

Association of the COMT val158met Variant with Antidepressant Treatment Response in Major Depression

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In several previous biochemical, pharmacological, and genetic studies, the catechol-*O*-methyltransferase (COMT) has been suggested to be involved in the pathogenesis as well as the pharmacological treatment of affective disorders. In the present study, 256 patients with major depression (DSM-IV) of Caucasian descent were genotyped for the functional COMT val158met polymorphism and characterized for clinical response to antidepressive pharmacological treatment as measured by intra-individual changes of Hamilton Depression (HAM-D-21) scores over 6 weeks. The COMT 158val/val genotype conferred a significant risk of worse response after 4–6 weeks of antidepressant treatment in patients with major depression (week 4: $p = 0.003$; week 5: $p < 0.0001$; week 6: $p < 0.0001$) after Bonferroni correction for multiple comparisons. The present results strongly point toward a negative influence of the higher activity COMT 158val/val genotype on antidepressant treatment response during the first 6 weeks of pharmacological treatment in major depression, possibly conferred by consecutively decreased dopamine availability. This finding suggests a potentially beneficial effect of an antidepressive add-on therapy with substances increasing dopamine availability individually tailored according to COMT val158met genotype.

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INTRODUCTION

Genetic factors have been suggested to play a pivotal role in the individual response to antidepressant treatment. Pharmacogenetic studies aim at identification of genetic variations that influence drug targets or factors interfering with drug action. A number of pharmacogenetic studies have examined association of response to antidepressants with variation in candidate genes, particularly those involved in the serotonergic system (eg, serotonin transporter (5-HTT), serotonin receptor 2A (5-HT_{2A}), monoamine oxidase A, tryptophan hydroxylase, for review see Serretti *et al*, 2005). Only few studies have focused on candidate genes implicated in the noradrenergic or dopaminergic systems, which, however, have been shown to have a significant impact on the pathogenesis of depression and also to interact with serotonergic pathways in the pharmacological treatment of the disease. In line with the monoamine hypothesis of depression, a deficit in brain norepinephrine

and dopamine has been demonstrated in patients with major depression, which was reversible following pharmacological blockade of the norepinephrine transporter with desipramine. However, the patients' clinical improvement was most significantly correlated with dopamine turnover (Lambert *et al*, 2000). Accordingly, in the Flinders sensitive line rat model of depression, decreased availability of extracellular dopamine in the nucleus accumbens was found to be reversible by treatment with serotonergic antidepressants accompanied by improvements in depressive-like behavior (Zangen *et al*, 2001; Dremencov *et al*, 2004). Reciprocally, blockade of dopamine D₂/D₃ receptors has been reported to acutely reverse the antidepressant effect of selective serotonin reuptake inhibitors (SSRIs) in animal models of depression as well as in patients suffering from major depression (Willner, 2002; Willner *et al*, 2005). This is in line with the clinical finding that augmentation of antidepressant treatment with sustained-release bupropion, an inhibitor of dopamine reuptake, as well as the dopamine agonists pramipexole and ropinirole resulted in significant reduction in the number and severity of depressive symptoms after failure of therapy with SSRIs (Trivedi *et al*, 2006; Cassano *et al*, 2004, 2005). Additionally, pramipexole has been shown to ameliorate depressive symptoms in addition to its effects on motor symptoms in Parkinson's disease (Barone *et al*, 2006).

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The catechol-*O*-methyltransferase (COMT) plays a pivotal role in the degradation of norepinephrine and dopamine (Mannisto and Kaakkola, 1999) and therefore serves as a promising candidate in pharmacogenetic studies of antidepressant action. In patients with major depression, significantly elevated erythrocyte COMT activity was reported (Shulman *et al*, 1978; Davidson *et al*, 1979). Accordingly, tolcapone, a COMT inhibitor, has been shown to reverse an anhedonic state in a rat model of depression, suggesting a potential role of tolcapone in the treatment of depression in addition to its efficacy in Parkinson's disease (Moreau *et al*, 1994). In a clinical pilot study on the efficacy of tolcapone in the treatment of major depressive disorder, a significant reduction in depression severity was observed (Fava *et al*, 1999).

The COMT gene (NM_000754) maps to chromosome 22q11.2, and contains a functional 472G/A single-nucleotide polymorphism (rs4680) causing an amino-acid substitution from valine to methionine in codon 158 (val158met) of the membrane-bound form of the enzyme (codon 108 (val108met) of the soluble form). The valine allele (472G) has initially been reported to result in a three- to fourfold higher COMT activity as compared to the methionine allele (472A) (Lachman *et al*, 1996). However, the valine allele appears to be less expressed in the brain as compared to the methionine allele (Bray *et al*, 2003; Zhu *et al*, 2004), which slightly mitigates the effect to about 40% increased enzyme activity as conferred by the valine allele (Chen *et al*, 2004). The COMT val158met polymorphism has repeatedly been investigated for association with major depression with contradictory reports of no association (Kunugi *et al*, 1997; Frisch *et al*, 1999; Cusin *et al*, 2002; Serretti *et al*, 2003), possible association with the valine allele (Massat *et al*, 2005; Funke *et al*, 2005) or conversely the methionine allele (Ohara *et al*, 1998). Two published studies on the role of the COMT val158met polymorphism in antidepressant treatment response investigating samples of 102 and 346 patients, respectively, report a tentative negative effect of the COMT 158met/met genotype on mirtazapine and citalopram response in major depression (Szegedi *et al*, 2005; Arias *et al*, 2006).

In the present study, the influence of the COMT val158met polymorphism on clinical response to antidepressants was investigated in samples of Caucasian patients with major depression and bipolar disorder, major depressive episode, by means of a novel approach analyzing the intra-individual rather than the averaged course of therapy response, in an attempt to follow the recently published American College of Neuropsychopharmacology (ACNP) task force guidelines on response and remission in major depressive disorder (Rush *et al*, 2006) and therefore to possibly further clarify the role of COMT gene variation in antidepressant treatment response. Since biochemical and pharmacological studies provide support for decreased availability of dopamine and norepinephrine as a detrimental factor in the pathomechanism of depression as well as response to pharmacological antidepressive treatment, higher COMT activity, as conferred by the COMT 158val allele leading to decreased dopamine and norepinephrine availability, was hypothesized to have a negative effect on antidepressant drug response in depression. In addition, given the inconsistent data on COMT val158met impact

on major depression published so far, we aimed at further elucidation of the influence of the COMT val158met polymorphism on the pathogenesis of major depression using a categorical association study design.

MATERIALS AND METHODS

Samples

Samples of 268 unrelated Caucasian patients with a current major depressive episode (mean age: 49.7 ± 15.4 years; $f=154$, $m=114$) and 72 patients with bipolar disorder, major depressive episode, admitted for inpatient treatment were consecutively recruited at the Department of Psychiatry, University of Muenster, Germany, between 2004 and 2006. For pharmacogenetic analyses, only patients with an HAM-D admission score >10 and a treatment cycle of at least 6 weeks from baseline were considered, leaving a sample of $N=256$ patients with major depression (mean age: 50.4 ± 14.9 years; $f=145$, $m=111$) and 65 patients with bipolar disorder, major depressive episode (mean age: 45.9 ± 14.5 years; $f=39$, $m=26$). Patients with schizoaffective disorders or comorbid substance abuse disorders, mental retardation, neurological or neurodegenerative disorders, impairing psychiatric evaluation were not included in this analysis. In order to minimize the risk of ethnic stratification, Caucasian descent was ascertained by Caucasian background of both parents.

The control group consisted of 557 (mean age: 50.2 ± 14.2 years; $f=302$, $m=255$) age- and gender-matched healthy subjects of German descent representative of the general population, where the presence of clinically relevant depressive symptoms was excluded using the Centre for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977).

The ethics committee of the University of Muenster (Muenster, Germany) approved the study. After complete description of the study to the subjects, written informed consent was obtained.

Assessment

Patients' diagnoses were obtained by the use of a structured clinical interview (SCID-I) according to the criteria of DSM-IV (Wittchen *et al*, 1997), and all patients were characterized for family history of psychiatric disorders in first-degree relatives. Clinical course of depression was assessed with the Hamilton Depression (HAM-D-21) scale, the Beck's Depression Inventory (BDI), the Clinical Global Impression (CGI) scale, and the Global Assessment of Functioning (GAF) scale. While scores on the HAM-D-21 were obtained on a weekly basis, BDI, CGI, and GAF scores were obtained at admission and discharge only. Side effects were not systematically assessed in detail; however, there were no dropouts due to side effects. Age- and gender-matched healthy controls were assessed for depressive symptoms using the CES-D scale.

Response

Clinical response to treatment was measured by the intra-individual changes of HAM-D-21 scores over the 6 weeks

study period. This is in accordance with the recently published ACNP task force guidelines on response and remission in major depressive disorder, which recommend monitoring of changes within a subject (for whom initial severity is fixed) rather than comparing response rates between subjects for whom initial values range widely (Rush *et al*, 2006). The intra-individual weekly change score introduced here considered the weekly changes in HAM-D scores after week 1 up to week 6. The initial changes in HAM-D occurring during week 1 were not included, as HAM-D changes during this period were most likely not related to antidepressant effects since antidepressants have been regularly switched in this cohort of inpatients during week 1. Thus, the intra-individual weekly change on the HAM-D scale per subject was captured by calculating the raw HAM-D score at weeks 2–6 minus HAM-D at the end of week 1. Negative numbers of the change score (based on raw scores) indicate a reduction on the HAM-D score (larger numbers indicate better progress than lower numbers) over time, whereas positive scores indicate increase of HAM-D scores and a deterioration of mental state over time, respectively. In additional analyses (Figure 2), a weekly percent change scores was obtained as percent change relative to week 1. This model allows for direct comparison of intra-individual response dynamics over time. In addition, it corrects for improvements unrelated to antidepressant action occurring in the first week after admission due to the admission itself or concomitant benzodiazepine and antipsychotic medication with rapid onset of action.

Medication

Patients were treated in a naturalistic setting with a variety of antidepressant medication (mirtazapine: $N=28$ (10.9%), citalopram/escitalopram: $N=38$ (14.8%), venlafaxine: $N=45$ (17.6%), mirtazapine plus citalopram/escitalopram: $N=38$ (14.8%), mirtazapine plus venlafaxine: $N=63$ ($n=24.6\%$), other (TCA, MAO inhibitors, lithium): $N=44$ (17.2%). As co-medication atypical neuroleptics (quetiapine, olanzapine, risperidone: $N=121$, 47.3%) as well as mood stabilizers (lithium, valproate acid: $N=60$, 23.4%) were used in addition to antidepressant treatment. Benzodiazepines were used in three cases only.

Genotyping

According to published protocols (Domschke *et al*, 2004), fragments containing the COMT val158met polymorphism were amplified with primers COMT-F (5'-TCACCATC GAGATCAACCCC) and COMT-R (5'-ACAACGGGTCAGG CATGCA). Standard PCR was carried out in a 20 μ l volume containing 60 ng of genomic DNA, 10 pmol of each primer, 200 μ M dNTPs, 0.4 U TaqTM DNA polymerase (Eppendorf AG, Hamburg, Germany), 50 mM KCl, 2.5 mM MgCl₂, and 10 mM Tris-HCl (pH 8.4). After an initial 5 min denaturation at 94°C, 35 cycles were carried out consisting of 30 s at 94°C, 30 s at the annealing temperature of 64°C, and 60 s at 72°C, followed by a final extension time of 10 min at 72°C in a T-Gradient PCR System (Biometra, Goettingen, Germany). Genotyping was performed by means of a restriction fragment length polymorphism (RFLP) assay with the

restriction enzyme *Nla*III (3 U), as recommended by the manufacturer (New England Biolabs, Frankfurt, Germany), resulting in 64, 18, and 13 bp bands for the A-allele (158met) and 82 and 13 bp bands for the G-allele (158val), respectively. A 6.7 μ l portion of the digested product was mixed with 10 μ l denaturing solution and separated for 2 h on a 15% polyacrylamide gel (acrylamide:bisacrylamide = 37.5:1; Multigel-Long/Biometra, Goettingen, Germany) containing 1 \times TBE at 230 V/cm. Bands were visualized by silver-staining. To minimize the risk of genotyping errors, 60 randomized patients and 120 healthy controls were additionally genotyped by TaqMan 5'-exonuclease assays using different colored fluorophores for allele labeling and allelic discrimination by fluorescence signal detection (Applied Biosystems, Darmstadt, Germany), which yielded a 100% congruence rate with results obtained using the RFLP assay. Preparation of PCR reaction mixtures was performed by Genesis Workstation RSP 150 (Tecan, Crailsheim, Germany). For PCR amplification and allelic discrimination, the ABI Prism 7900HT Sequence Detection System and SDS software version 2.1 (Applied Biosystems) were used. These combined genotyping methods yielded a genotyping completion rate of 100% for all included patients and controls. Genotypes were determined by investigators blinded for clinical diagnoses.

Statistical Analysis

The categorical association analysis of allele and genotype distribution across patients with major depression ($N=268$) and age- and gender-matched healthy controls ($N=557$) was performed by means of Armitage's trend test, as provided by the program DeFinetti available as an online source (<http://ihg.gsf.de/cgi-bin/hw/hwa1.pl>; Sasiene, 1997).

Comparisons of HAMD, BDI, CGI, and GAF baseline scores across genotype groups were carried out with one-way ANOVA (>2 categories) (Table 1). The pharmacogenetic investigation of COMT val158met genotype effects on HAM-D change scores over 6 weeks of antidepressant treatment was performed using an overall ANOVA with repeated measures (genotype as fixed factor, and time point as repeated measure; adjusted for age, gender, and family history of psychiatric disorders) with *post hoc* Bonferroni correction for multiple comparisons (Table 2).

In addition to the overall ANOVA with repeated measures, we performed separate multiple ANOVAs with *post hoc* Bonferroni test (adjusted for age, gender, and family history of psychiatric disorders) to obtain results on the weekly intra-individual HAM-D change scores across genotype groups. Bonferroni correction for multiple comparisons (15 tests per independent variable in Table 3) set the limit of the *p*-value to $p \leq 0.003$. In addition, stratified analyses for gender and family history of mental disorders were performed as shown in Tables 2 and 3.

With these parameters, for continuous measurements, our sample had a high power (80%) to detect a difference of at least 2.4 points on the HAM-D scale between two genotypes. Hardy-Weinberg equilibrium was examined using the program Finetti provided as an online source (<http://ihg.gsf.de/cgi-bin/hw/hwa1.pl>; Sasiene, 1997).

Table 1 COMT val158met Genotype Frequencies and Genotype Comparisons for Clinical Characteristics at Baseline Stratified for Gender and Family History

COMT V158M genotype	Patients with major depression			p-value
	val/val	val/met	met/met	
N = 256				
<i>Total (n)</i>	54	133	69	
HAMD baseline (mean)	22.9	23.4	22.8	>0.05
BDI baseline (mean)	26.6	27.5	28.1	>0.05
GAF baseline (mean)	43.7	42.1	44.1	>0.05
CGI baseline (mean)	5.5	5.6	5.4	>0.05
<i>Males (n)</i>	27	51	33	
HAMD baseline (mean)	21.7	24.4	21.3	>0.05
BDI baseline (mean)	24.6	29.3	26.9	>0.05
GAF baseline (mean)	44.1	44.5	42.8	>0.05
CGI baseline (mean)	5.4	5.7	5.3	>0.05
<i>Females (n)</i>	27	82	36	
HAMD baseline (mean)	24.2	22.7	24.2	>0.05
BDI baseline (mean)	28.5	26.4	29.2	>0.05
GAF baseline (mean)	43.4	42.3	43.7	>0.05
CGI baseline (mean)	5.5	5.5	5.6	>0.05
<i>Family history positive (n)</i>	20	57	35	
HAMD baseline (mean)	20.3	24.2	22.5	>0.05
BDI baseline (mean)	25.4	27.6	27.0	>0.05
GAF baseline (mean)	47.0	42.5	44.2	>0.05
CGI baseline (mean)	5.3	5.7	5.3	>0.05
<i>Family history negative (n)</i>	34	76	34	
HAMD baseline (mean)	24.5	22.7	23.2	>0.05
BDI baseline (mean)	27.3	27.5	29.3	>0.05
GAF baseline (mean)	42.0	41.8	43.9	>0.05
CGI baseline (mean)	5.6	5.5	5.6	>0.05

p-value of comparisons between genotypes by one-way ANOVA.

RESULTS

In our sample of 268 patients and an age- and gender-matched control sample of 557 healthy probands, no association of the COMT val158met polymorphism with major depression was observed (patients: val/val: 55, val/met: 142, met/met: 71; controls: val/val: 112, val/met: 275, met/met: 170; common odds ratio = 1.091, $\chi^2 = 0.73$, $p = 0.3916$). Hardy-Weinberg equilibrium was fulfilled for the case ($p = 0.30$) as well as the control sample ($p = 0.97$).

The pharmacogenetic sample was comprised of 256 patients with major depression (mean age: 50.4 ± 14.9 ; $f = 145$, $m = 111$). The subsamples stratified for gender and family history of mental diseases did not significantly differ for age, education, marital status, or comorbidity with anxiety disorders. COMT val158met genotype frequencies in the overall pharmacogenetic sample of patients with major depression as well as the respective subgroups

stratified for gender and family history of mental diseases are given in Table 1. The distribution of COMT val158met genotypes did not significantly differ from the expected numbers calculated on the basis of observed allele frequencies according to the Hardy-Weinberg equilibrium ($p = 0.53$).

The mean HAM-D score at admission was 23.1 ± 7.3 and at discharge was 6.0 ± 5.0 , without showing any differences between gender and family history of mental disorders. Table 1 shows no significant differences of HAM-D, BDI, GAF, and CGI baseline scores between COMT val158met genotypes in the overall sample as well as stratified for gender or family history of mental illness in first-degree relatives.

The raw HAM-D scores over the course of 6 weeks are presented in Figure 1, indicating only a marginal change over time for patients with the COMT158val/val genotype (mean change of -1.6 ± 0.8 ; $p = 0.13$). Moreover, while HAM-D scores significantly decreased over 6 weeks in patients with either the val/met (mean change of -5.6 ± 0.7 ; $p < 0.05$) or met/met (mean change of -4.5 ± 1.0 ; $p < 0.05$) genotypes, after an initial slight decline, patients with the val/val genotype showed no major change in HAM-D scores after 3 weeks of antidepressant treatment.

Table 2 presents results of the overall ANOVA with repeated measures (genotype as fixed factor, and time point as repeated measure; *post hoc* Bonferroni correction) for the HAM-D change scores over 6 weeks (dependent variable) of antidepressant treatment across genotype groups stratified for gender and family history. The COMT 158val/val genotype as compared to the heterozygous 158val/met genotype conferred a significant increased risk of worse response to antidepressant treatment over 6 weeks. In analyses stratified for gender and family history, the COMT 158val/val genotype as compared to the heterozygous 158val/met genotype showed an increased risk for worse antidepressant treatment response after 6 weeks in men ($p < 0.049$), women ($p < 0.005$), and subjects with a negative ($p < 0.005$) or positive ($p < 0.05$) family history for psychiatric disorders in first-degree relatives (Table 2). Figure 2 demonstrates the HAM-D percent changes relative to week 1 across genotypes. While patients with the val/val genotype hardly showed any changes on the HAM-D score over time, the other two genotypes were related to a reduction in HAM-D scores with pronounced effects for the val/met genotype (Figure 2).

In Table 3, separate multivariable ANOVA analyses of the HAM-D weekly change between weeks 1 and 6 (based on raw scores) were performed across genotype groups, stratified for gender and family history, and results were adjusted for Bonferroni correction for multiple comparisons (significance level set to $p \leq 0.003$). The COMT 158val/val genotype as compared to the heterozygous 158val/met genotype conferred a significant risk of worse response to antidepressant treatment for the overall change score at weeks 4 ($p < 0.003$), 5 ($p < 0.0001$), and 6 ($p < 0.0001$). In addition, stratified analyses for history of psychiatric diseases in first-degree relatives revealed a significant effect of the COMT 158val/val genotype as compared to the heterozygous 158val/met genotype in subjects without family history of psychiatric disorders ($p < 0.001$) at week 5 after start of antidepressant treatment (Table 3). Similar

Table 2 Overall Reduction in Mean HAM-D Scores Across COMT val158met Genotypes Stratified for Gender and Family History during a 6-Week Course of Antidepressant Treatment

COMT V158M genotype	Patients with major depression			p-value
	val/val mean HAM-D reduction	val/met mean HAM-D reduction	met/met mean HAM-D reduction	
N = 256				
<i>Total</i>				
HAM-D change score ^{ab}	-1.6	-5.6	-4.5	<0.0001*
<i>Males</i>				
HAM-D change scores ^{bc}	-2.3	-5.9	-4.7	<0.049*
<i>Females</i>				
HAM-D change scores ^{bc}	-1.1	-5.3	-4.5	<0.005*
<i>Family history positive</i>				
HAM-D change scores ^{bd}	-1.7	-5.6	-4.3	<0.05*
<i>Family history negative</i>				
HAM-D change scores ^{bd}	-1.7	-5.6	-4.6	<0.005*

p-value of ANOVA with repeated measures adjusted for age, gender, and family history of psychiatric illness (^aage, gender, and family history, ^cage and family history, ^dage and gender) and with *post hoc* Bonferroni correction.

^bMultivariable ANOVA with repeated measures for intra-individual HAM-D change scores over 6 weeks.

*Comparison of 158val/val vs 158val/met genotypes.

results were obtained using ANOVA with repeated measures (overall change at weeks 1–6) and separate ANOVAs (weekly change), when a HAM-D percent change relative to week 1 was employed (data not shown).

When investigating subgroups stratified for the type of antidepressant medication, the negative influence of the COMT 158val/val genotype on response was significant for medication with mirtazapine plus venlafaxine or citalopram/escitalopram ($N=101$; $p<0.005$), as compared to the COMT 158val/met genotype. This effect was most prominent after 4, 5, and 6 weeks of treatment (week 4: $p<0.019$; week 5: $p<0.001$; week 6: $p<0.001$). No significant COMT val158met genotype effects on HAM-D treatment response were found among patients receiving single antidepressants (escitalopram, mirtazapine, venlafaxine). Exposure to atypical neuroleptics or mood stabilizers was not different between carriers of the COMT 158val and 158met alleles, and atypical antipsychotics or mood stabilizers were not related to treatment response after 6 weeks.

Significant effects of the COMT val158met genotype on BDI, GAF, and CGI change scores between admission and discharge were not observed (each measure was assessed at baseline and discharge) (data not shown).

In the subsample of patients with bipolar disorder, major depressive episode ($N=65$; val/val: 12, val/met: 35, met/met: 18), no influence of the COMT val158met variant on HAM-D change scores could be detected (mean reduction in HAM-D scores between weeks 1 and 6: val/val: -4.31 ; val/met: -4.87 ; met/met: -3.91 ; ANOVA with repeated measures $p=0.786$). Furthermore, there was no significant difference when comparing genotype frequencies between patients with major depression and patients with

bipolar disorder, major depressive episode ($\chi^2=0.12$; $p=0.729$).

DISCUSSION

The present observations do not support a major role of the COMT val158met variant in the pathogenesis of major depression, confirming previous findings (Kunugi *et al*, 1997; Frisch *et al*, 1999; Cusin *et al*, 2002; Serretti *et al*, 2003).

However, applying an innovative intra-individual assessment approach of response to treatment, our results suggest a strong detrimental effect of the higher activity COMT 158val/val genotype on antidepressant treatment response in patients with major depression, but not with bipolar disorder. In major depressive patients homozygous for the COMT 158val allele, increased COMT activity resulting in a decreased availability of dopamine and norepinephrine might impair the pharmacological efficacy of serotonergic and noradrenergic antidepressants during the first 6 weeks of treatment and thus be, in part, responsible for 30–40% of patients not initially responding to antidepressant medication (Sackeim, 2001).

In the first of two previously published studies on COMT gene influence on antidepressant response, German patients carrying the COMT 158met/met genotype showed a slightly slower and poorer response to treatment with mirtazapine ($N=53$) (Szegedi *et al*, 2005). Arias *et al* (2006) observed a disadvantage for homozygous carriers of the COMT 158met allele in early remission at the 6th/8th week of treatment with citalopram in a Spanish sample of 139 patients with

Table 3 Weekly Reduction of Raw HAM-D Scores Across COMT val158met Genotypes Stratified for Gender and Family History

COMT V158M genotype	Patients with major depression			p-value
	val/val mean	val/met mean	met/met Mean	
<i>Total</i>				
HAMD change score at week 2 ^{a-d}	-0.5	-3.0	-2.5	0.018
HAMD change score at week 3 ^{a-d}	-1.2	-4.1	-3.2	0.024
HAMD change score at week 4 ^{a-d}	-2.0	-5.8	-5.1	0.003**
HAMD change score at week 5 ^{a-d}	-1.8	-6.9	-5.6	0.0001**
HAMD change score at week 6 ^{a-d}	-1.7	-8.1	-6.1	0.0001**
<i>Males</i>				
HAMD change score at week 2 ^{a,b,d}	-0.7	-2.7	-2.5	0.630
HAMD change score at week 3 ^{a,b,d}	-1.7	-4.2	-3.3	0.400
HAMD change score at week 4 ^{a,b,d}	-2.7	-6.6	-5.7	0.071
HAMD change score at week 5 ^{a,b,d}	-2.7	-7.2	-5.3	0.024
HAMD change score at week 6 ^{a,b,d}	-3.5	-9.1	-6.9	0.030
<i>Females</i>				
HAMD change score at week 2 ^{a,b,d}	-0.01	-3.2	-2.5	0.029
HAMD change score at week 3 ^{a,b,d}	-0.8	-4.0	-3.3	0.085
HAMD change score at week 4 ^{a,b,d}	-1.2	-5.1	-4.8	0.054
HAMD change score at week 5 ^{a,b,d}	-1.2	-6.7	-6.0	0.006
HAMD change score at week 6 ^{a,b,d}	-1.8	-7.4	-5.6	0.020
<i>Family history positive</i>				
HAMD change score at week 2 ^{a-c}	-1.2	-3.4	-2.6	0.140
HAMD change score at week 3 ^{a-c}	-0.6	-4.2	-2.6	0.161
HAMD change score at week 4 ^{a-c}	-2.4	-5.7	-4.4	0.280
HAMD change score at week 5 ^{a-c}	-2.6	-6.3	-5.8	0.165
HAMD change score at week 6 ^{a-c}	-2.5	-8.8	-6.8	0.027
<i>Family history negative</i>				
HAMD change score at week 2 ^{a-c}	-0.5	-2.7	-2.2	0.164
HAMD change score at week 3 ^{a-c}	-1.6	-4.1	-3.8	0.206
HAMD change score at week 4 ^{a-c}	-1.5	-5.9	-5.7	0.013
HAMD change score at week 5 ^{a-c}	-1.5	-7.3	-5.7	0.001**
HAMD change score at week 6 ^{a-c}	-2.5	-7.8	-5.8	0.019

^aSingle multivariable ANOVA for weekly reduction of raw HAM-D change scores.

p-value of 158val/val vs 158val/met genotypes comparisons yielded from separate multivariable ANOVAs per weekly change score adjusted for age^b, gender^c, family history of psychiatric illness^d and with *post hoc* Bonferroni correction.

**Significant p-value for comparison of 158val/val vs 158val/met genotypes after Bonferroni correction for multiple comparisons (15 tests per independent variable sets p-value to 0.003).

major depression. These findings of a negative influence of the 158met/met genotype appear to be in contrast with the present observation of the 158val/val genotype conferring higher risk of non-response. However, the presently observed 158val/val genotype effect was most prominent when compared to the 158val/met genotype rather than the 158met/met genotype. This might be explained in analogy to the proposed 'inverted U' relationship between dopamine levels and prefrontal function. Under this model, function

has been suggested to be optimal within a narrow range of dopamine activity, with too little or too much dopamine having relatively deleterious effects (Mattay *et al*, 2003). Thus, both the 158met/met genotype increasing dopamine levels as well as the 158val/val genotype impairing dopamine availability might contribute to the risk of non-response to antidepressant treatment, which across different studies might be modulated by factors extrinsic to the COMT 158val/met locus such as a specific constellation of

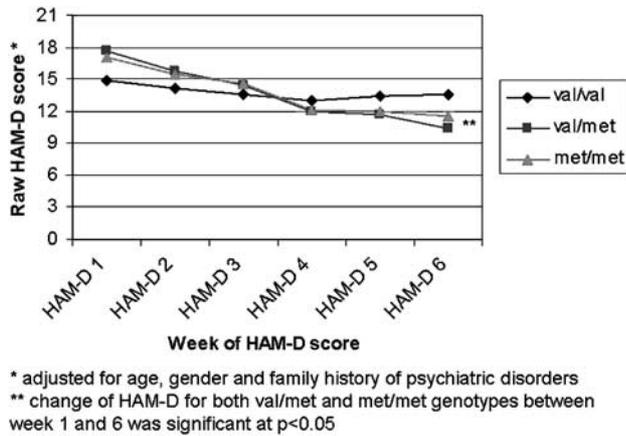


Figure 1 Raw HAM-D scores between weeks 1 and 6 of antidepressant treatment across COMT val158met genotypes in 256 subjects with major depression.

genetic risk factors within the dopaminergic system, differential environmental risk factors, or different sub-clinical characteristics related to reduced or increased dopamine tonus in the respective samples of patients with depression (for review see Dailly *et al*, 2004). This notion of dose-dependency in the dopaminergic tonus with respect to depressive symptoms can be further illustrated by a case report observing improved depressive symptomatology on augmentation of antidepressant medication with bromocriptine 2.5–5 mg/day, whereas an increased dose of bromocriptine 15 mg/day resulted in a deteriorated clinical status (Wada *et al*, 2001). Additionally, differences in antidepressive medication across studies may account for the discrepant findings with regard to the associated allele.

Interestingly, stratification of patients with major depression for gender revealed that the association of the COMT 158val/val genotype with poor outcome after 5–6 weeks of treatment was slightly more pronounced in the female subsample. This observation is in accordance with previous studies in obsessive-compulsive disorder, panic disorder, and schizophrenia reporting association of the COMT val158met polymorphism preferably in female patients (Alsobrook *et al*, 2002; Dömschke *et al*, 2004; Kremer *et al*, 2003). Gender-specific effects of COMT gene variation also fit well with findings of sexually dimorphic COMT activity (Boudikova *et al*, 1990), which might be due to the fact that estrogen can regulate COMT transcription by binding to estrogen response elements in the promoter region of the COMT gene (Xie *et al*, 1999). Thus, gender-specific effects of the COMT val158met polymorphism might be due to hormonal influences, gene–gene interaction (eg, with a sex-linked gene), or gene–environment interaction with a gender-specific exposure possibly affecting an intermediate phenotype common to several different psychiatric diseases including major depression.

Our study indicates that the use of HAM-D might be more suitable for the detection of differences in psychopathology across COMT val158met genotypes as compared to the subjective measure of the BDI and measures assessing functionality (GAF and CGI), as those measures showed no differences across COMT val158met genotypes. However, this possible interpretation needs to be considered with

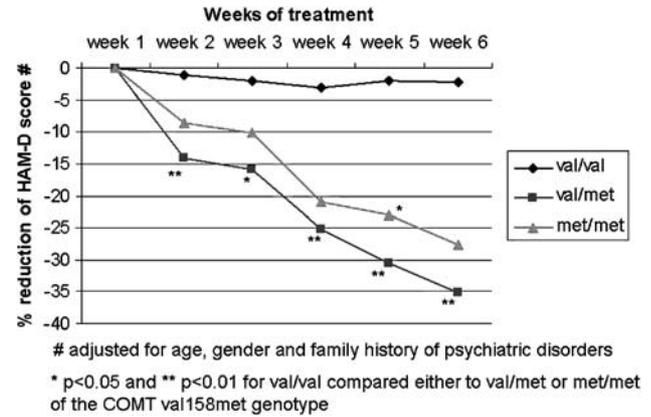


Figure 2 Percent reduction of HAM-D scores over 6 weeks of antidepressant treatment across COMT val158met genotypes in 256 subjects with major depression.

caution and warrants further clarification as the BDI, GAF, and CGI were only measured at admission and discharge as opposed to the weekly assessment using the HAM-D scale.

The following limitations have to be mentioned and considered while interpreting the present results: patients were recruited in a naturalistic setting allowing for a large sample size, however, implying treatment with a variety of antidepressants, no standardized dosage regime, and no standardized control for plasma drug levels. Also, since *a priori* only patients with a treatment cycle of at least 6 weeks from baseline were included in the present study, no dropouts due to non-response could be accounted for. However, there were no dropouts because of side effects. Furthermore, the sample sizes of patients with bipolar disorder, major depressive episode, and of subgroups of patients receiving a single antidepressive medication (as opposed to the more frequently used combination treatment) might have been too small to detect a minor genetic effect, thus increasing the risk of a false-negative result. Finally, although in all samples Caucasian ancestry was ascertained by Caucasian background of both parents, ethnic stratification even within the German population cannot be excluded (Steffens *et al*, 2006), particularly since no genomic control has been performed on the samples presently under study.

In conclusion, the present results point toward a negative influence of the higher activity COMT 158val/val genotype on antidepressant treatment response during the first 6 weeks of pharmacological treatment in major depression, possibly conferred by consecutively decreased norepinephrine and dopamine availability. The latter would be in line with a rat model of depression, where reduced dopamine availability in response to serotonergic stimulation in the nucleus accumbens, possibly conferred by the more active COMT variant, has been suggested to constitute an essential factor in the pathogenesis and course of depression as well as a target for modulation by antidepressant drugs (Zangen *et al*, 2001; Dremencov *et al*, 2004). Accordingly, given that in pharmacological studies the COMT inhibitor, tolcapone, has proven to reverse an anhedonic state in a rat model of depression and to reduce symptom severity in the treatment of major depression (Moreau *et al*, 1994; Fava *et al*, 1999),

the present findings support a potentially beneficial effect of an antidepressive add-on therapy with substances increasing dopamine availability individually tailored according to COMT val158met genotype with homozygous carriers of the COMT 158val allele potentially profiting most. Robust identification of the COMT val158met variant as a clinical predictor for treatment response might aid in identifying the 30–40% of patients not responding to initial treatment and thus provide the basis for more efficient, economical, and time saving treatment decisions. Therefore, replication studies preferably in large, well-characterized samples are warranted to further clarify the role of COMT gene variation in antidepressant treatment response.

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DISCLOSURE/CONFLICT OF INTEREST

All authors declare no conflict of interest.

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