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The COMT Val158Met polymorphism and cognition in depressed and nondepressed older adults

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SUMMARY

Objective—The objective of the current study was to examine the relationship between the COMT Val¹⁵⁸Met polymorphism and neuropsychological performance in depressed and nondepressed older adults.

Methods—One hundred and twenty-six clinically depressed older adults and 105 nondepressed comparison participants were compared on neuropsychological performance and COMT Val¹⁵⁸Met (Val/Val, Val/Met, Met/Met).

Results—Based on multivariate regression models, the COMT Val¹⁵⁸Met polymorphism was not associated with cognitive performance among depressed or nondepressed individuals, nor did this polymorphism account for the fact that depressed individuals performed worse than nondepressed individuals on several neuropsychological tests that are typically affected by depression. There was also no difference in frequency of the COMT Val¹⁵⁸Met alleles between depressed and nondepressed individuals.

Conclusions—Although the current study found no association between COMT Val¹⁵⁸Met polymorphism on a number of clinical neuropsychological tests that are typically found to be sensitive to depression, differential effects of the COMT Val¹⁵⁸Met polymorphism on dopamine transmission in psychiatric and non-psychiatric populations may be further clarified by clinical research with neuroscience-based paradigms that segregate cognitive tasks into component processes with precise neural substrates, particularly with respect to the complex functions of the prefrontal cortex. Negative results can be important to narrowing down target processes and understanding the influence of clinical and demographic characteristics in studies of psychiatric genetics.

Keywords

geriatric depression; aging; Catechol-0-Methyltransferase; neuropsychology; cognition

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CONFLICT OF INTEREST

None known.

INTRODUCTION

The dopamine neurotransmitter system plays an important role in cognition via its activity in the prefrontal cortex (Savitz *et al.*, 2006). Dopamine activity, and thus its affect on cognition, may be influenced by the intracellular Catechol-*O*-Methyltransferase (COMT) enzyme, which catabolizes dopamine. Genetic polymorphisms that alter the function of this enzyme may affect dopamine concentrations, which in turn would affect cognition.

The COMT Val¹⁵⁸Met polymorphism appears particularly critical to COMT efficiency by virtue of a G-to-A transition that produces a valine-to-methionine substitution at codon 158 on chromosome 22. The polymorphism results in reduced thermostability and lower activity of the Met allele (Lachman *et al.*, 1996; Chen *et al.*, 2004) such that homozygosity for ¹⁵⁸Met has been associated with a 3- to 4-fold reduction in enzymatic activity relative to ¹⁵⁸Val homozygotes (Lachman *et al.*, 1996). The Met variant's reduced activity results in slower degradation of dopamine in the brain and a presumed increase in dopamine availability that appears to increase the efficiency of prefrontally mediated activities like complex attention and other executive functions (Weinberger *et al.*, 2001; Arnsten and Li, 2005). Because dopamine is involved in a number of psychiatric conditions (Baumeister and Francis, 2002; Klimek *et al.*, 2002) as well as normal aging (Channon *et al.*, 1993; Backman *et al.*, 2006), the COMT Val¹⁵⁸Met polymorphism may yield important insights into cognition in both normal aging and psychiatric disorders in later life.

Although not extensively studied, there has been some work examining the effect of the COMT Val¹⁵⁸Met polymorphism in mentally healthy older adults. Higher Met allele load is associated with better episodic memory performance in men (de Frias *et al.*, 2004), while another study found that heterozygous individuals performed better on a test of prose recall than either homozygous genotype (Harris *et al.*, 2005). Another study found no overall effects of COMT genotype on a number of neuropsychological tests, but it did identify sex differences, in which Val homozygous men performed better on a test of delayed prose recall than men with the other two COMT genotypes, and heterozygous women exhibited better naming performance than homozygous women (O'Hara *et al.*, 2006).

There is little research on the role of the COMT Val¹⁵⁸Met polymorphism in Major Depressive Disorder despite depression being associated with prefrontally mediated changes in both mood and cognition. The majority of studies examining gene frequency have found no difference in Val¹⁵⁸Met allele frequency between depressed and nondepressed participants (Kunugi *et al.*, 1997; Frisch *et al.*, 1999; Russ *et al.*, 2000; Cusin *et al.*, 2002), except for an association between the Val/Val genotype and early onset of a mood episode before 26 years of age (Massat *et al.*, 2005). None of these studies examined an older depressed population, where the association between depression and cognitive changes is more pronounced and includes deficits in executive functions (Boone *et al.*, 1995; Elderkin-Thompson *et al.*, 2003), processing speed (Boone *et al.*, 1994; Boone *et al.*, 1995; Elderkin-Thompson *et al.*, 2003), verbal recall (Channon *et al.*, 1993; Elderkin-Thompson *et al.*, 2003), and verbal fluency (Boone *et al.*, 1994). Part of this cognitive vulnerability in older depressed individuals may reflect the role of dopamine in age-related cognitive changes (Backman *et al.*, 2006), but may also be related to the pathogenesis of depression, which involves dopaminergic pathways in prefrontal and hippocampal regions that regulate both cognition and affect (Millan *et al.*, 2000; Phillips *et al.*, 2003). Patterns of cognitive dysfunction that may exist in geriatric depression may represent a phenotype for genetic effects of COMT Val¹⁵⁸Met on cognition in brain regions sensitive to dopamine, with the gene effect being heightened due to these age-related changes.

In this study, we examined the relationship between the COMT Val¹⁵⁸Met polymorphism and neuropsychological performance in depressed and nondepressed older adults, particularly focusing on neuropsychological measures that tend to be adversely affected by depression. We hypothesized that the Val158 allele, which codes for the more active version of COMT, would be associated with poorer cognitive function overall, with a greater effect of the VAL158 allele in depressed elders who generally exhibit cognitive deficits in the context of this mood disorder.

METHODS

Participants

All participants were aged 60 and over and enrolled in the National Institute of Mental Health-sponsored Conte Center for the Neuroscience of Depression in Late Life at Duke University Medical Center (DUMC). All depressed participants met DSM-IV criteria for Major Depressive Disorder as diagnosed using the Diagnostic Interview Schedule (DIS; Robins *et al.*, 1981) and confirmed via a clinical evaluation by a geriatric psychiatrist. Exclusion criteria included: (1) another major psychiatric illness, including bipolar disorder, schizophrenia, or dementia; (2) history of alcohol or drug abuse or dependence; (3) primary neurologic illness, including dementia; and (4) medical illness, medication use, or disability that would prevent the participant from completing neurocognitive testing. Depressed participants were recruited from clinics, referrals, and advertisements. The Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) was completed by the study psychiatrist at enrollment and was used as a measure of depression severity. Depressed participants were enrolled in a treatment study that is described elsewhere (Steffens *et al.*, 2004) that included a standardized treatment algorithm (Steffens *et al.*, 2002).

Nondepressed comparison participants were community-dwelling individuals recruited through advertisements and from the Aging Center Subject Registry at Duke University. Eligible participants had a non-focal neurological examination, no self-report of neurologic or psychiatric illness, and no evidence of a current or past psychiatric disorder based on the Diagnostic Interview Schedule.

The study protocol was approved by the Duke University Medical Center Institutional Review Board. All participants provided written informed consent before beginning study procedures.

Procedure and measures

Participants were excluded from the study if they had dementia or suspected dementia at baseline. Dementia screening was conducted by a study geriatric psychiatrist and included a clinical evaluation, medical record review, and consultation with referring physicians when applicable. All participants completed the Mini-Mental State Examination (MMSE; Folstein *et al.*, 2001) at study entry, which was used to exclude individuals below a predetermined cutoff for suspected dementia (MMSE <25). Depressed individuals who were below this cutoff at study entry were followed through an acute eight-week phase of treatment to determine if cognition improves. Individuals whose MMSE scores remained below 25 were excluded from the current study (Steffens *et al.*, 2004).

All participants completed a neuropsychological evaluation assessing multiple domains of function, based on a battery developed for epidemiological and clinical research purposes. This evaluation occurred before depressed participants started antidepressant medications as part of the larger study, however they may have been taking antidepressant medications prescribed clinically before study enrollment. The domains selected for the current study

were: (1) global cognitive function (MMSE); (2) timed attentional processing as assessed by Parts A and B of the Trail Making Test (Reitan, 1992) and the Symbol-Digit Modalities Test (SDMT; Smith, 1982); (3) attention/working memory assessed by the forward and backward Digit Span from the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1987); (4) verbal memory assessed by the Logical Memory I (immediate recall) and Logical Memory II (delayed recall) subtests from the Wechsler Memory Scale—Revised (Wechsler, 1987); and lexical fluency assessed by the Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWA; Benton *et al.*, 1983). Premorbid intellect was represented by the Shipley Vocabulary Test (Zachary, 1991) and was used as a covariate in modeling the effects of COMT on neuropsychological performance. Raw test scores were used for all analyses.

Genetic analyses

DNA was extracted from fresh and frozen blood and stored according to previously reported methods (Rimmeler *et al.*, 1998; Taylor *et al.*, 2007). An aliquot of DNA was used for COMT genotyping (Lachman *et al.*, 1996), using PCR amplification with a Taqman by-design assay (Applied Biosystems) that recognized the single nucleotide polymorphism (SNP) which defines the Val158 Met polymorphism (rs4680). The samples were examined with an ABI7900 DNA analyzer and the genotypes determined with the SDS software package (Applied Biosystems). Greater than 95% genotyping efficiency was required before data were submitted for further analysis.

Analytic strategy

Descriptive statistics were used to examine means and distributions of variables. Harvey-Weinberg equilibrium was tested for the depressed and nondepressed cohorts separately, and chi-square tests were used to examine the allele frequency of COMT between depressed and nondepressed participants. Multivariate general linear regression models were used to examine the effects of the three Val¹⁵⁸Met genotypes on neuropsychological performance along with covariates of depression status, age, education, sex, and premorbid intellect (Shipley Vocabulary). We also included an interaction variable between depression status and COMT genotype, which was removed from the model if it did not reach statistical significance. The raw score of each neuropsychological measure was regressed on these independent variables in a separate model, with planned comparisons of the Val/Val, Val/Met, and Met/Met genotypes. The probability level for statistical significance was specified as $p < 0.05$. At this probability level, we were powered to detect a small-to-medium sized effect ($f = 0.21$) among three groups with beta at 0.80 (Cohen, 1988).

RESULTS

The sample consisted of 126 depressed and 105 non-depressed participants (Table 1). There were statistically significant differences between depressed and non-depressed participants with respect to education and sex, but not age. We tested for deviation from Hardy-Weinberg equilibrium separately in depressed and nondepressed participants, and found no evidence of deviation in either group. Analysis of COMT genotype by depression status indicated that allele frequency did not differ between depressed and nondepressed (depressed: Met/Met = 23.81%, Val/ Met = 53.17%, Val/Val = 23.02%; nondepressed: Met/Met = 29.52%, Val/Met = 47.62%, Val/Val = 22.86%). Similar to an approach used by others (Massat *et al.*, 2005), we identified an early-onset subset of the depressed population who had a first depressive episode at or before age 25. When these 27 early-onset participants were compared with the nondepressed sample, there continued to be no difference in COMT genotype frequency (early-onset: Met/Met = 14.8%, Val/Met = 55.6%, Val/ Val = 29.6%; 2 df, $\chi^2 = 2.43$, $p = 0.2962$).

There were no differences between COMT genotypes in age, education level, or sex. Examining the relationship between COMT genotype and neuropsychological test performance among all participants (Table 2) demonstrated no significant differences in neuropsychological test performance based on genotype. Results from multivariate analyses also revealed no significant effects of COMT genotype on neuropsychological test performance.

Examining the effects of depression status on neuropsychological performance in these multivariate models indicated significantly better performances among nondepressed individuals on 6/9 measures, including timed attentional processing (Trail Making A and B, SDMT), verbal fluency (COWA), and verbal memory (Logical Memory I and II), but with no group differences on tests of attention (Digit Span forward and backward) or global cognitive function (MMSE). Testing for an interaction of depression status and COMT genotype found no significant interactions among COMT genotype, depression status, and neuropsychological performance. Examination of the remaining covariates indicated that other factors contribute to better neuropsychological performance, including lower age (7/9 measures), higher education (3/9 measures), and higher premorbid intellect (9/9 measures). Sex was not a significant predictor of neuropsychological performance.

In addition to the *a priori* models, we conducted analyses to further explore an association of any Val allele on the COMT Val¹⁵⁸Met polymorphism to neuropsychological performance (de Frias *et al.*, 2004). Models comparing Met/Met alone to a combined group of Val/Met and Val/Val yielded no significant association with neuropsychological performance. We analyzed the results separately for depressed and nondepressed participants and again found no significant effects of COMT genotype.

DISCUSSION

The primary finding of this study is that no association was found between the COMT Val¹⁵⁸Met polymorphism and cognitive performance among depressed or nondepressed individuals, nor did this polymorphism account for the fact that depressed individuals performed worse than nondepressed individuals on several neuropsychological tests that are typically affected by depression. There also was no difference in frequency of the COMT Val¹⁵⁸Met alleles between depressed and nondepressed individuals, which to our knowledge has not yet been reported in a geriatric sample. Thus, although the COMT Val¹⁵⁸Met polymorphism may be associated with cognitive differences in other age groups and psychiatric populations (Egan *et al.*, 2001; Malhotra *et al.*, 2002; Rosa *et al.*, 2004), this was not observed in a sample including both depressed and non-psychiatric elders.

The current results are broadly concordant with previous research finding limited or inconsistent effects of the COMT Val¹⁵⁸Met polymorphism in older adults, but our findings extend to older adults with depression. Similar to a previous study, we did not find an overall cognitive effect of the COMT Val¹⁵⁸Met polymorphism among older adults (O'Hara *et al.*, 2006), although that study found gender effects for specific tests that were not replicated in the current study. Other studies have found conflicting associations between COMT Val¹⁵⁸Met and episodic memory, in one case reporting better performance on episodic memory tasks with higher Met allele load (de Frias *et al.*, 2004), and in another case finding better memory among heterozygotes compared with either Val or Met homozygotes (Harris *et al.*, 2005). One previous study in community-dwelling elders in their seventh decade reported that the Val/Val genotype has a detrimental effect on cognition, but this was based on an aggregation of several different tests and the influence of individual cognitive abilities is unclear (Starr *et al.*, 2007).

Discrepancies in our negative findings for non-depressed older adults may reflect sample differences. Overall, the nondepressed cohort was highly educated with many participants broadly in the high normal range of cognitive ability. This was also seen in the O'Hara *et al.* study (2006), which also found no overall influence of the COMT Val¹⁵⁸Met polymorphism on cognitive function; thus, it is possible that the cognitive effects of this polymorphism may be more evident in samples with a broader distribution of cognitive ability. It is also possible that the heterogeneous influences on cognitive aging may mask the more modest effects of this polymorphism (Deary *et al.*, 2004). We would agree with the assessment of Harris *et al.* (2005) that the effect of the COMT Val¹⁵⁸Met polymorphism is likely to be small for most cognitive processes when it is present, and this suggests the need for additional research on the specific cognitive role of COMT in elderly psychiatric and nonpsychiatric populations.

One study limitation is that we do not have data on clinically prescribed antidepressants that each participant was taking on the specific date of neuropsychological assessment, so we cannot test for medication effects in a sufficient proportion of the sample. Our findings of neuropsychological deficits in depressed relative to nondepressed elders are consistent with numerous other studies, including medication-free studies (Boone *et al.*, 1995), and both clinical community-based studies with multiple psychotropic medications used among the sample (Beats *et al.*, 1996; Airaksinen *et al.*, 2004; Bierman *et al.*, 2005). Although it is possible that varying influences of specific agents on depression symptoms or dopamine transmission may have resulted in additional error variance in predicting neurocognitive performance, we do not believe it would have been in a significant or systematic manner that would confound the interpretation of our results.

Another consideration is that we looked at cognition using several tests that are typically sensitive to the cognitive deficits of depression, but our study did not include some of the tests that have been associated with the COMT Val¹⁵⁸Met polymorphism in studies of schizophrenics and healthy adults, which have shown a positive association with Met allele load for perseveration (Egan *et al.*, 2001; Malhotra *et al.*, 2002), working memory as assessed by N-back and letter-number sequencing tasks (Bruder *et al.*, 2005), and 'tuning' of working memory efficiency on a continuous performance task (Stefanis *et al.*, 2005). Even these findings, however, have not been replicated consistently, as negative findings are reported for the N-back in nonpsychiatric adults (Bruder *et al.*, 2005), for continuous performance in people with schizophrenia and healthy adults (Goldberg *et al.*, 2003), and for perseveration among people with schizophrenia (Barnett *et al.*, 2007).

We agree with researchers who argue that segregation of cognitive tasks into component processes with precise neural substrates will help clarify the differential effects of the COMT Val¹⁵⁸Met polymorphism on dopamine transmission in psychiatric and non-psychiatric populations (Murphy and Alexopoulos, 2006), and we note that negative results are important to narrowing down target processes and understanding the influence of clinical and demographic characteristics on these processes. Further, it is helpful to determine what factors may influence specific cognitive domains throughout the lifespan, and how the strength of the effect of these factors on cognition may change with aging.

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KEYPOINTS

- The COMT Val¹⁵⁸Met polymorphism was not associated with cognitive performance among depressed or nondepressed individuals, nor did this polymorphism account for the fact that depressed individuals performed worse than nondepressed individuals on several neuropsychological tests that are typically affected by depression.
- There was no difference in frequency of the COMT Val¹⁵⁸Met alleles between depressed and nondepressed individuals.

Table 1

Participant characteristics by depression status

	Depressed (n = 126)	Nondepressed (n = 105)	p-value
	M (SE)	M (SE)	
Age	69.49 (0.58)	70.00 (0.53)	0.51
Education	14.42 (0.26)	16.16 (0.22)	<0.01
Sex (% female)	57.14	75.24	<0.01
Age of Depression Onset	42.2 (20.0)	—	—
MMSE	27.84 (0.21)	29.01 (0.17)	<0.01
TMT A	49.22 (3.16)	34.81 (1.10)	<0.01
TMT B	124.36 (6.60)	79.67 (2.80)	<0.01
SDMT	36.80 (0.97)	46.16 (0.81)	<0.01
DSF	8.59 (0.23)	9.17 (0.25)	0.09
DSB	7.05 (0.23)	7.89 (0.25)	0.02
LM I	24.62 (0.72)	30.09 (0.64)	<0.01
LM II	20.48 (0.85)	26.65 (0.72)	<0.01
COWA	39.28 (0.99)	46.85 (1.09)	<0.01

COWA =Controlled Oral Word Association; DSB = Digit Span Backward; DSF = Digit Span Forward; LM I = Logical Memory I; LM II = Logical Memory II; MMSE = Mini-Mental State Examination; SDMT = Symbol-Digit Modalities Test; TMT A =Trail Making Test A; TMT B = Trail Making Test B.

Note: Trail Making is timed in seconds; lower scores reflect better performance.

Table 2

Participant characteristics by COMT Val¹⁵⁸Met polymorphism

	Val/Val n = 53 M (SE)	Val/Met n = 117 M (SE)	Met/Met n = 61 M (SE)	1 vs 2 prob. 0.92	1 vs 3 prob. 0.90	2 vs 3 prob. 0.79
Age	69.74 (0.84)	69.63 (0.56)	69.89 (0.78)	0.92	0.90	0.79
Education	14.94 (0.38)	15.36 (0.25)	15.16 (0.35)	0.36	0.67	0.65
% female	66.04	58.97	77.05	0.38	0.19	0.02
Shipley	34.19 (0.65)	33.32 (0.44)	34.66 (0.61)	0.27	0.60	0.07
% depressed	54.72	57.26	49.18	0.76	0.56	0.31
MADRS [†]	17.04 (1.79)	20.38 (1.17)	16.48 (1.76)	0.12	0.83	0.07
Age of Depression Onset [‡]	39.1 (3.8)	41.3 (2.6)	47.5 (3.9)	0.65	0.13	0.19
MMSE	28.57 (0.28)	28.26 (0.19)	28.44 (0.26)	0.83	0.79	0.58
TMT A	42.17 (3.85)	44.16 (2.59)	40.33 (3.59)	0.67	0.73	0.39
TMT B	109.83 (8.20)	102.79 (5.67)	98.31 (7.77)	0.48	0.31	0.64
SDMT	40.34 (1.47)	40.72 (1.00)	42.64 (1.39)	0.83	0.26	0.26
DSF	8.70 (0.36)	8.72 (0.24)	9.15 (0.33)	0.96	0.35	0.29
DSB	8.04 (0.36)	7.20 (0.24)	7.30 (0.33)	0.05	0.13	0.80
LM I	28.04 (1.07)	26.01 (0.72)	28.33 (0.99)	0.12	0.84	0.06
LM II	23.75 (1.23)	22.22 (0.84)	25.02 (1.16)	0.30	0.46	0.05
COWA	44.17 (1.61)	41.48 (1.09)	43.87 (1.50)	0.28	0.99	0.26

[†]MADRS and age of onset data are for depressed participants only: n = 29 (Val/Val), 67 (Val/Met), and 30 (Met/Met).

COWA = Controlled Oral Word Association; DSB = Digit Span Backward; DSF = Digit Span Forward; LM = Logical Memory; MADRS = Montgomery-Asberg Depression Rating Scale, depressed participants only; MMSE = Mini-Mental State Examination; SDMT = Symbol-Digit Modalities Test; Shipley = Shipley Vocabulary; TMT A = Trail Making Test A; TMT B = Trail Making Test B.

Note: Trail Making is timed in seconds; lower scores reflect better performance.