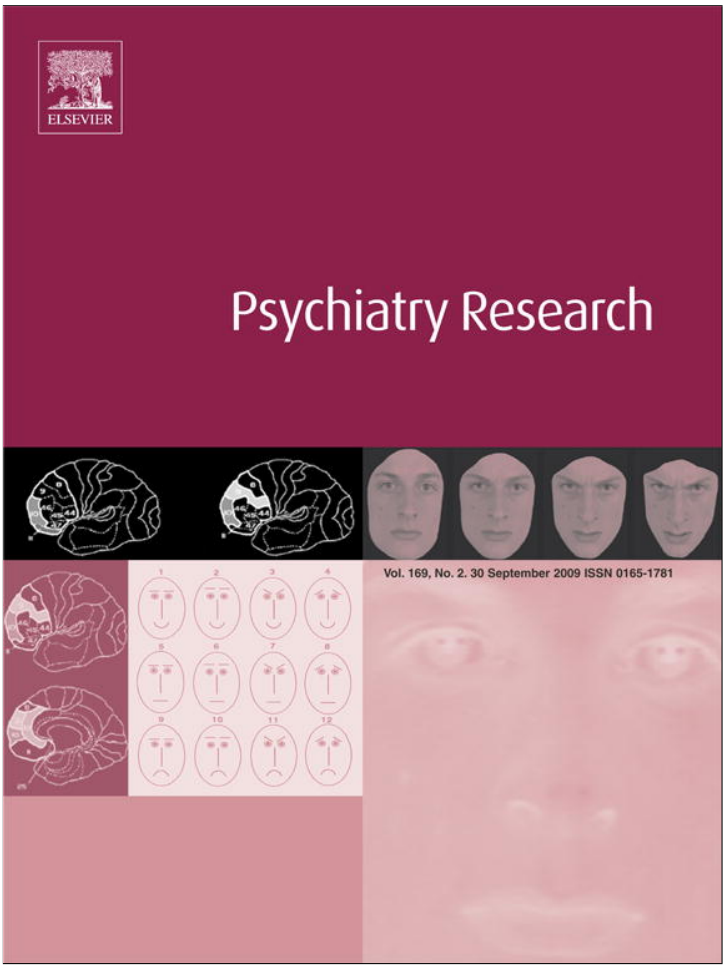

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Brief report

# COMT val$^{158}$met genotype and smooth pursuit eye movements in schizophrenia

H. Magnus Haraldsson [a,*], Ulrich Ettinger [b], Brynja B. Magnusdottir [a,b], Thordur Sigmundsson [a], Engilbert Sigurdsson [a], Andres Ingason [c], Hannes Petursson [a]

[a] Division of Psychiatry, Landspitali-University Hospital, Reykjavik, Iceland
[b] Institute of Psychiatry, King's College London, London, UK
[c] Institute of Biological Psychiatry, Copenhagen University, Roskilde, Denmark

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ABSTRACT

The association between the catechol-*O*-methyltransferase (COMT) val$^{158}$met polymorphism (rs4680) and smooth pursuit eye movements (SPEM) was investigated in 110 schizophrenia patients and 96 controls. Patients had lower steady-state pursuit gain and made more frequent saccades than controls. Genotype was not associated with schizophrenia or SPEM, in either group or the combined sample. SPEM deficits in schizophrenia appear to be determined by genotypes other than rs4680, although the study may have lacked power to detect small effects.



## 1. Introduction

Abnormal smooth pursuit eye movements (SPEM) are promising endophenotypes for genetic studies of schizophrenia (Trillenberg et al., 2004). SPEM involves complex co-ordinations of multiple sensory-motor brain areas (Petit and Haxby, 1999). Deficits in SPEM in medication-naïve schizophrenia patients and their first-degree relatives have been linked to frontal brain dysfunctions in functional imaging studies (O´Driscoll et al., 1999; Keedy et al., 2006). The genetic factors involved in SPEM deficits in schizophrenia are not known, but important headway was made when two independent groups reported that impaired SPEM performance was associated with markers on chromosome 6p (Arolt et al., 1996, 1999; Matthysse et al., 2004).

Animal and human studies have shown that dopamine plays an important role in prefrontal cognitive functions (Sawaguchi and Goldman-Rakic, 1991). Catechol-*O*-methyltransferase (COMT) is involved in the regulation of prefrontal dopamine levels (Tunbridge et al., 2006). A functional polymorphism (val$^{158}$met, rs4680) in the COMT gene has been associated with performance on tasks measuring frontal brain function (Egan et al., 2001; Goldberg et al., 2003). The met$^{158}$ variant has three to four times less active dopamine degradation than the val$^{158}$ variant (Lachman et al., 1996). There is considerable support for involvement of abnormal prefrontal brain function in schizophrenia (Weinberger et al., 2001) and some evidence for COMT val$^{158}$met being a risk genotype for schizophrenia or frontal dysfunction (Williams et al., 2007).

We are aware of two previous studies of COMT val$^{158}$met and SPEM (Rybakowski et al., 2002; Thaker et al., 2004). Thaker et al. (2004) found that healthy met$^{158}$ homozygotes had better predictive pursuit gain than healthy val$^{158}$ homozygotes, but a non-significant reverse pattern was observed in schizophrenia patients. In a study by Rybakowski et al. (2002), met$^{158}$ homozygous male schizophrenia patients had lower mean intensity of saccades during SPEM than male patients carrying at least one val allele, but no such effect was found in females.

The aim of the present study was to further investigate the association between the COMT val$^{158}$met polymorphism and SPEM velocity gain and the frequency of saccades during pursuit in large groups of schizophrenia patients and healthy controls drawn from the genetically homogenous Icelandic population.

## 2. Methods

Genotype and eye movement data were obtained from 110 schizophrenia patients (mean age = 41 years (S.D. = 10); 72% males) and 96 healthy control subjects (mean age = 41 (S.D. = 9); 64% males). Diagnoses were confirmed using the Schedule for Affective Disorders and Schizophrenia — Lifetime Version (SADS-L) (Spitzer and Endicott, 1977). Over 90% of patients were on stable treatment with antipsychotic medications. Control subjects with history of axis I psychiatric disorders and those with first- or second-degree relatives with a psychotic illness were not recruited. Subjects with a history of neurological illness (e.g. stroke, seizures, Parkinson's disease), ophthalmological abnormalities, head injury (causing loss of consciousness), and substance abuse/dependence in the past 12 months were excluded. The Icelandic Scientific Ethics Committee approved the study. All participants were Caucasian, 18–55 years old, and provided written informed consent.

Eye movements were recorded using infrared oculography (IRIS 6500) at 500 Hz. A triangular target waveform was employed at 12°, 24° and 36°s, and 16.5 half-cycles were run at each target velocity, resulting in durations of 33 s, 16.5 s, and 11 s, respectively. The SPEM task and analysis method is described in detail elsewhere (Ettinger et al., 2003).

SPEM analysis was carried out using LabView. All data were scored blind to group status by one rater (HMH) and confirmed by a second rater (UE). Inter- and intra-rater

* Corresponding author. Division of Psychiatry, Landspitali-University Hospital, Hringbraut, 101, Reykjavik, Iceland. Tel.: +354 5434050; fax: +354 5434016.
*E-mail address:* hmagnus@landspitali.is (H.M. Haraldsson).

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reliabilities were high ($r = 0.95$–$0.99$). Smooth pursuit velocity gain was calculated by dividing mean eye velocity by target velocity. Saccades were automatically identified on the basis of minimum amplitude (1°) and velocity (30°/s). The number of saccades was established at each target velocity and divided by the duration of the task to yield measures of saccadic frequency (N/s).

DNA was isolated from whole blood or lymphoblastoid cell lines using an extraction column method (Qiagen Inc., Valencia, CA USA). Genotyping of the COMT val$^{158}$met polymorphism was carried out using the Centaurus platform (Nanogen Inc. San Diego, CA, USA). The COMT allele distribution did not differ significantly from a distribution expected under Hardy–Weinberg equilibrium ($\chi^2 = 0.23$; $P = 0.89$).

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS), version 11 (SPSS, Inc., Chicago, IL, USA). Level of significance was set to $P<0.05$. Smooth pursuit data were analyzed using repeated measures analysis of variance (ANOVA) with Velocity (12°/s, 24°/s, 36°/s) as the within-subjects variable and Diagnosis (patient, control), Gender (male, female) and Genotype (met/met, val/met, val/val) as the between-subjects variables. If assumptions of sphericity were violated, Greenhouse–Geisser epsilon corrections of degrees of freedom were used.

## 3. Results

There were 39 (38%) patients with the met/met genotype, 52 (47%) with the val/met genotype, and 19 (17%) with the val/val genotype. The control group included 30 (31%) with the met/met genotype, 53 (55%) with the val/met genotype, and 13 (14%) with the val/val genotype. The genotype distribution did not differ significantly between patients and controls ($\chi^2 = 1.36$, $df = 2$, $P = 0.51$).

Descriptive statistics for SPEM velocity gain and saccade frequency by Genotype and Group are shown in Table 1. For SPEM velocity gain, the main effects of Velocity ($F[2,343] = 278.10$; $P<0.001$) and Diagnosis ($F[1,200] = 20.20$; $P<0.001$) were significant, and there was a significant Velocity–Diagnosis interaction ($F[2,314] = 12.19$; $P<0.001$). Pursuit gain deteriorated with increasing target velocity, patients had lower pursuit gain than controls, and the difference between patients and controls increased with increasing target velocity. There were no significant Diagnosis–Genotype ($F[2,200] = 0.25$; $P = 0.25$) or Velocity–Genotype ($F[3,314] = 0.63$; $P = 0.60$) interactions. Furthermore, there was no main effect of Gender ($F[1,194] = 0.06$; $P = 0.81$) and the following interactions were not significant; Gender–Velocity ($F[2,194] = 2.15$; $P = 0.13$), Gender–Diagnosis ($F[1,194] = 1.82$; $P = 0.18$), Gender–Genotype ($F[2,194] = 2.40$; $P = 0.09$), Diagnosis–Gender–Genotype ($F[2,194] = 0.87$; $P = 0.42$), Velocity–Diagnosis–Genotype ($F[3,314] = 0.13$; $P = 0.95$) and the four-way Gender–Genotype–Diagnosis–Velocity ($F[4,194] = 0.99$; $P = 0.40$).

However, inspection of Table 1 reveals that for all three target velocities the patient val/val homozygotes had numerically lower (3–5%) pursuit gain than the patient met/met homozygotes with small effect size ($d = 0.16$–$0.23$). A power calculation showed that 230 subjects for both genotype groups are needed for the difference to be significant at 12°/s and 400–500 subjects for the 24°/s and 36°/s target velocities ($\alpha$ error = 5%, $\beta$ error = 20%).

For SPEM saccade frequency the main effects of Velocity ($F[2,343] = 278.09$; $P<0.001$) and Diagnosis ($F[1,198] = 15.54$; $P<0.001$) were significant, but there was no significant Velocity-by-Diagnosis interaction ($F[2,343] = 0.91$; $P = 0.39$). Saccadic frequency increased with increasing target velocity and patients made more saccades than controls. The Diagnosis–Genotype ($F[2,192] = 0.63$; $P = 0.54$) and Velocity–Genotype ($F[4,192] = 0.92$; $P = 0.44$) interactions were not significant. There was no main effect of Gender ($F[1,192] = 1.01$; $P = 0.32$) and the following interactions were not significant; Gender–Velocity ($F[2,192] = 1.23$; $P = 0.29$), Gender–Diagnosis ($F[1,192] = 0.90$; $P = 0.34$), Gender–Genotype ($F[2,192] = 0.52$; $P = 0.60$), Diagnosis–Gender–Genotype ($F[2,192] = 0.83$; $P = 0.44$), Velocity–Diagnosis–Genotype ($F[4,192] = 1.29$; $P = 0.28$) and the four-way Gender–Genotype–Diagnosis–Velocity ($F[4,192] = 1.93$; $P = 0.12$). There was only 1–2% difference in saccade frequency between val/val and met/met subjects, and the direction of this genotype difference was not consistent between target velocities (Table 1).

**Table 1**
Descriptive statistics of smooth pursuit variables.

| *N* (%) | Patients | | | Controls | | |
|---|---|---|---|---|---|---|
| | Val/Val | Val/Met | Met/Met | Val/Val | Val/Met | Met/Met |
| | 19 (17) | 52 (47) | 39 (38) | 13 (14) | 53 (55) | 30 (31) |
| *Gain %* | | | | | | |
| 12°/s | 90.2 (11.4) | 92.0 (11.1) | 94.1 (10.4) | 95.3 (10.4) | 94.9 (6.8) | 95.5 (9.1) |
| 24°/s | 81.7 (16.1) | 84.2 (14.3) | 84.4 (16.6) | 91.0 (15.0) | 93.1 (11.0) | 92.3 (10.0) |
| 36°/s | 64.0 (21.5) | 64.9 (18.5) | 69.3 (21.8) | 80.4 (17.5) | 79.1 (17.3) | 80.5 (13.7) |
| *Saccades N/s* | | | | | | |
| 12°/s | 1.46 (0.66) | 1.53 (0.55) | 1.54 (0.55) | 1.40 (0.91) | 1.06 (0.43) | 1.24 (0.51) |
| 24°/s | 2.43 (0.87) | 2.37 (0.68) | 2.17 (0.71) | 1.78 (0.96) | 1.83 (0.71) | 2.06 (0.89) |
| 36°/s | 3.01 (1.20) | 3.05 (0.89) | 2.83 (0.90) | 2.47 (0.84) | 2.58 (0.75) | 2.67 (1.06) |

Legend: Data are given in means (standard deviations) for smooth pursuit variables by Group (patient, control) and COMT Genotype (val/val, val/met, met/met).

## 4. Discussion

In the present study schizophrenia patients had significantly lower steady-state gain and higher saccade frequency than controls at all three target velocities, replicating most previous studies using similar methods (Trillenberg et al., 2004). No significant association was found between COMT val$^{158}$met genotype and SPEM steady-state gain or saccade frequency in large groups of schizophrenia patients and healthy controls. However, for all three target velocities, the patient val$^{158}$ homozygotes had numerically lower pursuit gain than met$^{158}$ homozygotes, in accordance with previous findings of worse neurocognitive performance in val allele carriers (Egan et al., 2001; Goldberg et al., 2003). The study may therefore lack power to detect a small COMT effect on SPEM velocity gain in patients.

Similar to our observations, Thaker et al. (2004) did not find the COMT val$^{158}$met genotype to be associated with steady-state pursuit gain in 53 healthy subjects and 62 schizophrenia patients. However, they found that healthy subjects with the met/met genotype had higher predictive pursuit gain than healthy subjects with the val/val genotype, whereas met/met patients had non-significantly lower predictive pursuit than patients with the val/val genotype. In the predictive pursuit task the target is intermittently masked in order to specifically test extra-retinal processes involved in SPEM whereas the traditional steady-state pursuit task involves both retinal and extra-retinal processes (Lencer et al., 2004; Hong et al., 2005). The findings in Thaker's study suggest that extra-retinal SPEM processes may be more sensitive to differences in prefrontal dopamine levels. A recent study found that predictive pursuit had stronger sibling-pair correlations and larger heritability estimates than the steady-state SPEM task (Hong et al., 2006). Predictive pursuit deficits may therefore represent a more refined endophenotype with a less complicated genetic basis than steady-state pursuit deficits. The explanation for the failure to find COMT val$^{158}$met effects on SPEM pursuit gain in the present study could relate to our use of the traditional steady-state SPEM task, which may be a more global assessment of the pursuit system than the predictive pursuit task.

Rybakowski et al. (2002) found that male schizophrenia patients with the met/met genotype had lower mean saccade intensity than those with the val/met and val/val genotypes, while no significant genotype effects were found in female patients or healthy controls. They did not directly study saccade frequency. Instead they classified the intensity of saccade disturbance into four categories using a 0–3 scale, ranging from no saccades to high saccade frequency, and compared clinical and genotype groups using non-parametric tests. It may therefore be difficult to compare these results with the present findings. We did not find any Genotype-by-Gender interactions for SPEM velocity gain or saccade frequency in patients or controls.

We did not analyze the spatial accuracy of saccades during SPEM. While previous work has used this information to refine the endophenotype (Ross et al., 2002), the issue needs to be investigated in future studies.

In conclusion, studies to date have not found any clear association between the COMT val$^{158}$met genotype and the well-established impairments in SPEM steady-state gain or saccade frequency in schizophrenia, but one previous study showed that this polymorphism modulates SPEM predictive pursuit.

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