtis CE, Iacono WG, Grove WM. Antisaccade performance is impaired in medically and psychiatrically healthy biological relatives of schizophrenia patients. *Schizophr Res*. 2004;71(1):167–178.
21. Ettinger U, Picchioni M, Hall MH, et al. Antisaccade performance in monozygotic twins discordant for schizophrenia: the Maudsley twin study. *Am J Psychiatry*. 2006;163(3): 543–545.
22. Karoumi B, Ventre-Dominey J, Vighetto A, Dalery J, d'Amato T. Saccadic eye movements in schizophrenic patients. *Psychiatry Res*. 1998;77(1):9–19.

23. Klein C, Heinks T, Andresen B, Berg P, Moritz S. Impaired modulation of the saccadic contingent negative variation preceding antisaccades in schizophrenia. *Biol Psychiatry*. 2000; 47(11):978–990.
24. Thaker GK, Cassady S, Adami H, Moran M, Ross DE. Eye movements in spectrum personality disorders: comparison of community subjects and relatives of schizophrenic patients. *Am J Psychiatry*. 1996;153(3):362–368.
25. Thaker GK, Ross DE, Cassady SL, Adami HM, Medoff DR, Sherr J. Saccadic eye movement abnormalities in relatives of patients with schizophrenia. *Schizophr Res*. 2000;45(3): 235–244.
26. Ettinger U, Kumari V, Crawford TJ, et al. Smooth pursuit and antisaccade eye movements in siblings discordant for schizophrenia. *J Psychiatr Res*. 2004;38(2):177–184.
27. Fukushima J, Fukushima K, Miyasaka K, Yamashita I. Voluntary control of saccadic eye movement in patients with frontal cortical lesions and parkinsonian patients in comparison with that in schizophrenics. *Biol Psychiatry*. 1994;36(1): 21–30.
28. Pierrot-Deseilligny C, Rosa A, Masmoudi K, Rivaud S, Gaymard B. Saccade deficits after a unilateral lesion affecting the superior colliculus. *J Neurol Neurosurg Psychiatry*. 1991; 54(12):1106–1109.
29. Everling S, DeSouza JF. Rule-dependent activity for prosaccades and antisaccades in the primate prefrontal cortex. *J Cogn Neurosci*. 2005;17(9):1483–1496.
30. Funahashi S, Chafee MV, Goldman-Rakic PS. Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature*. 1993;365(6448):753–756.
31. McDowell JE, Brown GG, Paulus M, et al. Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biol Psychiatry*. 2002;51(3):216–223.
32. O'Driscoll GA, Alpert NM, Matthysse SW, Levy DL, Rauch SL, Holzman PS. Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. *Proc Natl Acad Sci USA*. 1995;92(3):925–929.
33. Sweeney JA, Mintun MA, Kwee S, et al. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J Neurophysiol*. 1996;75(1): 454–468.
34. Myles-Worsley M, Coon H, McDowell J, et al. Linkage of a composite inhibitory phenotype to a chromosome 22q locus in eight Utah families. *Am J Med Genet*. 1999;88(5):544–550.
35. Stefanis NC, Van Os J, Avramopoulos D, et al. Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. *Biol Psychiatry*. 2004;56(7):510–515.
36. Haraldsson HM, Ettinger U, Magnusdottir BB, Sigmundsson T, Sigurdsson E, Petursson H. Eye movement deficits in schizophrenia: investigation of a genetically homogenous Icelandic sample. *Eur Arch Psychiatry Clin Neurosci*. [published online ahead of print April 24, 2008].
37. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35(6):773–782.
38. Spitzer R, Endicott J. *The Schedule for Affective Disorders and Schizophrenia, Lifetime Version.* 3rd ed New York, NY: NewYork State Psychiatric Institute; 1977.
39. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
40. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59:(suppl 20):22–33; quiz 34–57.
41. Rosa A, Peralta V, Cuesta MJ, et al. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *Am J Psychiatry*. 2004;161(6):1110–1112.
42. Clementz BA, McDowell JE, Zisook S. Saccadic system functioning among schizophrenia patients and their first-degree biological relatives. *J Abnorm Psychol*. 1994;103(2):277–287.
43. Nieman D, Becker H, van de Fliert R, et al. Antisaccade task performance in patients at ultra high risk for developing psychosis. *Schizophr Res*. 2007;95(1–3):54–60.
44. Crawford TJ, Puri BK, Nijran KS, Jones B, Kennard C, Lewis SW. Abnormal saccadic distractibility in patients with schizophrenia: a 99mTc-HMPAO SPET study. *Psychol Med*. 1996;26(2):265–277.
45. Ettinger U, Kumari V, Collier DA, et al. Catechol-O-methyltransferase (COMT) Val^{158}Met genotype is associated with BOLD response as a function of task characteristic. *Neuropsychopharmacology*.[published online ahead of print January 30, 2008].
46. Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology*. 2004;29(11):1943–1961.
47. Duka T, Lupp A. The effects of incentive on antisaccades: is a dopaminergic mechanism involved? *Behav Pharmacol*. 1997;8(5):373–382.
48. Jazbec S, McClure E, Hardin M, Pine DS, Ernst M. Cognitive control under contingencies in anxious and depressed adolescents: an antisaccade task. *Biol Psychiatry*. 2005; 58(8):632–639.
49. Enoch MA, Xu K, Ferro E, Harris CR, Goldman D. Genetic origins of anxiety in women: a role for a functional catechol-O-methyltransferase polymorphism. *Psychiatr Genet*. 2003; 13(1):33–41.
50. Woo JM, Yoon KS, Choi YH, Oh KS, Lee YS, Yu BH. The association between panic disorder and the L/L genotype of catechol-O-methyltransferase. *J Psychiatr Res*. 2004;38(4):365–370.
51. Karayiorgou M, Altemus M, Galke BL, et al. Genotype determining low catechol-O-methyltransferase activity as a risk factor for obsessive-compulsive disorder. *Proc Natl Acad Sci U S A*. 1997;94(9):4572–4575.
52. Kirov G, Murphy KC, Arranz MJ, et al. Low activity allele of catechol-O-methyltransferase gene associated with rapid cycling bipolar disorder. *Mol Psychiatry*. 1998;3(4):342–345.
53. Li T, Vallada H, Curtis D, et al. Catechol-O-methyltransferase Val158Met polymorphism: frequency analysis in Han Chinese subjects and allelic association of the low activity allele with bipolar affective disorder. *Pharmacogenetics*. 1997;7(5):349–353.
54. Reuter M, Kirsch P, Hennig J. Inferring candidate genes for attention deficit hyperactivity disorder (ADHD) assessed by the World Health Organization Adult ADHD Self-Report Scale (ASRS). *J Neural Transm*. 2006;113(7):929–938.
55. Ohara K, Nagai M, Suzuki Y, Ohara K. Low activity allele of catechol-o-methyltransferase gene and Japanese unipolar depression. *Neuroreport*. 1998;9(7):1305–1308.

56. Smyrnis N, Evdokimidis I, Stefanis NC, et al. Antisaccade performance of 1,273 men: effects of schizotypy, anxiety, and depression. *J Abnorm Psychol*. 2003;112(3):403–414.
57. Rosenberg DR, Dick EL, O'Hearn KM, Sweeney JA. Response-inhibition deficits in obsessive-compulsive disorder: an indicator of dysfunction in frontostriatal circuits. *J Psychiatry Neurosci*. 1997;22(1):29–38.
58. Tien AY, Pearlson GD, Machlin SR, Bylsma FW, Hoehn-Saric R. Oculomotor performance in obsessive-compulsive disorder. *Am J Psychiatry*. 1992;149(5):641–646.
59. Katsanis J, Kortenkamp S, Iacono WG, Grove WM. Antisaccade performance in patients with schizophrenia and affective disorder. *J Abnorm Psychol*. 1997;106(3):468–472.
60. Sereno AB, Holzman PS. Antisaccades and smooth pursuit eye movements in schizophrenia. *Biol Psychiatry*. 1995;37(6):394–401.
61. Goldman-Rakic PS, Muly EC, III, Williams GV. D(1) receptors in prefrontal cells and circuits. *Brain Res Brain Res Rev*. 2000;31(2–3):295–301.
62. Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-methyltransferase, cognition, and psychosis: val158met and beyond. *Biol Psychiatry*. 2006;60(2):141–151.
63. Sutrala SR, Goossens D, Williams NM, et al. Gene copy number variation in schizophrenia. *Schizophr Res*. 2007;96(1–3):93–99.
64. Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. *Nat Rev Neurosci*. 2007;8(5):355–367.
65. Meyer-Lindenberg A, Nichols T, Callicott JH, et al. Impact of complex genetic variation in COMT on human brain function. *Mol Psychiatry*. 2006;11(9):867–877, 797.
66. Polli FE, Barton JJ, Cain MS, Thakkar KN, Rauch SL, Manoach DS. Rostral and dorsal anterior cingulate cortex make dissociable contributions during antisaccade error commission. *Proc Natl Acad Sci U S A*. 2005;102(43):15700–15705.
67. Weissman DH, Roberts KC, Visscher KM, Woldorff MG. The neural bases of momentary lapses in attention. *Nat Neurosci*. 2006;9(7):971–978.
68. Ungerleider LG, Courtney SM, Haxby JV. A neural system for human visual working memory. *Proc Natl Acad Sci U S A*. 1998;95(3):883–890.
69. McDowell JE, Myles-Worsley M, Coon H, Byerley W, Clementz BA. Measuring liability for schizophrenia using optimized antisaccade stimulus parameters. *Psychophysiology*. 1999;36(1):138–141.
70. Strous RD, Lapidus R, Viglin D, Kotler M, Lachman HM. Analysis of an association between the COMT polymorphism and clinical symptomatology in schizophrenia. *Neurosci Lett*. 2006;393(2–3):170–173.
71. Wonodi I, Mitchell BD, Stine OC, et al. Lack of association between COMT gene and deficit/nondeficit schizophrenia. *Behav Brain Funct*. 2006;2:42.
72. Strous RD, Nolan KA, Lapidus R, Diaz L, Saito T, Lachman HM. Aggressive behavior in schizophrenia is associated with the low enzyme activity COMT polymorphism: a replication study. *Am J Med Genet B Neuropsychiatr Genet*. 2003;120(1):29–34.
73. Ohmori O, Shinkai T, Kojima H, et al. Association study of a functional catechol-O-methyltransferase gene polymorphism in Japanese schizophrenics. *Neurosci Lett*. 1998;243(1–3):109–112.
74. Rujescu D, Giegling I, Gietl A, Hartmann AM, Moller HJ. A functional single nucleotide polymorphism (V158M) in the COMT gene is associated with aggressive personality traits. *Biol Psychiatry*. 2003;54(1):34–39.
75. Fan JB, Zhang CS, Gu NF, et al. Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. *Biol Psychiatry*. 2005;57(2):139–144.
76. Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry*. 2005;57(10):1117–1127.
77. Nicodemus KK, Kolachana BS, Vakkalanka R, et al. Evidence for statistical epistasis between catechol-O-methyltransferase (COMT) and polymorphisms in RGS4, G72 (DAOA), GRM3, and DISC1: influence on risk of schizophrenia. *Hum Genet*. 2007;120(6):889–906.
78. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry*. 2005;10(1):40–68; image 45.