Well-being and co-morbidity in recent onset schizophrenia
van Nimwegen, L.J.M.

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Chapter 2.2

The catechol-o-methyltransferase gene and obsessive-compulsive symptoms in patients with recent onset schizophrenia


Janneke Zinkstok, Lonneke van Nimwegen, Therese van Amelsvoort, Lieuwe de Haan, Maryan Abdulkadir Yusuf, Frank Baas, Don Linszen.
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Abstract

The catechol-O-methyltransferase (COMT) gene is a candidate gene for schizophrenia because of its role in the breakdown of dopamine in the prefrontal cortex. The COMT gene contains a functional polymorphism changing enzyme activity, which has been associated with some neuropsychiatric (endo) phenotypes, e.g. cognitive performance and anxiety. In this study we investigated association between the COMT Val^{158}Met polymorphism and obsessive-compulsive symptoms in patients with schizophrenia. Severity of obsessive-compulsive symptoms in 77 male patients with recent-onset schizophrenia was assessed using the Y-BOCS and the COMT Val^{158}Met polymorphism was genotyped for these patients. We found a significant effect of COMT genotype on Y-BOCS scores: the Val/Val genotype was associated with highest Y-BOCS scores, whereas patients with Met/Met genotype had lowest Y-BOCS scores. Our data suggest that the COMT high-activity Val allele is associated with more obsessive-compulsive symptoms in young patients with schizophrenia. These results support the hypothesis that the COMT Val^{158}Met polymorphism may be a modifier gene for the symptomatology of schizophrenia.
Introduction

The enzyme catechol-O-methyltransferase (COMT) is involved in degradation of catecholamines, including dopamine. The COMT gene contains a functional polymorphism (Val^{158}Met) changing enzyme activity: the relatively unstable Met/Met variant leads to a 40% decrease in enzyme activity in comparison to the Val/Val variant. The COMT gene is located on the chromosomal region at 22q11, which is deleted in people with velocardiofacial syndrome (VCFS), a syndrome associated with a high prevalence of neuropsychiatric disorders, including schizophrenia-like psychosis and obsessive-compulsive disorder (OCD) (Gothelf et al 2004, Murphy et al 1999). For this reason, and because dopamine is hypothesized to be involved in the pathophysiology of schizophrenia, association between the COMT Val^{158}Met polymorphism and the prevalence of schizophrenia has been investigated extensively. Although results from a recent meta-analysis show that the Val^{158}Met polymorphism does not increase risk for schizophrenia (Munafo et al 2005), there is evidence that the COMT Val^{158}Met polymorphism modifies the schizophrenia phenotype by influencing performance of tasks relying on prefrontal cortex integrity (Egan et al 2001). Thus, COMT is probably not a susceptibility gene but merely a modifier gene for schizophrenia, meaning COMT may influence clinical features and symptom dimensions associated with schizophrenia without altering disease liability itself (Fanous and Kendler 2005, Tunbridge et al 2006). A well-established, frequently occurring and disabling symptom complex in schizophrenia is the co-occurrence of obsessive-compulsive symptoms (OCS) (Byerly et al 2005, Nechmad et al 2003, Ongur and Golff 2005, Poyurovsky et al 1999).

In this study we investigated the role of COMT as a modifier gene in schizophrenia: we explored whether there is a relation between COMT Val^{158}Met genotype and OCS in a group of patients with recent-onset schizophrenia.

Methods

Subjects

All patients were admitted to the Adolescent Clinic of the Academic Medical Center in Amsterdam. After complete description of the study to the subjects, written informed consent was obtained. The Medical Ethics Committee of the Academic Medical Center in Amsterdam approved the study. Patients who met DSM-IV (American Psychiatric Association 2004) criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder were included in the study. Exclusion criteria
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were organic brain syndrome, endocrine disorder, and substance-induced psychosis. Diagnosis at discharge was established according to DSM-IV criteria and was based on a semi-structured clinical interview by 2 independent psychiatrists as described previously (de Haan et al 2002); diagnoses were based on all available clinical information including the semi-structured interview, examination of case-records and information from relatives and mental health professionals. On admission, symptoms were rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987); the extent of OCS was assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al 1989). The Y-BOCS consists of 10 topics with scores ranging from 0 (no symptoms) to 4 (severe symptoms). Obsessions were defined as persistent, intrusive, unwanted, and repetitive thoughts not related to the patient’s delusions. Compulsions were defined as repetitive goal-directed rituals clinically distinguishable from schizophrenic mannerisms or posturing.

DNA extraction and genetic analysis

Blood samples were collected from all subjects for DNA isolation. Genomic deoxyribonucleic acid (DNA) was extracted using a filter-based method (QIAamp DNA Mini Kit, Qiagen Ltd, United Kingdom). Genotyping of the COMT Val158Met polymorphism (rs4680) was performed by primer extension and analyzed using matrix-assisted laser-desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) as previously described (Sauer and Gut 2002). All DNA samples were genotyped in duplicate to ensure reliability. In brief, a polymerase chain reaction (PCR) was performed to amplify the fragments of DNA containing the Val/Met polymorphism using the following primers: forward 5’-CAC CTG TGC TCA CCT CTC CT-3’ and reverse 5’-GGG TTT TCA GTG AAC GTG GT-3’. For the PCR the following reagents were used: 1x PCR buffer, 2.5 mM MgCl2, 0.2 mM dNTPs, 5 ng forward primer, 5 ng reverse primer, 0.5 U HotFirePol DNA polymerase (Solis Biodyne, Estonia), 20 ng genomic DNA template, dH2O to a final reaction volume of 10 μL. PCR was carried out on a Biometra Thermocycler machine, using the following conditions: initial 15-minutes denaturing step at 95º, followed by 35 cycles of 95º for 1 min, 58º for 1 min, 72º for 1.5 min, and a final extension phase of 72º for 10 min. Five μl of PCR product was treated with 0.2 U shrimp alkaline phosphatase (USB) on 37º for 45 min to dephosphorylate remaining dNTPs. Next, single base primer extension (PEX) using ddNPTs was performed to generate short, single stranded allele-specific products. We used a biotinylated UV-cleavable PEX primer with the following sequence: 5’-GATGTTGGAT-L-TCGCTGGC-3’; the UV-cleavable site is indicated by L (BioTeZ, Berlin, Germany). For PEX the following reagents were used: 5mM MgCl2, 0.4 μM PEX primer, 0.2 mM ddATP, 0.2 mM ddGTP, 2.5 U ThermPol (Thermipol, Solis
Biodyne, Estonia), dH₂O to a final reaction volume of 10 μL. Primer extension was carried out on a Biometra Thermocycler machine, using the following conditions: initial 5-minute denaturing step at 95°C, followed by 70 cycles of 95°C for 15 sec, 40°C for 30 sec, 72°C for 30 sec. Dependent on the genotype, the primer was elongated with either a ddATP or a ddGTP. The primer extension product was purified using a 384-well streptavidin coated plate (Bruker Daltonics, Germany) according to the manufacturer’s instructions. After exposure to UV light (366nm, 8 watt) for 10 minutes, the 3′ end was released and dissolved into 10 μL dH₂O and subsequently spotted onto a MALDI plate (Bruker Daltonics, Germany). Time-of-flight MS was performed on a Bruker III Daltonics Mass Spectrometer using FlexControl v2.0 software. As the varying incorporated nucleotides differ in their mass, the allele-specific products can be determined in the mass spectrum. Data were analyzed using Genotools v2.0 software (Bruker Daltonics, Germany).

Statistics

Analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 12.0. The population was divided in three groups according to COMT genotype. We tested for between-group differences in age, educational level and PANSS scores using analysis of variance (ANOVA). Correlations between Y-BOCS scores and PANSS scores were calculated using Pearson’s Rho. Between-group differences in the use of medication were assessed using Fisher’s exact test. Because data were not normally distributed, we used non-parametric testing (2-tailed) to determine between-group differences in Y-BOCS scores (Kruskal-Wallis and Mann-Whitney U). Several reports have been published of induction of OCS in patients with schizophrenia by olanzapine and clozapine (de Haan et al 1999, Morrison et al 1998, Mottard et al 1999). Therefore, we looked at the use of these antipsychotics in the 3 genotype groups using Fisher’s exact test to test whether medication use could be a confounding factor. In addition, we analyzed differences in mean Y-BOCS scores between COMT genotype groups controlling for the use of antipsychotic medication with analysis of covariance (ANOVA), entering medication as fixed factor in the model. Level of statistical significance was defined as P<0.05.

Results

Our initial sample consisted of 86 patients with recent-onset schizophrenia. However, since gender-specific effects have been reported for COMT (Alsobrook et al 2002, Karayiorgou et al 1997, 1999) we decided to use only male patients in our
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final analyses. In total, 77 male patients with recent-onset schizophrenia were analyzed (paranoid, disorganized or undifferentiated type; n=69 [89.5%]; schizoaffective disorder n=8 [10.5%]; mean age=22.17, S.D.=2.91, age range 18-30). Mean total PANSS score was 71.3 (S.D.=21.4), the PANSS Positive subscale score was 17.5 (S.D.=7.4), the PANSS Negative subscale score was 19.0 (S.D.=7.1), and the PANSS general psychopathology subscale score was 34.7 (S.D.=10.5). Y-BOCS scores ranged from 0-24 (mean=3.78, S.D.=6.42). In the patients with a Y-BOCS score >0 (24/77, 31%), mean Y-BOCS score was 12.13 (S.D.=5.54) and the median was 12.0. No correlation between Y-BOCS scores and PANSS Positive, Negative or General Psychopathology Subscale scores and total PANSS scores was observed (data not shown). At time of testing most patients were using antipsychotic medication (olanzapine, N=26; risperidone, N=22; quetiapine, N=2; clozapine, N=13; haloperidol, N=3; no medication, N=11).

Genotype counts did not deviate from those expected according to the Hardy-Weinberg equilibrium ($\chi^2=2.14$, df=2, $P=0.3$). The population was divided in three groups according to COMT genotype. Neither age ($F=0.61$, df=2;74, $P=0.5$) nor educational level ($F=0.87$, df=2;74, $P=0.4$) differed significantly between genotype groups (Table 2.2.1). No differences in total PANSS scores ($F=0.93$, df=2;53, $P=0.4$) or in PANSS subscale scores were found between genotype groups (PANSS Positive subscale score: $F=0.33$, df=2;73, $P=0.7$; PANSS Negative subscale score: $F=0.87$, df=2;73, $P=0.4$).

Table 2.2.1 Patient Characteristics by Genotype. All Subjects are Male.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Val/Val N=22</th>
<th>Val/Met N=44</th>
<th>Met/Met N=11</th>
<th>Test statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>21.86 (± 2.95)</td>
<td>21.77 (± 3.05)</td>
<td>22.91 (± 3.56)</td>
<td>$F=0.61$</td>
<td>$P=0.5$</td>
</tr>
<tr>
<td>Educational level</td>
<td>4.41 (1.05; 2-6)</td>
<td>4.14 (1.13; 2-6)</td>
<td>3.91 (0.94; 2-5)</td>
<td>$F=0.87$</td>
<td>$P=0.4$</td>
</tr>
</tbody>
</table>

### Antipsychotics:

- No medication | 2 | 6 | 3 | Fisher’s Exact=8.97
- Olanzapine | 8 | 16 | 2 | $P=0.5$
- Risperidone | 7 | 12 | 3 | $P=0.5$
- Clozapine | 5 | 7 | 1 | $P=0.5$
- Quetiapine | 0 | 2 | 0 | $P=0.5$
- Typical antipsychotics | 0 | 1 | 2 | $P=0.5$

| SSRI's y/n | 3/19 | 2/42 | 1/10 | Fisher’s Exact=2.05 | $P=0.4$ |

<table>
<thead>
<tr>
<th>Mean Y-BOCS score (SD) (minimum-maximum)</th>
<th>7.32 (8.80-24)</th>
<th>2.95 (4.93-16)</th>
<th>0.00 (0.00-0)</th>
<th>Kruskal-Wallis $\chi^2=8.79$</th>
<th>$P=0.012$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-BOCS score ≥ 12</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>Fisher’s Exact=5.23</td>
<td>$P=0.045$</td>
</tr>
<tr>
<td>Y-BOCS score ≥ 16</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>Fisher’s Exact=11.14</td>
<td>$P=0.002$</td>
</tr>
</tbody>
</table>
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F=0.89, df=2;73, P=0.4; PANSS general psychopathology subscale score: F=0.25, df=2;73, P=0.8). Patient characteristics in the 3 genotype groups are listed in Table 2.2.1.

There was a significant between-group difference in mean Y-BOCS scores (Kruskal-Wallis: \( \chi^2=8.79, df=2, P=0.012 \)). Further exploration with Mann-Whitney U testing revealed that mean Y-BOCS scores in the Val/Val group (\( n=22, \) mean Y-BOCS score=7.32, S.D.=8.80) were significantly higher than those in the Met/Met group (\( n=11, \) mean Y-BOCS score=0.00, S.D.=0.00) (\( Z=-2.58, P=0.010 \)). Also, Y-BOCS scores in the Val/Met group (\( n=44, \) mean Y-BOCS score=2.95, S.D.=4.93) were significantly higher than those with Met/Met genotype (\( Z=-2.12, P=0.034 \)).

Figure 2.2.1 Y-BOCS Scores in the 3 COMT Genotype Groups. Using Kruskal-Wallis testing, there was a significant between-group difference in mean Y-BOCS scores (\( P=0.012 \)). Y-BOCS Scores in the Val/Val group were significantly higher than those in the Met/Met group (\( P=0.01 \)). Also, Y-BOCS scores in the Val/Met group were significantly higher than those with Met/Met genotype (\( P=0.034 \)). There was a trend for a difference in Y-BOCS scores between the Val/Val and the Val/Met group (\( P=0.065 \)).
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There was a trend for a difference in Y-BOCS scores between the Val/Val and the Val/Met group \((Z=-1.85, P=0.065)\) (Figure 2.2.1). In addition, mean Y-BOCS scores in Val carriers (Val/Val and Val/Met individuals, \(N=66\)) were significantly higher when compared to Met homozygotes (\(N=11\)) \((Z=-2.34, P=0.019)\).

We did not observe differences in the use of clozapine and olanzapine between genotype groups (Fisher’s exact=2.99, \(P=0.2\)). Also, mean Y-BOCS scores in patients using olanzapine or clozapine \((n=39, \text{mean Y-BOCS score}=3.74, \text{S.D.}=5.61)\) were not significantly different than in those using other antipsychotic agents \((n=27, \text{mean Y-BOCS score}=3.59, \text{S.D.}=6.99)\) (Mann-Whitney U test: \(Z=-0.58, P=0.6\)). The effect of COMT genotype on Y-BOCS scores remained significant when we analyzed our data correcting for medication as a possible confounding factor \((F=9.15, \text{df}=2;62, P<0.001)\). We found no evidence for an effect of antipsychotic medication on Y-BOCS scores \((F=0.80, \text{df}=5;62, P=0.6)\) or for COMT x medication interaction \((F=1.37, \text{df}=7;62, P=0.2)\). Six of the 77 patients (8%) used selective serotonin re-uptake inhibitors (SSRIs) in addition to their antipsychotic medication: 3 in the Val/Val group, 2 in the Val/Met group and 1 in the Met/Met group (Table 2.2.1). Using Chi-square tests, no significant difference in the use of SSRIs between the 3 genotype groups was found (Fisher’s Exact=2.05, \(P=0.4\)).

Discussion

In our sample of male patients with recent-onset schizophrenia we found the COMT high-activity Val allele to be associated with more severe OCS. To our best knowledge, this is the first report of association between COMT Val158Met genotype and OCS in a population of patients with schizophrenia.

**COMT and risk for OCD without schizophrenia**

It is still unclear whether the Val158Met polymorphism increases risk of OCD: although 3 studies reported that the Met allele increased risk of OCD (Alsobrook et al 2002, Karayiorgou et al 1997, 1999), 5 studies either failed to replicate this (Azzam et al 2003, Erdal et al 2003, Meira-Lima et al 2004) or found association with either homozygosity (Schindler et al 2000) or heterozygosity (Niehaus et al 2001) at this locus. Therefore, similar to results from studies investigating association between COMT and schizophrenia (Munafo et al 2005), association between the COMT Val158Met polymorphism and OCD is still inconclusive. However, 3 out of 8 studies reported association between OCD and the low-activity Met allele, whereas we found association between the high-activity Val allele and more OCS
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in schizophrenia. It is important to emphasize that we have investigated effects of COMT genotype on OCS in patients with schizophrenia; therefore – making it difficult to compare our results with those from studies investigating association between COMT genotype and OCD without schizophrenia. Also, most studies looking at COMT and OCD investigated the risk of OCD in the presence of a specific COMT genotype, whereas we took a dimensional approach using Y-BOCS scores as a quantitative phenotype. One study that used a similar approach reported association between the COMT high-activity Val allele and phobic anxiety in a large sample of over 1200 subjects (McGrath et al. 2004). In this respect, the Val allele could be considered a risk allele for anxiety symptoms.

Limitations and advances of the study

This study has several limitations. Sample size is relatively small; therefore results should be considered preliminary. However, two recent studies (Wahlstrom et al. 2006, McIntosh et al. 2006) reported on the effect of the COMT Val<sup>158</sup>Met polymorphism in samples of similar size (70 and 77 subjects respectively). Thus, our sample size is small but not uncommon. A second limitation of our study is genetic heterogeneity. Since the effect of COMT Val<sup>158</sup>Met genotype on the extent of OCS remained significant when we analyzed our data including male patients from Dutch ancestry only (N=54; Kruskal-Wallis: χ<sup>2</sup>=6.60, df=2, P=0.037), we think it is unlikely our results are false-positive. Also, since the COMT Val<sup>158</sup>Met polymorphism is functional, i.e. leads to an amino acid substitution known to affect thermostability of the COMT protein (Chen et al. 2004), it is likely that effects on enzymatic activity are similar across ethnic populations. Moreover, Chen et al (2004) established effects of the COMT Val<sup>158</sup>Met polymorphism on COMT protein stability using postmortem brain tissue from an ethnically mixed sample including white Caucasian and African American subjects: 66% of healthy controls and 52% of schizophrenia patients were African Americans. To our best knowledge, there is no evidence that ethnicity modulates functional effects of the COMT Val<sup>158</sup>Met polymorphism on COMT activity. However, the precise relationship between ethnicity and these functional effects has not yet been investigated; future research is needed to examine this. Previous studies reported that the Val allele is more frequent in non-Caucasian samples (Palmatier et al. 1999). Thus, ethnicity could confound our data if non-Caucasian subjects (who are likely to carry more Val alleles) would have more OCS than Caucasian subjects. However, in our sample Y-BOCS scores did not differ between ethnic groups. Therefore, we consider ethnicity an unlikely confounder in our study. Nevertheless, since this is the first report of association between the
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COMT Val^{158}Met polymorphism and OCS in patients with schizophrenia, our findings need to be replicated in a large and genetically homogeneous sample.

Several reports have described induction of OCS by clozapine and olanzapine (de Haan et al 1999, Mottard et al 1998, Ongur et al 2005). However, since no randomized controlled trials examining this have been performed yet, it is controversial whether these agents really induce OCS. In our study no difference in the use of olanzapine and clozapine between genotype groups was observed, therefore we do not think this to be a confounding factor. Furthermore, when we analyzed our data correcting for antipsychotic medication as a possible confounding factor, the effect of COMT genotype on Y-BOCS scores seemed increased in comparison to the ‘uncorrected’ analysis (P<0.001 and P=0.012 respectively). In a recent report, clozapine was reported to induce OCS in some patients with schizophrenia, whereas it was associated with decrease in existing OCS in others (de Haan et al 2004); it is possible that these differences can be explained by genetic variation.

Our analyses included only male patients with schizophrenia; future studies should investigate whether COMT genotype has similar effects on OCS in female patients with schizophrenia. Differentiating between males and females is important, since previous studies reported gender-specific effects of COMT genotype on the risk for OCD (Alsobrook et al 2002, Karayiorgou et al 1997, 1999). Furthermore, gender-specific effects of COMT have been reported in COMT-deficient mice (Gogos et al 1998) and may result from down-regulation of COMT expression by estrogens (Jiang et al 2003).

**Neurobiological mechanism**

Prefrontal dysfunction and impaired dopaminergic neurotransmission resulting in abnormal prefrontal regulation of striatal activity are mechanisms hypothesized to play a role in the pathophysiology of schizophrenia (Weinberger et al 2001). Disturbances in dopaminergic systems in schizophrenia may not only lead to psychotic symptoms, but also to OCS since recently evidence for increased dopaminergic neurotransmission in the striatum in patients with OCD was found (Denys et al 2004, van der Wee et al 2004). Disruption of frontostriatal circuits has been observed in both patients with schizophrenia and OCD. Structural MRI studies have identified specific parts of the frontostriatal system that are altered in OCD (Pujol et al 2004). Furthermore, patients with OCD show decreased fronto-striatal responsiveness during planning and executive tasks (van den Heuvel et al 2005), which is a finding similar to those in patients with schizophrenia (Morey et al 2005). It is possible that by indirect downstream effects on dopamine regulation of striatum and basal ganglia, the COMT gene may modulate the risk for OCS and OCD in schizophrenia.
Apart from dopamine, COMT is also important for degradation of noradrenalin: e.g. COMT-deficient mice show changes in the levels of dopamine and its metabolites, but also in noradrenalin levels (Gogos et al 1998, Huotari et al 2002). The noradrenergic system is involved in behavioral responses to stress, i.e. anxiety (Morlak et al 2005), and a relative increase of noradrenaline levels by selective serotonin and norepinephrine reuptake inhibitors (SNRIs) reduces anxiety in depressed patients (Blier and Szabo 2005). Similarly, people with the COMT Met/Met genotype (with relatively increased noradrenaline levels) may be less vulnerable for developing anxiety disorders (Eley et al 2006, Rothe et al 2006). Thus, the mechanism by which COMT influences severity of OCS in patients with schizophrenia may be via modulation of dopaminergic or noradrenergic systems; further research is needed to clarify which of these pathways is the most important one.

**COMT: a possible pharmacogenetic target?**

Recently, pharmacological inhibitors of COMT, e.g. entacapone and tolcapone, have received increased attention in the treatment of patients with Parkinson’s disease (Keating et al 2005, Rothe et al 2006). COMT inhibitors stabilize dopamine levels by reducing the breakdown of dopamine (Muller et al 2006) and have been reported to ameliorate cognitive symptoms in patients with Parkinson’s disease (Gasparini et al 1997). Tolcapone, a COMT inhibitor acting both in the peripheral and in the central nervous system (Keating et al 2005), may have important therapeutic implications for patients with schizophrenia. However, further research is warranted to investigate safety and efficacy of the use of COMT inhibitors in patients with schizophrenia.

In conclusion, our preliminary data suggest that the COMT high-activity Val allele is associated with more obsessive-compulsive symptoms in young males with schizophrenia. Therefore, our results further support the hypothesis that the COMT Val158Met polymorphism may be a modifier gene for the symptomatology of schizophrenia.
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