Published in final edited form as:

Neurosci Lett. 2006 December 6; 409(3): 205–209.

COMT Genotype, Gender and Cognition in Community-Dwelling, Older Adults

Ruth O'Hara, Ph.D.^{1,2}, Elana Miller, B.A.¹, Chun-Ping Liao, B.A.², Nate Way, B.A.¹, Xiaoyan Lin, M.S.¹, and Joachim Hallmayer, M.D.¹

¹Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University, Stanford, CA

²Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC).

Abstract

A common polymorphism (Val158Met) in the gene encoding for the catechol-*O*-methyltransferase (COMT) enzyme has been associated with differences in prefrontal cognitive function in schizophrenic patients and healthy adults. While several studies indicate that the Met allele is associated with better performance on measures of executive function, working memory and verbal fluency, results have been inconsistent. Furthermore, fewer studies have investigated this relationship in older adults, a group known to experience impairments in prefrontal cognitive functions. Additionally, findings vary according to the gender distribution of study participants.

Keywords

Catechol-*O*-methyltransferase; cognition; older adults; gender

We examined whether COMT genotype interacted with gender to impact cognition in a cohort of 163 healthy, older adults. Memory, verbal ability and areas of prefrontal cognitive function, including attention, speed-of-processing, and executive function, were assessed. We found no significant association between COMT genotype and any cognitive measure. However, gender interacted with COMT genotype to impact cognitive performance. Males homozygous for the Val allele performed better than both the Val/Met and Met/Met groups on measures of delayed recall. Heterozygous women performed better than their homozygous counterparts on the measure of verbal ability. These findings suggest that gender may be an important variable in consideration of the impact of COMT on cognition. Further, when gender is taken into consideration, any negative impact of COMT genotype may extend to cognitive domains other than those associated with prefrontal regions.

Cognitive impairment in older adults is well-documented and several genetic markers have been proposed to moderate this effect [28]. One genetic marker documented to impact cognitive functioning is COMT, the gene that codes for catechol-*O*-methyltransferase, a critical enzyme in the metabolic degradation of dopamine in the prefrontal cortex. This gene, mapped to

Address correspondence to Ruth O'Hara, Ph.D., Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305-5550. E-mail: roh@leland.stanford.edu. Telephone: (650)852-3287. FAX: (650) 852-3297.

This work was supported in part by National Institutes of Health grants AG 18784; AG 17824, MH070886 and the Department of Veteran Affairs, Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

chromosome 22q11, contains a common functional polymorphism where valine (Val) is substituted for methionine (Met) at the 158/108 locus on the peptide sequence. The Val allele results in a substantial (4-fold) increase in enzyme activity, and therefore may result in increased dopamine degradation and decreased dopamine signaling [1,21]. Given that dopamine signaling is implicated in cognitive functioning, specifically in the prefrontal cortex, it has been suggested that COMT genotype may contribute to differences in working memory and executive function [1,37].

The majority of investigations of the relationship between COMT genotype and cognition focus on schizophrenic populations in which the COMT Val allele is typically associated with impairments in prefrontal abilities [10,12,18]. However, the relationship between the COMT Val allele and prefrontal abilities in healthy subjects is less clear. While some have observed an association between the lower-activity Met allele of the COMT gene and better performance on measures of prefrontal executive functioning [7,23,29] and working memory [12], several others find no association between COMT genotype and cognitive performance [3,17,32,33]. Interestingly, Ho et al. [17] found no significant interaction between COMT genotype and neuropsychological measures of executive function but did find evidence of prefrontal cortical inefficiency in schizophrenic Val carriers using positron emission tomography (PET), suggested by an increase in regional cerebral blood flow in the dorsolateral prefrontal cortex and the right medial frontal lobe during performance of a working memory and attention task. Similarly, Tsai et al. [33] observed no COMT genotype differences in executive function in healthy adults, but found increased P300 latencies to be associated with the Val allele. These two studies examined subjects significantly younger than the samples employed in other investigations. Therefore, it is possible that the neuropsychological measures utilized are not sufficiently sensitive to impairments in prefrontal function in younger adults.

Older adults experience well-documented age-related impairments and decline in cognitive and prefrontal abilities such as speed of processing and executive function [30,36], raising the possibility that this effect is moderated by the COMT polymorphism. To date, few studies have investigated this issue specifically in healthy older adults. In a random sample of non-demented men over a broad age range, de Frias et al. [4] found that compared to Val carriers overall, Met/Met individuals performed better on measures of executive function, visuospatial abilities, and episodic and semantic memory but among the older participants, Met/Met individuals declined in episodic memory performance over a 5-year period. On the other hand, Harris et al. [16] found that among healthy older adults Val/Met heterozygotes had higher scores on measures of verbal declarative memory than both homozygous groups. It is interesting to note that among these studies of older adults, COMT effects were also observed on other cognitive domains, suggesting that the impact of the Val allele extends beyond prefrontal abilities in these subjects. A limitation of many previous studies is that the authors elect a priori to examine only measures of prefrontal cognition, thus not investigating if any effect of COMT generalizes to other cognitive domains.

Inconsistencies among studies also may reflect an interaction between age and gender. In the largest studies to date, de Frias et al. [4,5] found a significant negative impact of the Val allele on several cognitive domains across a wide age range, in an all-male sample. Conversely, Stefanis et al. [32], found no effect of the Val allele in a large male cohort of younger subjects. Studies with substantial representations of women tend to less consistently observe a positive association of COMT and prefrontal cognitive function [14,16,17,26,33]. Yet, to date, few studies have systematically considered gender effects.

In the current investigation, we examined the relationship of COMT Val/Met polymorphism to cognitive performance in a cohort of healthy older adults. The cognitive domains assessed

included processing speed and attention, executive function, immediate and delayed verbal recall, and verbal fluency and confrontation naming.

Participants were 163 community-dwelling older adults participating in an ongoing investigation of age-related cognitive decline. They were recruited through advertisements, contacts with local senior centers, or had previously participated in studies at Stanford University. All subjects provided informed consent in accordance with Stanford University IRB regulations. An initial evaluation included self-reported current and past medical status the Mini-Mental State Exam (MMSE) [9], the SCID Screen Patient Questionnaire and a clinical interview to rule out for Axis I disorders [8]. Individuals with a MMSE less than 26 (indicating possible dementia) or any Axis I disorder were not included. All participants had sufficient visual and auditory acuity for cognitive testing. Subjects were 101 females and 62 males between 60 and 100 years of age ($M = 71.14$; $SD = 8.8$), with an average of 16.17 years of education ($SD = 2.8$). Participants were administered the following cognitive tests: the Symbol-Digit Modalities Test (SDMT) [31] to measure information processing speed and attention, the Wechsler Memory Scale-Revised (WMS-R), Logical Memory: I and II [34] to measure immediate and delayed verbal memory, the Stroop Color and Word Test (SCW) [13] to measure executive function, selective attention and cognitive flexibility, WMS-R: Digit Span Backwards [25], as a measure of working memory, attention and executive function, and the Boston Naming Test (BNT) [19] as a measure of verbal ability, particularly confrontation naming. Raw scores were employed and the following indices served as the outcome measures for each test: Total number correct for the SDMT; total number recalled correctly for the WMS-R: Logical Memory I and II; time taken to read all words on the Color-Word Page of the SCW; number of trials correctly recalled for Digit Span Backwards; total number of items correctly named with and without cue stimulus cue for the BNT.

In order to establish COMT genotype, whole blood samples were drawn at the Clinical Research Unit and transported immediately to the genetics laboratory. DNA was extracted from 200 μ l blood using the Qiagen DNeasy Kit. The target 217bp COMT gene fragment was amplified using sense primer 5'-TCG TGG ACG CCG TGA TTC AGG-3' and the antisense primer 5'-AGG TCT GAC AAC GGG TCA GGC-3'. PCR reactions were carried out in a final volume of 15 μ l consisting of 50ng of genomic DNA, 50ng each of each primers, 7.5 μ l of Taq PCR Master mix (Qiagen, Cat.#201445) and 10% DMSO. The PCR conditions included an initial denaturation step at 95°C for 3 min, followed by 35 cycles of denaturation at 95°C for 30s, annealing at 55°C for 45s and extension at 72°C for 1 min, with a final extension of 10 min at 72°C. The PCR products were digested at 37°C for 3 hours with 5 U of the restriction enzyme *Nla* III (New England Biolabs, Cat.#R0125S). Products were electrophoresed on a 10% Polyacrylamide gel (Acrylamide/bis-Acrylamide ratio 19:1) at 150 V for 40 min. A 10bp marker was used to measure the fragments size. The H allele, high activity Val-108, showed 2 bands, at 136bp and 81bp. The L allele, low activity Met-108, showed 3 bands, at 96bp, 81bp and 40bp.

The COMT genotype distribution for the 163 subjects was: Val/Val=33, Val/Met=90, Met/Met=40. Allele frequencies did not differ significantly from Hardy-Weinberg equilibrium ($\chi^2 = 1.84$; $p=0.17$). To compare demographics and cognitive performance across the three allele groups (Val/Val, Val/Met and Met/Met) we conducted a one-way ANOVA. No significant differences were observed with respect to age or years of education. Additionally, χ^2 analysis revealed no differences in the distribution of gender across the three allele groups (see Table 1).

To investigate the relationship of COMT and Gender to cognitive performance we conducted a 2 (Gender: Male; Female) by 3 (COMT Genotype: Val/Val, Val/Met and Met/Met) Multivariate Analysis of Variance.

No main effects of COMT genotype were observed with respect to any of the cognitive domains, including those assessing prefrontal cognitive function, namely the SDMT, the SCW and Digit Span Backwards. However, a significant main effect of gender was observed for the BNT measure of confrontation naming, with men exhibiting better performance ($F=6.7[1, 154]; p=.01$). We also observed a significant interaction of gender and COMT genotype on the BNT, with heterozygous Val/Met females performing significantly better than both female homozygous groups ($F=3.3[2, 152]; p=.03$; see Figure 1). With respect to WMS-R delayed, men with the Val/Val genotype performed significantly better than Val/Met or Met/Met men ($F=3.9[2, 152]; p=.02$; see Figure 2), while there was no difference in the performance among the women. Our findings did not change when covaried for age and education.

In the current study, we observed no overall effects of COMT genotype on measures of memory, verbal ability, attention, speed-of-processing and executive functioning in community-dwelling, older adults. Despite the increased age of our sample, no significant associations with performance on prefrontal tasks were observed.

We did observe significant interactions of gender and COMT genotype. Males homozygous for the Val allele performed better than both the Val/Met and Met/Met groups on the WMS-R measure of delayed verbal recall. No significant association between COMT genotype and WMS-R was observed for female participants. However, women with the Val/Met genotype exhibited significantly better performance on the BNT measure of confrontation naming than women homozygous for both Val and Met alleles. This association was not observed in men. Neither of these observations is consistent with findings that suggest that presence of the Val allele has a negative impact on cognitive functioning, particularly prefrontal function.

The most consistent association of the COMT Val allele and poorer prefrontal cognitive function has been observed in patients with schizophrenia. Since schizophrenia is hallmarked by relative decreases in prefrontal dopamine activity [35], individuals with this disorder who are also carriers of the Val allele, may be at particular risk for degradations in dopaminergic activity in prefrontal areas with associated decrements in prefrontal cognitive function [1,37]. Individuals with normal dopamine activity may be less vulnerable to any negative effects of the Val allele on dopamine signaling. Although the evidence suggests that older adults experience a loss of dopaminergic function [2], age-related depletions occur across several neurotransmitter systems, and such decrements are likely heterogeneous. Thus, the variable effects of COMT genotype on prefrontal ability in normals may reflect less vulnerability to any negative effect of the Val allele on dopamine signaling and/or greater individual variation in dopamine activity in this cohort.

Indeed, one explanation previously proposed for inconsistent effects of COMT genotype on cognition is that there may be an "ideal" level of dopamine signaling in the brain and that this amount may vary based on age and baseline memory performance [11,16,24]. Studies experimentally manipulating the level of dopamine signaling in the brain lend support to the theory that there is an inverted-"U" shaped functional response curve to increased dopamine signaling, and that response can vary according to baseline working memory capacity and COMT genotype [24]. Gibbs and D'Esposito [11] found that behavioral response to the dopamine agonist bromocriptine depended on the subjects' baseline working memory performance. Subjects with lower initial scores on a listening span task improved their performance while subjects with higher initial scores diminished their performance after bromocriptine administration. Similarly, Mattay et al. [24] found that administering the dopamine agonist amphetamine enhanced prefrontal cognitive efficiency in Val/Val individuals while reducing efficiency in Met/Met individuals in higher load trials.

In explaining why heterozygous individuals performed better than either homozygous group in a population of healthy older adults, Harris et al. [16] suggested that the level of dopamine signaling ideal for enhanced cognitive function may be lower in this age cohort, since there may be a reduction in dopamine receptors with age. Our observation that the Met allele was associated with poorer performance on the WMS-R delayed recall in men only, combined with our finding that heterozygous women exhibited better confrontation naming ability on the BNT than both Val/Val and Met/Met women while Met/Met men scored the highest on this cognitive domain, may indicate that the optimal level of dopamine signaling is different in men than in women and also may be cognitive domain specific. As such, the optimal level of dopamine may be influenced by genotype particularly in interaction with such variables as gender and cognitive domain.

Traditionally, women perform better than men on verbal learning tasks [20,27]. However, given that estrogen regulates dopamine transmission [15,22,27], sex hormones may contribute to observed gender differences in verbal learning tasks. Therefore, any positive effect of estrogen on verbal cognitive tasks may diminish post-menopause with an associated reduction in the advantage conferred by presence of the Met allele.

Indeed, the relationship of COMT to cognitive function may vary according to developmental stages in the lifespan. While de Frias et al. [4] found that healthy males homozygous for the Met allele performed best overall on measures of episodic memory and semantic fluency, among older men, those homozygous for the Met allele declined in episodic memory performance across a five-year period, approaching the level of same-aged Val carriers at follow-up. In our investigation men homozygous for the Met allele exhibited the lowest delayed verbal recall performance. Given that our cohort was older overall and had a wider age-range than the study by de Frias et al [4], this raises the possibility that the memory performance of individuals homozygous for the Met allele may continue to decline, eventually falling lower than their Val carrier counterparts. Longitudinal studies are required to more fully elucidate the relationships among COMT genotype, age, gender and cognitive performance.

Our study has several limitations which must be considered in interpreting our results. Any lack of observation of an association between COMT genotype and prefrontal tasks may have been limited by the fact that we did not employ measures such as the WCST or the N-back task, which may be more sensitive to deficits in executive function than the SCW, SDMT or Digit Span Backwards employed in the current investigation. Further, our sample was composed of extremely high functioning, well-educated older adults and the literature suggests that neuropsychological measures may have limited sensitivity in such individuals due to the increased potential for cognitive and neurophysiological reserve [6]. When categorized by gender and COMT genotype our sample sizes are limited, which may have reduced our power, such that lack of gender differences with respect to prefrontal tasks must be interpreted cautiously.

Overall, in our investigation we did not observe any impact of COMT genotype on measures of prefrontal function in a sample of healthy, older adults. However, our findings suggest that gender may be an important variable in consideration of the impact of COMT on cognition. Additionally, our findings support the view that there may be an optimal level of dopamine function that is influenced by genotype particularly in interaction with such variables as cohort, gender and cognitive domain. Further, when gender is taken into consideration, any negative impact of COMT genotype may extend to cognitive domains other than those associated with prefrontal regions.

References

- [1]. Akil M, Kolachana BS, Rothman DA, Hyde TM, Weinberger DR, Kleinman JE. Catechol-*O*-methyltransferase genotype and dopamine regulation in the human brain. *Journal of Neuroscience* 2003;23:2008–2013. [PubMed: 12657658]
- [2]. Backman L, Nyberg L, Lindenberg U, Li SC, Farde L. The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neurosci Biobehav Rev* 2006;30(6):791–807. [PubMed: 16901542]
- [3]. Bruder GE, Keilp JG, Xu H, Shikhman M, Schori E, Gorman JM. Catechol-*O*-methyltransferase (COMT) genotypes and working memory: Associations with differing cognitive operations. *Biol. Psychiatry* 2005;58:901–907. [PubMed: 16043133]
- [4]. de Frias CM, Annerbrink K, Westberg L, Eriksson E, Adolfsson R, Nilsson LG. COMT gene polymorphism is associated with declarative memory in adulthood and old age. *Behav. Genet* 2004;34:533–539. [PubMed: 15319576]
- [5]. de Frias CM, Annerbrink K, Westberg L, Eriksson E, Adolfsson R, Nilsson LG. Catechol *O*-methyltransferase Val158Met polymorphism is associated with cognitive performance in nondemented adults. *J. of Cogn. Neurosci* 2005;17:1018–1025. [PubMed: 16102234]
- [6]. Drebing CE, Van Gorp W, Stuck AE, Mitrushina M, Beck J. Early detection of cognitive decline in higher cognitively functioning older adults: Sensitivity and specificity of a neuropsychological screening battery. *J Neuropsychology* 1994;8:31–37.
- [7]. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158Met genotype on frontal lobe function and risk for schizophrenia. *Proc. Natl. Acad. Sci* 2001;98:6917–6922. [PubMed: 11381111]
- [8]. First, MB.; Gibbon, M.; Williams, JB.; Spitzer, RL. SCID Screen Patient Questionnaire (SSPQ). Multi-Health Systems Inc; Toronto, ON: 1999.
- [9]. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res* 1975;12:189–198. [PubMed: 1202204]
- [10]. Galderisi S, Maj M, Kirkpatrick B, Piccardi P, Mucci A, Invernizzi G, Rossi A, Pini S, Vita A, Cassano P, Stratta P, Severino G, del Zompo M. Catechol-*O*-methyltransferase Val158Met polymorphism in schizophrenia: Associations with cognitive and motor impairment. *Neuropsychobiology* 2005;52:83–89. [PubMed: 16037677]
- [11]. Gibbs SE, D'Esposito M. Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. *Cogn. Affect. Behav. Neurosci* 2005;5:212–221. [PubMed: 16180627]
- [12]. Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR. Executive subprocesses in working memory: Relationship to catechol-*O*-methyltransferase Val158Met genotype and schizophrenia. *Arch. Gen. Psychiatry* 2003;60:889–896. [PubMed: 12963670]
- [13]. Golden, CJ.; Freshwater, SM. Stroop Color and Word Test. Stoelting Co.; Wood Dale, IL: 2002.
- [14]. Guo JF, Yang YK, Chiu NT, Yeh TL, Chen PS, Lee IH, Chu CL. The correlation between striatal dopamine D2/D3 receptor availability and verbal intelligence quotient in healthy volunteers. *Psychol. Med* 2006;36:547–554. [PubMed: 16359604]
- [15]. Halbreich U. Role of estrogen in postmenopausal depression. *Neurology* 1997;48:16–19.
- [16]. Harris SE, Wright AF, Hayward C, Starr JM, Whalley LJ, Deary IJ. The functional COMT polymorphism, Val158Met, is associated with logical memory and the personality trait intellect/imagination in a cohort of healthy 79 year olds. *Neurosci. Lett* 2005;385:1–6. [PubMed: 15979789]
- [17]. Ho BC, Wassink TH, O'Leary DS, Sheffield VC, Andreasen NC. Catechol-*O*-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Mol. Psychiatry* 2005;10:287–298.
- [18]. Joobar R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, Benkelfat C, Labelle A. Catechol-*O*-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Arch. Gen. Psychiatry* 2002;59:662–663. [PubMed: 12090821]
- [19]. Kaplan, E.; Goodglass, H.; Weintraub, S. Boston Naming Test. Lee & Febiger; Philadelphia: 1983.

- [20]. Kramer JH, Delis DC, Kaplan E, O'Donnell L, Prifitera A. Developmental sex differences in verbal learning. *Neuropsychopathology* 1997;11:577–584.
- [21]. Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-*O*-methyltransferase polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 1996;6:243–250. [PubMed: 8807664]
- [22]. Lindamer LA, Lohr JB, Harris MJ, Jeste DV. Gender, estrogen, and schizophrenia. *Psychopharmacol. Bull* 1997;33:221–228. [PubMed: 9230634]
- [23]. Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am. J. Psychiatry* 2002;159:652–654. [PubMed: 11925305]
- [24]. Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. Catechol *O*-methyltransferase Val158-Met genotype and individual variation in the brain response to amphetamine. *Proc. Natl. Acad. Sci* 2003;100:6186–6191. [PubMed: 12716966]
- [25]. Mefford RB, Wieland BA, James WE. Repetitive psychometric measures: digit span. *Psychol. Rep* 1966;18:3–10. [PubMed: 5908501]
- [26]. Mozley LH, Gur RC, Mozley PD, Gur RE. Striatal dopamine transporters and cognitive functioning in healthy men and women. *Am. J. Psychiatry* 2001;158:1492–1499. [PubMed: 11532737]
- [27]. Nordstrom AL, Olsson H, Halldin C. A PET study of D2 dopamine receptor density at difference phases of the menstrual cycle. *Psychiatry Res* 1998;83:1–6. [PubMed: 9754700]
- [28]. O'Hara R, Yesavage JA, Kraemer HC, Mauricio M, Friedman LF, Murphy GM Jr. The APOE epsilon4 allele is associated with decline on delayed recall performance in community-dwelling older adults. *J. Am. Geriatr. Soc* 1998;46:1493–1498. [PubMed: 9848808]
- [29]. Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martínez-Larrea A, Fañanás L. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *Am. J. Psychiatry* 2004;161:1110–1112. [PubMed: 15169701]
- [30]. Salthouse TA. Working memory as a processing resource in cognitive aging. *Develop. Rev* 1990;10:101–124.
- [31]. Smith, A. Symbol Digit Modalities Test (SDMT): Manual (revised). Western Psychological Services; Los Angeles: 1982.
- [32]. Stefanis NC, Van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Hantoumi I, Stefanis CN. Variation in catechol-*O*-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. *Biol. Psychiatry* 2004;56:510–515. [PubMed: 15450787]
- [33]. Tsai SJ, Yu YWY, Chen TJ, Chen JY, Liou YJ, Chen MC, Hong CJ. Association study of a functional catechol-*O*-methyltransferase-gene polymorphism and cognitive function in healthy females. *Neurosci. Lett* 2003;338:123–126. [PubMed: 12566168]
- [34]. Wechsler, D. The Wechsler Memory Scale Revised. Psychological Corporation; New York: 1987.
- [35]. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch. Gen Psychiatry* 1987;44:660–669. [PubMed: 3606332]
- [36]. West RL. An application of prefrontal cortex function theory to cognitive aging. *Psychol. Bull* 1996;120:272–292. [PubMed: 8831298]
- [37]. Winterer G, Goldman D. Genetics of human prefrontal function. *Brain Res. Rev* 2003;43:134–163. [PubMed: 14499466]

Figure 1: Interactive effect of COMT genotype and gender on BNT Confrontation Naming performance.

Scores on BNT Verbal Naming measure partitioned by genotype for Males (black bars) and Females (gray bars).

Figure 2: Interactive effect of COMT genotype and gender on Delayed Recall performance. Scores on WMS-R: Logical Memory Delayed Recall measure partitioned by genotype for Males (black bars) and Females (gray bars).

Table 1
Demographic Characteristics by COMT Genotype

	Val/Val (n=33) Mean (SD)	Val/Met (n=90) Mean (SD)	Met/Met (n=40) Mean(SD)	<i>P</i> Values
Age	72.5 (10.1)	70.2 (8.4)	72.1 (8.2)	.42
Years of Education	16.4 (2.4)	16.3 (2.4)	15.8 (3.0)	.51
Gender F/M	23/10	56/34	22/18	.47

Mean age and years of education, and distribution of females (F) and males (M) for the three COMT genotype groups are provided. Differences among the groups with respect to age and years of education were tested by one-way analysis of variance and the p values are provided. Chi-square analysis was conducted to test for differences in gender distribution across the COMT genotype groups and the p value is provided.

Table 2
Means and Standard Deviations for Cognitive Tests by COMT Genotype and Gender

	Val/Val (n=33)		Val/Met (n=90)		Met/Met (n=40)		P Values F/M
	F	M	F	M	F	M	
SDMT	44.1(11.9)	46.0(6.1)	48.0(10.5)	45.4(9.5)	46.9(9.5)	43.7(8.9)	.56
SCW	156.1(56.6)	153.1(29.2)	153.8(70.3)	164.3(48.5)	150.7(45.9)	148.6(35.7)	.79
Digit Span	7.27(2.23)	7.88(3.0)	7.54(2.0)	7.06(1.97)	6.82(1.82)	7.94(2.62)	.14
BNT	54.7(5.03)	55.5(4.60)	57.0(3.65)	56.9(4.05)	54.8(4.83)	56.3(4.22)	.03
WMS-R Logical Memory II	20.7(9.4)	27.0(5.8)	22.1(7.5)	18.9(9.2)	22.0(7.5)	17.8(9.1)	.02

COMT genotypes are subdivided by male (M) and female (F) groupings. Means and standard deviations for all cognitive tests, namely Symbol-Digit Modalities Test (SDMT), Stroop Color and Word Test (SCW), Digit Span Backwards, Boston Naming Test (BNT), and Wechsler Memory Scale-Revised: Logical Memory II subtest (WMS-R), are provided by COMT Genotype and Gender groupings. P-values are provided for the interaction of COMT genotype group and gender on the cognitive outcome measures.