Variations in the Catechol O-methyltransferase polymorphism and prefrontally-guided behaviors in adolescents

By: Dustin Wahlstrom, Tonya White, Catalina J. Hooper, Suzanne Vrshek-Schallhorn, William S. Oetting, Marcia J. Brott, Monica Luciana

Wahlstrom, D., White, T., Hooper, C.J., Vrshek-Schallhorn, S., Oetting, W.S., Brott, M.J., Luciana, M. (2007). Variations in the Catechol O-methyltransferase polymorphism and prefrontally-guided behaviors in adolescents. Biological Psychiatry, 61(5): 626-632.

Made available courtesy of Elsevier: https://doi.org/10.1016/j.biopsych.2006.05.045

Abstract:

Background The catechol-O-methyltransferase (COMT) gene codes for an enzyme that degrades prefrontal cortex (PFC) synaptic dopamine. Of two identified alleles (Met and Val), the Met allele results in COMT activity that is up to 4 times less pronounced than that conferred by the Val allele, resulting in greater PFC dopamine concentrations. Met-Met homozygotes perform better than individuals who possess the Val allele on PFC-mediated cognitive tasks. These genotypic variations and their associations with executive functions have been described in adults and prepubescent children, but there is a paucity of research assessing these relations in adolescent samples.

Methods In this study, 70 children aged 9–17 were genotyped for COMT and completed measures of working memory, attention, fine motor coordination, and motor speed.

Results COMT genotype modulated all but the motor speed measures. The Val-Met genotype was optimal for performance in this adolescent sample.

Conclusions Results are discussed within the context of developmental changes in the dopaminergic system during adolescence.

Keywords: adolescence | cognition | dopamine | genetics | prefrontal cortex | neuropsychology

Article:

The catechol O-methyltransferase (COMT) enzyme degrades synaptic catecholamines in the prefrontal cortex (PFC; Napolitano et al 1995, Weinshilboum et al 1999). The COMT gene resides

on the q11 region of chromosome 22 (Grossman et al 1992), where a functional missense mutation causes a single G-to-A base-pair substitution, resulting in a single nucleotide polymorphism (SNP) in exon 4. This polymorphism results in the substitution of Methionine (Met) for Valine (Val) at codons 108/158 (Lachman et al 1996). Individuals can be homozygous for the Met or Val alleles, or they can possess one of each allele. The Met allele results in a fourfold decrease in enzymatic activity relative to the Val allele, resulting in functionally significant increases in PFC catecholamine activity (Lachman et al 1996, Lotta et al 1995). The alleles are codominant. Heterozygotes exhibit intermediate levels of enzymatic activity relative to that of Val-Val and Met-Met individuals (Weinshilboum et al 1977). The Val108/158Met polymorphism's modulation of catecholamine levels is intriguing, because catecholamines modulate attention and working memory. Specifically, COMT's impact on dopamine activity has been of interest to investigators due to dopamine's modulation of PFC spatial working memory functions (Luciana and Collins 1997, Williams and Goldman-Rakic 1995). COMT genotype may partially underlie individual differences in the development of these functions.

COMT may play a specific role in the catabolism of PFC dopamine because of the relative lack of dopamine transporters in PFC (Moron et al 2002, Sesak et al 1998). COMT knockout mice demonstrate increased PFC dopamine, but striatal levels are unchanged (Gogos et al 1998, Huotari et al 2002). Psychopharmacologic challenges in mice suggest that COMT's influence on set-shifting performance is mediated specifically by dopaminergic systems, rather than generalized changes in other catacholamines (Tunbridge et al 2004).

Consistent with this proposed specificity, studies of healthy adults and those with psychopathology have linked variations in COMT genotype to performance on prefrontally dependent tasks such as the Wisconsin Card Sorting Test (WCST; Malhotra et al 2002, Rosa et al 2004) and the N-Back test (Goldberg et al 2003, Mattay et al 2003). Both tasks recruit lateral PFC regions. Successful performance relies on sufficient availability of prefrontal dopamine (Abi-Dargham et al 2002, Monchi et al 2004, Volkow et al 1998). Met-Met homozygosity predicts better task performance on both measures.

Additionally, COMT directly modulates task-related prefrontal activity (Egan et al 2001, Mattay et al 2003). Mattay et al (2003) demonstrated an interaction between COMT genotype, amphetamine response, and dorsolateral prefrontal activation during completion of the N-back task. Val-Val individuals generated more efficient prefrontal function (i.e., smaller BOLD responses) on amphetamine versus placebo despite no trade-off in performance. Conversely, Met-Met individuals demonstrated less efficient responses and impaired performance on the most difficult condition of the task in the amphetamine condition. The investigators suggested that COMT activity affects baseline levels of prefrontal dopamine. There appears to be an inverted U-shaped dose-response curve by which both deficient and excessive amounts of dopamine activity predict poor performance on cognitive tasks (Goldman-Rakic 1998, Granon et al 2000, Williams and Goldman-Rakic 1995). According to this model, individuals homozygous for the Met allele rest near the apex of this curve under basal conditions; heterozygous (Val-Met) and homozygous Val individuals lay toward the lower ends of the curve because of increased dopamine metabolism rates resulting from the Val allele (Figure 1B).

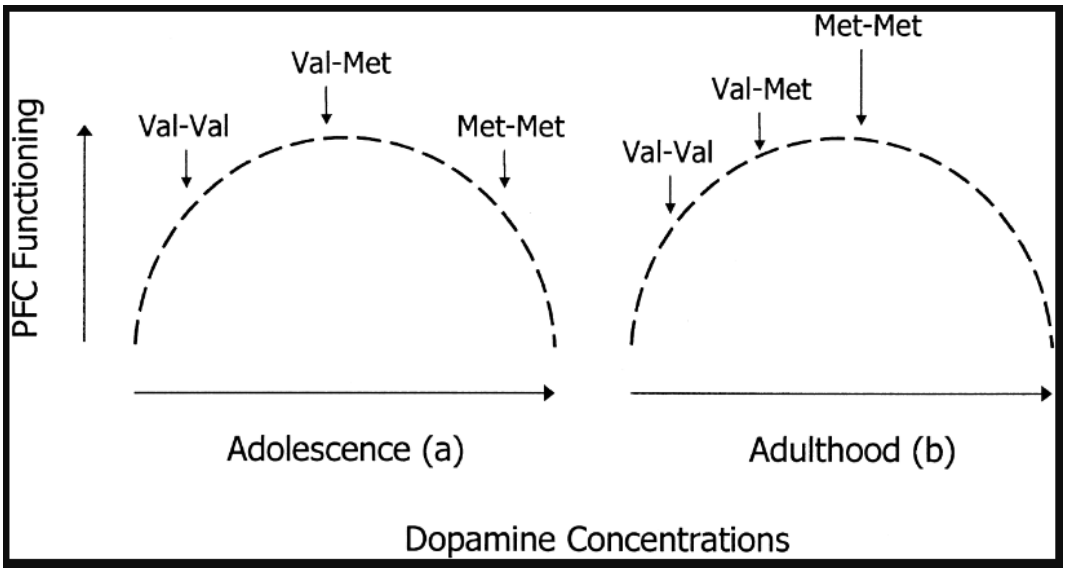

Figure 1. (A) Relationship of catechol O-methyltransferase (COMT) and basal dopamine concentrations to prefrontal functioning in typically developing adolescents as predicted by the data presented here. The heterozygote group performed better on prefrontal tasks than either homozygote group, suggesting these individuals lie closer to the apex of the inverted U-shaped curve as a result of their COMT genotype. This is consistent with literature suggesting basal prefrontal cortex dopamine concentrations increase in adolescents, shifting the relative place of each allele on the U-shaped curve to the right. (B) Inverted U-shaped curve representing the relationship of COMT allele and basal dopamine concentrations to prefrontal functioning as proposed by Mattay et al (2003). In typically developed adult samples, the Met-Met genotype predicts optimal prefrontal functioning and lies nearer to the apex of this curve than the Val-Met and Val-Val genotypes.

COMT and Development

Diamond et al (2004) related COMT genotype to prefrontal functioning in 8- to 14-year-olds, replicating adult findings by demonstrating a link between Met-Met homozygosity and better performance on a working memory/inhibitory control task. COMT genotype did not impact performance on a nondopaminergic dependent PFC task, thus demonstrating COMT's selective role in modulating behaviors dependent on both PFC and dopamine activity in children. Otherwise, investigations of COMT genotype–cognition relations in developmental samples are sparse and have focused on individuals with psychopathology (Bellgrove et al 2005, Mills et al 2004).

There is no research assessing the link between COMT and cognition in mid- to late-adolescence, an important omission given the multitude of changes within the dopamine system during that period. Dopamine cell density in Rhesus PFC decreases by up to 50% from the onset of adolescence to late adulthood (Goldman-Rakic et al 1981). In addition, basal dopamine levels in the PFC peak in early adolescence and decline thereafter (Andersen et al 1997), as do both dopamine turnover (Teicher et al 1993) and dopaminergic PFC input (Rosenberg and Lewis 1994, Rosenberg and Lewis 1995). Dopaminergic innervation of the PFC peaks during adolescence as evidenced by both dopamine cell fiber density and dopamine concentrations in the frontal pole (Kalsbeek et al 1998, Leslie et al 1991), suggesting that early- to mid-adolescence is characterized by increased PFC dopamine concentrations. Concentrations of D1 and D2 receptors in the PFC

are unchanged during adolescence. Changes in receptor concentrations do occur in the striatum during this same period (Seeman et al 1987, Tarazi et al 1999). More important, weanling rats exhibit only 70% of the dopamine transporter receptors found in adults, and these concentrations are not thought to reach adult levels until mid-adolescence (Coulter et al 1996). Overall, these data suggest that adolescence is characterized by increases in basal PFC dopamine levels.

The purpose of this study was to evaluate the relationship between COMT genotype and cognition in healthy children and adolescents between the ages of 9 and 17 years. Doing so allows us to link neurochemical development and behavior. Not only is little known about neurochemical development in humans, but numerous neuropsychiatric illnesses are treated using dopamine modulators with little understanding of how dopamine concentrations change during development. Neurochemical changes during development may explain developmental differences in medication response.

Three aspects of behavior, all dopamine modulated, were examined including working memory, attention, and fine motor dexterity (Luciana and Collins 1997, Wang et al 1998, Yang et al 2003). It was hypothesized that COMT would modulate these behaviors. Additionally, because adolescence is characterized by an excess of dopamine compared to childhood and adulthood, it was a possibility that Met-Met homozygosity would not predict optimal performance on tasks modulated by COMT.

Methods and Materials

Participants

The study protocol was approved by the University of Minnesota's Institutional Review Board. Participants were recruited from a database maintained by the University of Minnesota's Institute of Child Development. Parents of children within the desired age range were invited to participate. Seventy individuals (38 female, 32 male) aged 9 to 17 (M = 13.13, SD = 2.56 years) participated after providing informed consent and assent. Three additional participants were recruited but could not donate blood samples. One additional participant's blood sample could not be genotyped due to laboratory difficulties. Participants were free of neurologic or psychiatric disorders based on parent report. Pubertal status was assessed by self-report using the Tanner system (Marshall and Tanner 1969, Marshall and Tanner 1970). The questionnaire yields stages ranked from 1 (prepubertal) to 5 (postpubertal).

Protocol

Participants completed a large neuropsychological battery. The neuropsychological tasks presented here were selected a priori based on their hypothesized relationships to functions previously associated with dopaminergic functioning: motor dexterity (Wang et al 1998, Yang et al 2003, Yang et al 2004), attention (Glickstein et al 2005, Servan-Schreiber et al 1998), and working memory (Luciana et al 1992, Sawaguchi and Goldman-Rakic 1991). Individual tasks are described in Table 1. Motor speed (finger tapping) was also measured and was not expected to relate to COMT genotype.

Table 1. Neuropsychological Composites, Descriptions, and Cronbach's Alphas

Composite	Tasks	Task Description	Cronbach's Alpha
Motor	Halstead Finger Tapping Test (Dominant)	Participants tap a lever with their dominant hand. Yields an average number of taps over three trials (Halstead 1947).	.67
	Halstead Finger Tapping Test (Nondominant)	Average number of taps using the nondominant hand, averaged over three trials (Halstead 1947).	
	Delayed Response Task (0-msec Delay Reaction Time)	Speed with which participants touch a target stimulus (*) on a computer screen using a touch pen (FTG Data Systems, Inc.) (Luciana et al 1997).	
	Grooved Pegboard (Dominant)	Participants place small metal grooves into a 5 × 5 array of matching holes. Time to completion reported (Roy et al 1990).	
	Grooved Pegboard (Nondominant)	Time to completion with the nondominant hand on the grooved pegboard test (Roy et al 1990).	
	Delayed Response Task (0-msec Error)	Participants touch a target stimulus (*) on a computer screen using a touch pen. Accuracy with which participants were able to touch the target reported (Luciana et al 1997).	
Attention and Working Memory	Digit Span Forward	Participants repeat strings of numbers read by the examiner. Yields total raw score (Kaufman et al 1991, Wechsler 1991).	.78
	Spatial Span Forward	Participants touch blocks in the order touched by the examiner. Total raw score reported (Lezak et al 2004, Wechsler 1997b).	
	Delayed Response Task (500-msec Delay Error)	Target stimulus (*) displayed on the screen and disappears. Following a 500-msec delay, participants point to where * was before delay. Accuracy is reported (Luciana et al 1997).	
	Digit Span Backward	Participants repeat backward strings of words read by the examiner. Total raw score reported (Banken 1985)	
	Spatial Span Backward	Participants touch blocks in the reverse order touched by the examiner. Yields total raw score (Lezak et al 2004, Wechsler 1997b).	
	Delayed Response Task (8000-msec Delay Error)	Target stimulus (*) presented on screen, followed by an 8000-msec delay. Participants must touch screen after the delay where stimulus was. Yields accuracy score (Luciana et al 1997).	

Grouping of Variables

All task variables were converted into z scores, with higher scores representing better performance. They were then rationally grouped, averaged, and psychometrically evaluated to yield two composites of interest: working memory/attention and motor speed/dexterity (see Table 1).

In addition, based on our prior work, efficiency scores (error scores × reaction times for each delay condition) were created for performance on the Delayed Response Task (Luciana et al 2004). Higher efficiency scores represent poor performance because they are products of slower reaction times and higher error scores.

DNA Extraction Procedures

Blood was drawn into tubes containing ACD solution A as the anticoagulant. DNA was extracted from 15-mL whole blood using standard techniques. The isolated DNA was resuspended in TE (Tris/ethylenediamine tetraacetate) and stored at 4°C.

Determination of SNP Genotypes Using TaqMan Based Genotyping

The COMT1 polymorphism (V158M) was determined using the TaqMan-based genotyping technology from Applied Biosystems (Foster City, California). Briefly, the PCR and probe primers were designed by Applied Biosystems using its Assays-by-Design service. The forward polymerase chain reaction (PCR) primer was 5′-CCCAGCGGATGGTGGAT-3′, the reverse PCR primer was 5′-CAGGCATGCACACCTTGTC-3′. The probe reporter primers were VIC-TTCGCTGGCATGAAG and FAM-TCGCTGGCGTGAAG. Reactions and analysis were conducted in a 96-well plate format. The reaction components for each genotyping reaction were as follows: 20 ng of DNA, 12.5 IμL TaqMan master mix, .625 IμL of primer/probe mix and water up to a total volume of 25 IμL. The thermocycler conditions were as follows: 50°C for 2 min, 59°C for 10 min, and 40 cycles of 92°C 15 sec, and 60°C 1 min. The reaction was then analyzed using an Applied Biosystems PRISM sequence detection system model 7500.

Statistical Analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows (SPSS, Chicago, Illinois). Chi-square analyses were used for the comparison of categorical variables across COMT alleles (gender, ethnicity, and handedness). One-way analyses of variance (ANOVA) were used to compare continuous demographic variables, and repeated measures, univariate (ANCOVA) and multivariate analyses of covariance (MANCOVA) were used to compare cognitive constructs of interest. A three-level COMT variable (Val-Val, Val-Met, and Met-Met) was included in all ANCOVAs and MANCOVAs as the between-subject factor, and all analyses of test performance were covaried for age. Significant main effects were followed up by least significant difference (LSD) procedures. Prorated IQ was not initially covaried; however, adding it to the analyses did not alter the significance of the findings. For all tests, alpha levels below .05 were considered significant.

Results

Participant Demographics

Across 70 participants, there were 27 homozygotes (12 Val-Val; 15 Met-Met) and 43 heterozygotes (see Table 2). This distribution is consistent with expectations based on the Hardy–Weinberg equilibrium [$\chi 2(2, N = 70) = 3.73$, ns]. Groups were similar in age, pubertal status, gender, ethnicity, handedness, household income, and prorated full scale IQ based on Block Design and Vocabulary subtests (Wechsler 1991, Wechsler 1997a). Pubertal status was distributed within each COMT group, and only eight subjects were prepubertal. All findings presented in the following sections were maintained when these eight subjects were removed from the analyses.

Table 2. Participant Characteristics

	Genotype				
Variable	Val-Val	Val-Met	Met-Met	Test Statistic	Significance
n	12	43	15	$\chi 2(2) = 3.73$	.16
Age	13.2 (2.6)	12.9 (2.6)	13.8 (2.3)	$F(2,67) = .68$	.51
Sex (M/F)	4/8	20/23	8/7	$\chi 2(2) = 1.10$	.58
Tanner Pubertal Stage	2.96 (1.23)	2.87 (1.46)	3.27 (1.07)	$F(2,67) = .48$	.62
% Caucasian	83.3	88.4	100.0	$\chi 2(6) = 8.07$	.23
% Right-Handed[a]	100.0	86.0	86.7	$\chi 2(2) = 1.87$	.39
Household Income	$85,416.67	$72,906.98	$85,333.33	$F(2,67) = 1.32$	.27
FSIQ Estimate	110.6 (12.0)	118.6 (12.7)	115.2 (13.4)	$F(2,67) = 1.94$	.15

a Handedness was determined using the Edinburgh Inventory (Oldfield 1971).

Fine Motor Dexterity

An ANCOVA of the motor composite yielded a main effect of COMT genotype [$F(2,66) = 4.86$, $p < .05$]. Follow-up analyses revealed that the heterozygote group performed better on the composite than both the Val-Val ($p < .01$) and Met-Met group ($p < .05$). Val-Val individuals did not significantly differ from Met-Met individuals. Multivariate tests revealed that the overall effect was driven by performance on the dominant [$F(2,63) = 9.63$, $p < .01$] and nondominant [$F(2,63) = 4.08$, $p < .05$] conditions of the grooved pegboard task but not by the finger tapping test. Heterozygotes outperformed Val-Vals ($p < .01$) and Met-Mets ($p < .05$) on the dominant condition of the task. Met-Mets also performed better on the task compared with Val-Vals ($p < .05$). In the nondominant condition, heterozygotes outperformed the Val-Val group ($p < .05$) and (at a trend level) the Met-Met group ($p < .10$). The homozygote groups did not differ from one another.

Attention and Working Memory

There was a significant main effect of COMT genotype on the attention and working memory composite [$F(2,66) = 6.72$, $p < .01$]. This effect was due to the heterozygote group performing significantly better on the composite compared to the Met-Met group ($p < .01$), as well as the Val-Val group outperforming the Met-Met group at a trend level ($p < .10$). Heterozygotes did not differ from Val-Val individuals. A MANCOVA revealed significant differences in performance on the digit span backward [$F(2,64) = 4.31$, $p < .05$], spatial span backward [$F(2,64) = 3.10$, $p = .05$], and 500-msec error condition on the delayed response task [$F(2,64) = 3.33$, $p < .01$]. A trend was found

Table 3. Cognitive Task Performance and Multivariate Test Statistics across COMT Groups

	Genotype				
Composite	Val-Val	Val-Met	Met-Met	*F*	Post Hoc[b]
Motor					
Halstead Finger Tapping Test (Dominant)	−.12 (1.01)	−.01 (1.11)	.19 (.78)	.04	
Halstead Finger Tapping Test (Nondominant)	−.27 (.93)	.06 (1.09)	.12 (1.01)	.54	
Delayed Response Task (0-msec Delay Reaction Time)	.02 (1.06)	.17 (.86)	−.10 (1.09)	.79	
Grooved Pegboard (Dominant)	−.94 (1.60)	.32 (.52)	−.14 (1.08)	9.30[e]	VM > VV[e], VM > MM[d], MM > VV[d]
Grooved Pegboard (Nondominant)	−.61 (1.68)	.21 (.69)	−.19 (1.06)	4.08[d]	VM > VV[d], VM > MM[c]
Delayed Response Task (0-msec Delay Error)	.16 (.99)	.06 (1.04)	−.33 (.99)	1.49	
Attention and Working Memory					
Digit Span Forward	−.22 (.98)	.13 (1.04)	−.09 (.99)	1.67	
Spatial Span Forward	.37 (1.12)	.09 (1.02)	−.25 (.85)	2.51[c]	VM > MM[c], VV > MM[d]
Delayed Response Task (500-msec Delay Error)	−.07 (1.63)	.18 (.69)	−.45 (1.22)	3.33[d]	VM > MM[d]
Digit Span Backward	−.23 (1.28)	.25 (.97)	−.43 (.83)	4.31[d]	VM > MM[d]
Spatial Span Backward	−.03 (1.40)	.16 (.90)	−.37 (.80)	3.10[d]	VM > MM[c]
Delayed Response Task (8000-msec Delay Error)	−.04 (1.60)	.18 (.82)	−.24 (.87)	1.78	
Delayed Response Efficiencya					
0-msec Efficiency	3.03 (1.70)	3.08 (1.29)	4.31 (2.38)		
500-msec Efficiency	15.35 (16.96)	10.70 (4.89)	15.90 (10.20)		
8000-msec Efficiency	22.23 (20.77)	16.93 (9.08)	20.77 (8.86)		

Values (with the exception of delayed response efficiency, which is in thousands) represent z score means (± SD).
a Efficiency scores for the delayed response task were calculated by multiplying error rates (pixels) and reaction times (milliseconds). Thus, high scores reflect poor performance on the task.
b Multiple comparisons conducted using LSD procedure (VV = Val-Val; VM = Val-Met; MM = Met-Met.
c $p < .10$.
d $p < .05$.
e $p < .01$.

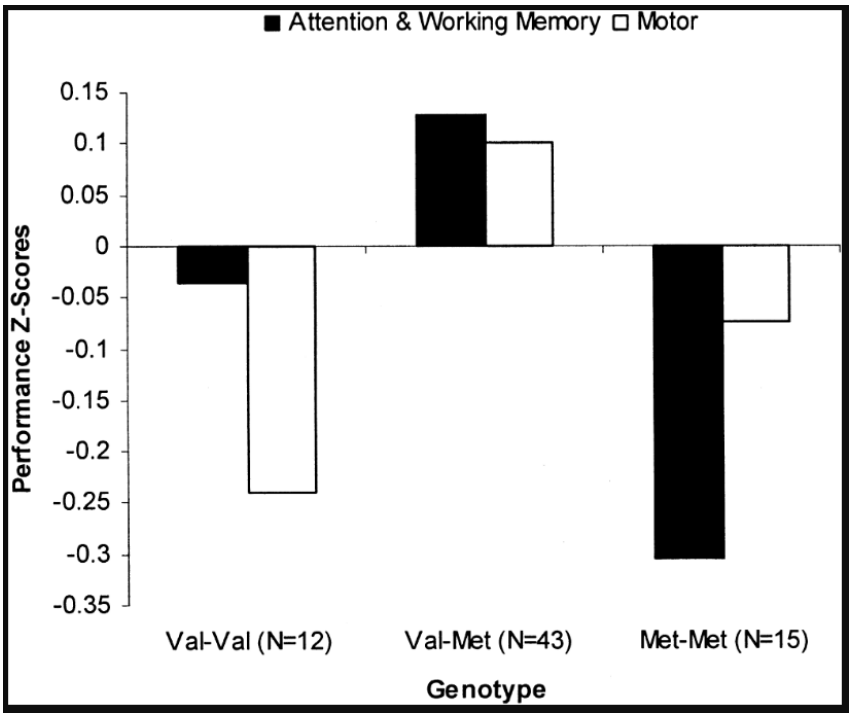

Figure 2. Performance on neuropsychologic composites as a function of catechol O-methyltransferase (COMT) genotype.

Delayed Response Task Efficiency

A main effect of COMT genotype was revealed for DRT efficiency [$F(2,65) = 3.42$, $p < .05$; Figure 3]. No COMT genotype by delay interaction was found. Follow-up analyses indicated that heterozygotes performed better than Met-Met individuals [$F(1,54) = 8.35$, $p < .01$]. A trend was found for the comparison between heterozygotes and the Val-Val group [$F(1,51) = 2.98$, $p < .10$], with heterozygotes performing better. No COMT genotype by delay interactions were found in any of the follow-up analyses.

Discussion

These findings demonstrate that the COMT polymorphism modulates performance on working memory, attention, and motor planning tasks shown to recruit prefrontal dopamine activity in a sample of children and adolescents aged 9–17. The Val-Met group performed better than both homozygote groups in motor coordination and better than the Met-Met group in attention and working memory. In addition, heterozygotes demonstrated better efficiency on a delayed response task compared with Met-Met and, to a lesser extent, Val-Val individuals. These results support previous findings (Diamond et al 2004) by demonstrating that COMT impacts cognitive functions dependent on prefrontal dopamine prior to adulthood. These findings are maintained with age and IQ covaried from the analyses and when prepubertal participants are excluded.

In addition, they extend past findings in two important ways: 1) by demonstrating that COMT does not influence adolescent performance on tasks (finger tapping) dependent on basal ganglia dopamine, consistent with reports suggesting its role in subcortical dopamine catabolism is negligible (Gogos et al 1998, Huotari et al 2002), and 2) demonstrating that COMT modulates cognitive performance in a sample that spans the full range of adolescence.

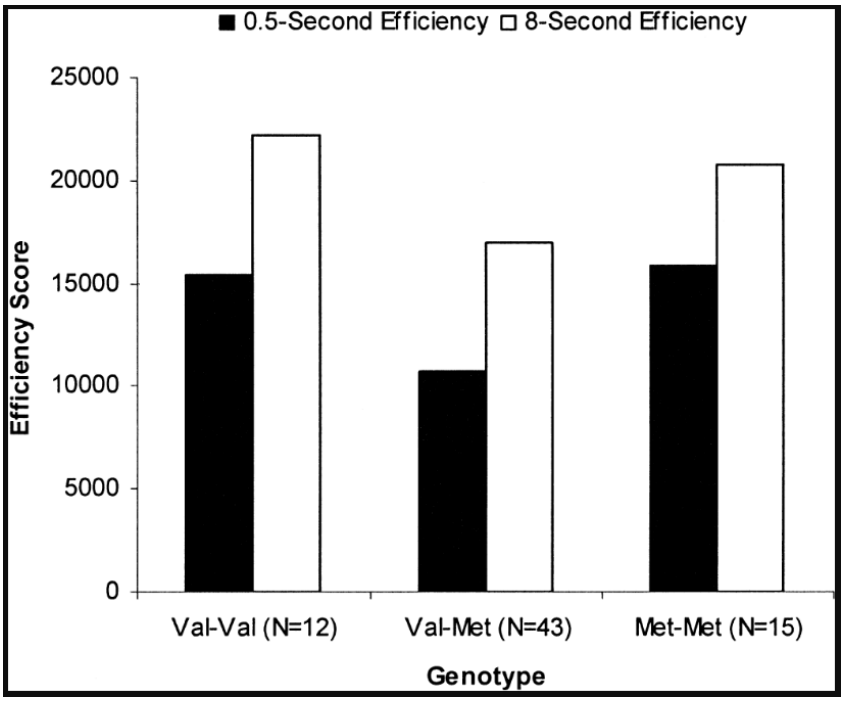

Figure 3. Efficiency on the delayed response task as a function of catechol O-methyltransferase (COMT) genotype.

Contrary to previous reports in both adults (Goldberg et al 2003, Malhotra et al 2002, Mattay et al 2003, Rosa et al 2004) and younger children (Diamond 2004), which found that the Met-Met polymorphism is associated with improved cognitive performance, the Val-Met polymorphism in our sample predicted better performance on all prefrontally mediated cognitive functions. This is the first report of such a pattern. The disparity between our findings and those reported by Diamond et al (2004) may be explained by a number of factors, including differences in the tasks used to assess prefrontal functions and age differences between the studies. Our sample is older (M = 13.13, range 9–17) than Diamond's (M = 10.1, range 8.0–14.6). Although the two samples seemingly overlap in age, Diamond and colleagues state that most of their participants were under age 12. Also, analysis of our frequency distribution and Diamond's standard deviations indicates that there are a small number of subjects across the studies that are similar in age. In addition, our findings are maintained when the eight prepubescent subjects were removed from our sample, all of whom were under 12 years.

Adolescence and the Inverted U-Shaped Curve

The age difference between this sample and Diamond's becomes especially relevant when placed into the pattern of neurochemical (e.g., dopaminergic) development as discussed earlier. Adolescence is characterized by increased dopamine reactivity. Integrating our study with studies reporting an inverted U-shaped relationship between PFC dopamine concentrations and cognitive performance (Goldman-Rakic 1998, Granon et al 2000, Mattay et al 2003, Williams and Goldman-Rakic 1995) suggests that, relative to adulthood, mid-adolescence is a period characterized by increased levels of basal PFC dopamine that may contribute to shifts in performance on some tasks. As proposed by Mattay et al (2003), adults with the Met-Met genotype lie somewhere near the apex of this inverted U, as evidenced by their improved efficiency on PFC-mediated cognitive tasks. If, as this research suggests, adolescence is characterized by increased levels of basal PFC

dopamine, the Met-Met genotype may increase dopamine concentrations to excessive (inefficient) levels. Thus, in adolescents, the Val-Met genotype may sit at the apex of the curve, with both homozygote groups representing either deficiencies (Val-Val) or excesses (Met-Met) in dopamine that result in poorer cognitive performance (Figure 1A). This conclusion would be consistent with the sometimes incongruent animal literature suggesting adolescence is characterized by increases in dopamine-modulated behaviors (i.e., novelty seeking, grooming, and sniffing) yet apparently attenuated responsivity to catecholamine agonists (Adriani et al 1998, Laviola et al 1995, Spear and Brake 1983). There may be further changes in optimal genotype that occur in the period from middle adulthood to old age as dopamine levels naturally decline.

Implications for Prefrontal Cortex Development

Elucidating the role of COMT across developmental periods serves a number of goals. First, and perhaps most important, is the role COMT may play in assisting our understanding of the mechanisms underlying cognitive dysfunction in disorders such as schizophrenia (Glatt et al 2003, Munafo et al 2005). Given that the onset of many psychiatric conditions occurs during adolescence (DSM-IV), the role of genetics in determining prefrontal cognition during this period is vital to our understanding of the development of these disorders. Further research could clarify relationships between the COMT polymorphism, developmental changes in basal levels of prefrontal dopamine, and cognitive performance. Of most importance would be the longitudinal assessment of age by genotype interactions, where we would expect to find the greatest rate of improvement on cognitive tasks from adolescence to adulthood in the Met-Met group due to their progression toward the peak of the hypothetical inverted-U function. Assessing changes in the relationship between COMT and cognitive performance across the life span would also be useful in determining whether adolescence is, in fact, a unique period.

In addition to understanding the specific relationship between genetics and prefrontal cognition, COMT can act as a marker used to inform us of other neural changes that occur in the PFC during adolescence. Prospective studies of this type, combining the COMT polymorphism with methodologies measuring cognition and/or physiologic markers of dopamine reactivity across age groups, will be instructive with respect to the information they provide regarding the interactions between genetics and neurobiology in the development of prefrontally mediated skills. Understanding these interactions may translate to differences in pharmacologic approaches to youth at various points along the developmental continuum.

Supported by Grant No. M01-RR00400 from the National Center for Research Resources, National Institutes of Health, and the Kempf Fund Award awarded to the second author by the American Psychiatric Association.

References

Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, et al (2002): Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci* 22:3708 –3719.

Adriani W, Chiarotti F, Laviola G (1998): Elevated novelty seeking and peculiar d-amphetamine sensitization in periadolescent mice compared with adult mice. *Behav Neurosci* 112:1152–1166.

Andersen SL, Dumont, NL, TeicherMH(1997): Developmental differences in dopamine synthesis inhibition by (/_)-7-OH-DPAT. *Naunyn Schmiedebergs Arch Pharmacol* 356:173–181.

Banken JA (1985): Clinical utility of considering digits forward and digits backward as separate components of the Wechsler Adult Intelligence Scale-Revised. J Clin Psychol 41:686–691.

Bellgrove MA, Domschke K, Hawi Z, Kirley A, Mullins C, Robertson IH, et al (2005): The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. Exp Brain Res. Available: http://www.springerlink.com/media/MFTA2GMGWG7QF0GUUBEX/Contributions/M/F/7/E/MF7ELW7ME7699THB_html/fulltext.html (accessed June 6, 2005).

Coulter CL, Happe HK, Murrin LC (1996): Postnatal development of the dopamine transporter: A quantitative autoradiographic study. Dev Brain Res 92:172–181.

Diamond A, Briand L, Fossella J, Gehlbach L (2004): Genetic and neurochemical modulation of prefrontal cognitive functions in children. Am J Psychiatry 161:125–132.

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al (2001): Effect of COMT Val108/158Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci of U S A 98:6917–6922.

Glatt SJ, Faraone SV, Tsuang MT (2003): Association between a functional catechol O-methyltransferase gene polymorphism and schizophrenia: Meta-analysis of case□control and family-based studies.AmJ Psychiatry 160:469–476.

Glickstein SB, DeSteno DA, Hof PR, Schmauss C (2005): Mice lacking dopamine D2 and D3 receptors exhibit differential activation of prefrontal cortical neurons during tasks requiring attention. Cereb Cortex 15:1016–1024.

Gogos J, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, Karayiorgou M (1998): Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci U S A 95:9991–9996.

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, et al (2003): Executive subprocesses in working memory: Relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch Gen Psychiatry 60:889–896.

Goldman-Rakic PS (1998): The cortical dopamine system: Role in memory and cognition. Adv Pharmacol 42:707–711. Goldman-Rakic PS, Brown RM (1981): Regional changes in monoamines in cerebral cortex and subcortical structures of aging rhesus monkeys. Neuroscience 6:177–187.

Granon S, Passetti F, Thomas KL, Dalley JW, Everitt BJ, Robbins TW (2000): Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. J Neurosci 20: 1208–1215.

Grossman MH, Emanuel BS, Budaf ML (1992): Chromosomal mapping of the human catechol O-methyltransferase gene to 22q11.1-q11.2. Genomics 12:822– 825.

Halstead WC (1947): Brain and Intelligence. A Quantitative Study of the Frontal Lobes. Chicago: University of Chicago Press.

Huotari M, Gogos J, Karayiorgou M, Koponen O, Forsberg M, Raasmaja A, et al (2002): Brain catecholamine metabolism in catechol-O-methyltransferase (COMT)-deficient mice. Eur J Neurosci 15:246 –256.

Kalsbeek A, Voorn P, Buijs RM, Pool CW, UylingsHBM(1998): Development of the dopaminergic innervation in the prefrontal cortex of the rat. J Comp Neurol 269:58 –72.

Kaufman AS, McLean J, Reynolds C (1991): Analysis of WAIS-R factor patterns by sex and race. J Clin Psychol 47:548 –557.

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski C, Weinshilboum R (1996): Human catechol O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6:243–250.

Laviola G, Wood RG, Kuhn C, Francis RLP (1995): Cocaine sensitization in preiadolescent and adult rats. J Psychopharmacol Exp Ther 275:345–357.

Leslie CA, Robertson MW, Cutler AJ, Bennett JP Jr (1991): Postnatal development of D1 dopamine receptors in the medial prefrontal cortex, striatum and nucleus accumbens of normal and neonatal 6-hydroxydopamine treated rats: A quantitative autoradiographic analysis. Dev Brain Res 62:109–114.

Lezak MD, Howieson DB, Loring DW (2004): Neuropsychological Assessment, 4th ed. New York: Oxford University Press.

Lotta T, Vidgren J, Tilgmann C, Ulmanen I, Melén K, Julkunen I, Taskinen J (1995): Kinetics of human soluble and membrane-bound catechol Omethyltransferase: A revised mechanism and description of the thermolabile variant of the enzyme. Biochemistry 34:4202– 4210.

Luciana M, Collins PF (1997): Dopaminergic modulation of working memory for spatial but not object cues in normal humans. J Cog Neurosci 9:330–347.

Luciana M, Depue RA, Arbisi P, Leon A (1992): Facilitation of working memory in humans by a D2 dopamine receptor agonist. J Cog Neurosci 4:58 – 68.

Luciana M, Hanson KL, Whitley CB (2004): A preliminary report on dopamine system reactivity in PKU: Acute effects of haloperidol on neuropsychological, physiological, and neuroendocrine functions. Psychopharmacology 175:18 –25.

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, GoldmanD(2002): A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 159:652– 654.

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al (2003): Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A 100:6186–6191.

Marshall WA, Tanner, JM (1969): Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291–303.

Marshall WA, Tanner, JM (1970): Variations in pattern of pubertal changes in boys. Arch Dis Child 45:13–23.

Mills S, Langley K, Van den Bree M, Street E, Turic D, Owen MJ, et al (2004): No evidence of association between Catechol-O-Methyltransferase (COMT) Val158Met genotype and

performance on neuropsychological tasks in children with ADHD: A case-control study. BMC Psychiatry 4:15–19.

Monchi O, Petrides M, Doyon J, Postuma RB, Worsley K, Dagher A (2004): Neural bases of set-shifting deficits in Parkinson's disease. J Neurosci 24:702–710.

Munafo MR, Bowes L, Clark TG, Flint J (2005): Lack of association of theCOMT (Val(158/108) Met) gene and schizophrenia: A meta-analysis of casecontrol studies. Mol Psychiatry. Available: http://www.nature.com/cgitaf/

DynaPage.taf?file /mp/journal/vaop/ncurrent/full/4001664a.html&filetype pdf (accessed June 6, 2005).

Moron JA, Brockington A, Wise RA, Rocha BA, Hope BT (2002): Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: Evidence from knock-out mouselines. J Neurosci 22:389 –395.

Napolitano A, Cesura AM, Da Prada M (1995): The role of monoamine oxidase and catechol O-methyltransferase in dopaminergic neurotransmission. J Neural Transm 45:35– 45.

Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia 9:97–113.

Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, Fananas L (2004): New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. Am J Psychiatry 161:1110 –1112.

Rosenberg DR, Lewis DA (1994): Changes in the dopaminergic innervation of monkey prefrontal cortex during late postnatal development: A tyrosine hydroxylase immunohistochemical study. Biol Psychiatry 36:272–277.

Rosenberg DR, Lewis DA (1995): Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: A tyrosine hydroxylase immunohistochemical analysis. J Comp Neurol 358:383– 400.

Roy EA, Square-Storer PA (1990): Evidence for common expressions of apraxia. In: Hammond GR, editor. Cerebral Control of Speech and Limb Movements. Amsterdam: North-Holland, 477–502.

Sawaguchi T, Goldman-Rakic PS (1991): D1 dopamine receptors in prefrontal cortex: Involvement in working memory. Science 251:947–950.

Seeman P, Bzowej NH, Guan HC, Bergeron C, Becker LE, Reynolds GP, et al (1987): Human brain dopamine receptors in children and aging adults. Synapse 1:399–404.

Servan-Schreiber D, Carter CS, Bruno RM, Cohen JD (1998): Dopamine and the mechanisms of cognition: Part II. D-amphetamine effects in human subjects performing a selective attention task. Biol Psychiatry 43:723–729.

Sesak SR, Hawrylak VA, Matus C, Guido MA, Levey AI (1998): Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. J Neurosci 18: 2697–2708.

Spear LP, Brake SC (1983): Periadolescence: Age-dependent behavior and psychopharmacological responsivity in rats. Dev Psychobiol 16: 83–109.

Tarazi FI, Tomasini EC, Baldessarini RJ (1999): Postnatal development of dopamine D1-like receptors in rat cortical and striatolimbic brain regions: An autoradiographic study. Dev Neurosci 21:43– 49.

Teicher MH, Barber NI, Gelbard HA, Gallitano AL, Campbell A, Marsh E, Baldessarini RJ (1993): Developmental differences in acute nigrostriatal and mesocorticolimbic system response to haloperidol. Neuropsychopharmacology 9:147–156.

Tunbridge EM, Bannerman DM, Sharp T, Harrison PJ (2004):COMTinhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. J Neurosci 24:5331–5335.

Wang Y, Chan GLY, Holden JE, Dobko T, Mak E, Schulzer M, et al (1998): Age-dependent decline of dopamine D1 receptors in human brain: A PET study. Synapse 30:56–61.

Volkow ND, Gur RC, Wang GJ, Fowler JS, Moberg PJ, Ding YS, et al (1998): Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatry 155:344 –349.

WechslerD(1991): Wechsler Intelligence Scale for Children—Third Edition. San Antonio, TX: Psychological Corporation.

Wechsler D (1997a): Wechsler Adult Intelligence Scale—Third Edition. San Antonio, TX: Psychological Corporation.

Wechsler D (1997b): Wechsler Memory Scale—Third Edition. San Antonio, TX: Psychological Corporation.

Weinshilboum RM, Otterness DM, Szumlanski CL (1999): Methylation pharmacogenetics: Catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. Annu Rev Pharmacol Toxicol 39:19 –52.

Weinshilboum RM, Raymond FA (1977): Inheritance of low erythrocyte catechol-o-methyltransferase activity in man. Am J Hum Genet 29:125–135.

Williams GV, Goldman-Rakic PS (1995): Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature 376:572–575.

Yang YK, Chiu NT, Chen CC, Chen M, Yeh TL, Lee IH (2003): Correlation between fine motor activity and striatal dopamine D2 receptor density in patients with schizophrenia and healthy controls. Psychiatry Res Neuroimaging 123:191–197.

Yang YK, Yeh TL, Chiu NT, Lee IH, Chen PS, Lee L, Jeffries KJ (2004): Association between cognitive performance and striatal dopamine binding is higher in timing and motor tasks in patients with schizophrenia. Psychiatry Res Neuroimaging 131:209 –216.