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The Roles of *COMT* val158met Status and Aviation Expertise in Flight Simulator Performance and Cognitive Ability

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Abstract

The polymorphic variation in the val158met position of the catechol-*O*-methyltransferase (COMT) gene is associated with differences in executive performance, processing speed, and attention. The purpose of this study is: (1) replicate previous COMT val158met findings on cognitive performance; (2) determine whether COMT val158met effects extend to a real-world task, aircraft navigation performance in a flight simulator; and (3) determine if aviation expertise moderates any

effect of *COMT* val158met status on flight simulator performance. One hundred seventy two pilots aged 41–69 years, who varied in level of aviation training and experience, completed flight simulator, cognitive, and genetic assessments. Results indicate that although no *COMT* effect was found for an overall measure of flight performance, a positive effect of the *met* allele was detected for two aspects of cognitive ability: executive functioning and working memory performance. Pilots with the *met/met* genotype benefited more from increased levels of expertise than other participants on a traffic avoidance measure, which is a component of flight simulator performance. These preliminary results indicate that *COMT* val158met polymorphic variation can affect a real-world task.

Keywords

COMT; Flight simulator performance; Cognitive performance; Aviation expertise; Age

Introduction

Catechol-*O*-methyltransferase (*COMT*) metabolizes synaptic dopamine, thereby limiting the length of time dopamine is available to activate its downstream receptors, and is particularly important in regulating dopamine signaling in the prefrontal cortex. Dopamine signaling in the prefrontal cortex is a critical modulator of working memory and executive function. There is a functional polymorphism in *COMT* involving a single amino acid substitution of methionine for valine (at position 108 in soluble *COMT* and at position 158 in membrane bound-*COMT*). The *met* variant results in a four-fold reduction in the *COMT* enzyme activity, leading to an increase in dopamine activity in the prefrontal cortex (Egan et al. 2001). This *val/met* polymorphism consistently has been shown to influence frontal lobe executive performance, as measured by the Wisconsin Card Sorting Task, and other measures of processing speed and attention (Backman et al. 2006). In particular, increased number of *met* alleles have been associated with better performance on executive function (Backman et al. 2006; Barnett et al. 2007; Bruder et al. 2005; Egan et al. 2001; Holtzer et al. 2008; Joobar et al. 2002; Malhotra et al. 2002; Nagel et al. 2008), working memory (Bruder et al. 2005; Egan et al. 2001; Goldberg and Weinberger 2004; Goldberg et al. 2003; Nagel et al. 2008), processing speed and attention (Bilder et al. 2002; Raz et al. 2009; Starr et al. 2007), episodic recall memory (de Frias et al. 2005; Raz et al. 2009), semantic memory (de Frias et al. 2005), visuospatial ability (Backman et al. 2006; de Frias et al. 2005), and reaction time (Stefanis et al. 2005). These results emerge across a wide range of the adult lifespan (de Frias et al. 2004, 2005; Dijkstra and Kaup 2005; Erickson et al. 2008; Nagel et al. 2008; Raz et al. 2009). Taken together, the studies to date suggest that expression of methionine at position 158 in *COMT* may confer an advantage to “effortful” processes, i.e., those under deliberate executive control.

The above results are based on computer-based or paper and pencil neuropsychological tests. Do these results extend to real-world tasks? To date, only one study has attempted to address this question. The relationship between *COMT* val158met status and gait performance, a task associated with attention and executive control processes, was studied in a sample of older adults. Among men, *met/met* carriers had significantly faster gait velocity (Holtzer et al. 2008). In the current study, we examine another real-world task, aircraft navigation in a flight simulator. Aircraft navigation places heavy demands on several cognitive abilities, notably executive function, processing speed, and working memory (Taylor et al. 2005). Thus, flight simulator performance provides an ideal way to determine whether *COMT* val158met status affects performance on a real world task.

Research also suggests that environmental factors may interact with the effects of *COMT val158met* status. In a sample of Plains American Indians, a *COMT* by education interaction was found on performance on the Information, Block Design, Similarities, and Digit Span subtests of Wechsler Adult Intelligence Scale-Revised (WAIS-R), tests that tap attention, crystallized knowledge, long-term and working memory, processing speed, and verbal comprehension (Enoch et al. 2009). Participants with at least one *met* allele benefited the most from additional years of education. For example, block design performance among *val/val* carriers improved very modestly with increased years of education. However, among those with at least one *met* allele, block design performance improved dramatically with additional years of education. Those *met* carriers with the least years of education performed the worst (i.e. lower than *val/val* carriers), whereas *met* carriers with the most years of education outperformed *val* carriers. Previous work indicates that a *COMT val158met* effect on cognitive performance increases as attentional demands increase (Blasi et al. 2005). Enoch et al. speculate that among those with few years of education, the cognitive tests required high levels of attentional demand, and consequently these participants were more influenced by *COMT val158met* status. Thus, as years of education increase, and presumably, training in performing paper and pencil type cognitive tasks increases, attentional demands of these tasks decrease. This reduction of attentional demand with additional years of education appears to be of greater benefit for *met* carriers.

We also sought to determine if there were environmental factors that may interact with *COMT val158met* status on flight simulator performance. One likely environmental factor is expertise, defined as the acquisition of specialized knowledge and perceptual motor skills through years of ‘deliberate practice’ (Ericsson et al. 1993). In aviation, Federal Aviation Administration (FAA) ratings provide a measure of flight expertise consistent with this definition, as higher ratings require additional hours of formal flight training and to advance skills beyond the basic level of a private pilot license. Thus, whereas education can be used as a measure of general cognitive training, FAA ratings provide measures of specialized skills training. Increased levels of flight expertise are consistently associated with better flight performance and decreased attentional demands of aircraft navigation (Bellenkes et al. 1997; Schriver et al. 2008). Attentional demands are greatest at the most basic levels of flight expertise (and the least amount of required deliberate practice) (Bellenkes et al. 1997; Schriver et al. 2008). Thus, like the results from the Enoch et al. (2009) study, it may be that *COMT val158met* status interacts with flight expertise, such that *COMT* influence on flight performance is greater among pilots with the lowest level of flight experience. Buttressing this idea is that interactions between flight expertise and age, apolipoprotein-ε4 status, and brain size on flight simulator performance have been found (Adamson et al. 2010; Kennedy et al. 2010; Taylor et al. in press; Taylor et al. 2007). These factors are associated with many of the same cognitive abilities as *COMT*, such as executive function (Greenwood 2007; Wolk and Dickerson 2010), working memory (Parasuraman et al. 2002), processing speed (Salthouse 1996; Schaie 1989; Sullivan et al. 2010), and episodic recall memory (Greenwood 2007; Luszcz et al. 1997; Raz et al. 2005).

We assessed flight simulator performance among a group of aviators varying in FAA ratings and *COMT val158met* status to investigate a possible genetic by environment interaction on a real-world task. Our goal in this study was to first attempt to replicate previous findings regarding *COMT* and neuropsychological measures among a group of participants with specialized training and second, to extend these findings to a real-world application. Specifically, we investigated whether a genetic by environment interaction is found between *COMT val158met* status and flight expertise on flight simulator performance among a sample of 172 general aviators. We made two predictions:

1. Increased number of *met* alleles will be associated with better performance on neuropsychological and flight simulator performance tasks.
2. A *COMT* by expertise interaction will be found such that those with *met/met* will benefit from increased expertise on flight performance measures more so than those with *val/val*.

Methods

Research participants

This paper reports findings on 172 pilots who had a known *COMT val158met* genotype and who were part of the ongoing longitudinal Stanford/VA Aviation Study approved by the Stanford University Institutional Review Board. Enrollment criteria were age between 40 and 69 years, current FAA medical certificate (Class III or higher) which entails an assessment of pilots' vision, hearing, and physical and mental health, and current flying activity between 300 and 15,000 h of total flight time. All participants gave written informed consent to participate in the study, with the right to withdraw at any time. At entry, each participant was classified into one of three levels of aviation expertise depending on which FAA pilot proficiency ratings had been attained by study entry: (1) least expertise: VFR (rated for flying under visual flight rules only); (2) moderate expertise: IFR (also rated for instrument flight); and (3) most expertise: CFII and/or ATP (certified flight instructor of IFR students or rated for flying air-transport planes). As reported in Taylor et al. (2007), all of the VFR pilots were recreational pilots, although a small minority were employed in aviation-related jobs such as aircraft sales or mechanics. Within the IFR group, the majority were recreational pilots, whereas approximately one-tenth were certified flight instructors, aviation analysts, or aviators during military service. Approximately one-half of the CFII/ATP participants were either air-transport pilots, CFIIs, or their job duties included aircraft piloting. Of the 249 participants who completed a test day by January 2008, 172 pilots had a known *COMT val158met* genotype. Table 1 lists demographic and flight experience characteristics of the sample.

Equipment

Pilots "flew" in a Frasca 141 flight simulator (Urbana, IL). Motion, vibration, and sound elements were not incorporated into this simulator protocol. The simulator was linked to a computer specialized for graphics (Dell Precision Workstation and custom C++ OpenGL Linux software) that generated a "through-the-window" visual environment and continuously collected data concerning the aircraft's position and communication frequencies. The simulator is located in a quiet, darkened room kept at a comfortable temperature with the cockpit independently lit from the projector display. The display is projected on a screen 15' in front of the pilot. The simulation occurred during normal working hours from 0900 to 1600 at the pilot's preference. Previous work in our lab indicates that the flight simulator has validity as it distinguishes performance between novice and expert aviators, and between younger and older aviators (Taylor et al. 2007; Taylor et al. 2005).

Measures

Flight simulator performance—The scoring system of the flight simulator-computer system produces 23 variables that measure deviations from ideal positions or assigned values (e.g., altitude in feet, heading in degrees, airspeed in knots), or reaction time in seconds (Yesavage et al. 1999). Because these individual variables have different units of measurement, the raw scores for each variable were converted to *z*-scores, using the baseline

visit mean and SD of 141 participants enrolled during 1996–2001 (scores on the morning and afternoon flights were averaged).

The *z*-scores on the individual measures were aggregated on the basis of previous principal component analyses into four component measures (Yesavage et al. 1999; Yesavage et al. 2002): (1) accuracy of executing the air traffic control (ATC) communications regarding the heading, altitude, radio frequency, and transponder code; (2) traffic avoidance; (3) scanning cockpit instruments to detect engine emergencies; (4) executing a visual approach to landing. A flight summary score, the average of the above four component measures, was used as the primary performance measure. Thus, one global and four component measures of flight performance were assessed.

Neuropsychological battery—Three aspects of cognitive ability were assessed: executive function, speed of processing, and working memory.

Executive function—The Discovery subtest of the Shifting Attention Test (Cogscreen-AE, (Kay 1995)) was used to measure cognitive flexibility, (ability to shift to a new rule), and the ability to maintain the set. As in the Wisconsin Card Sorting Test, participants use trial and error to discover which of multiple stimulus dimensions (such as object color) is currently relevant and then use that dimension as the sorting rule until feedback indicates it is no longer relevant (see Taylor et al. 2005) for additional information). Three types of performance were measured: (1) number of completed rule sets, (2) number of failures to maintain set, and (3) the percentage of correct responses. These three performance measures were standardized and averaged into a composite measure of executive function.

Speed of processing—Speed of processing was measured by a composite variable comprised of Pattern Comparison and Digit Copying (Salthouse 1992). In the Pattern Comparison task, participants make same-different decisions about pairs of patterns made of connected line segments. In the Digit Copying task, participants copy digits as rapidly as possible. For each task, participants complete two 30-s trials, and the number of correct responses was scored. Scores from the four trials were standardized and then averaged together to create a composite measure of processing speed (see Taylor et al. 2005).

Working memory—Working memory was assessed by a composite of two subtests of the Dual Task in Cogscreen-AE (Kay 1995), Dual Task Previous Number Alone Accuracy and Dual Task Previous Number Dual Accuracy. In Dual Task Previous Number Alone Accuracy, the subject attempts to recall the previous number shown while simultaneously encoding the current number for the next stimulus presentation. In Dual Task Previous Number Dual Accuracy, participants have the additional task of actively tracking the cursor on the computer screen. Scores from each subtest were standardized, then averaged together to create a composite measure of working memory.

Genotyping—DNA was extracted either from samples of frozen whole blood (see (Murphy et al. 1997) for description of this method) or from saliva samples collected using Oragene DNA kits (DNA Genotek, Ontario Canada; DNA extracted according to manufacturer's instructions). DNA was genotyped using the Human 610-Quad BeadChip (Illumina, San Diego CA) on an Illumina Beadstation using the manufacturer-provided procedures. The COMT val158met polymorphism can be directly detected using this chip. Call rates greater than 99% were achieved on all subjects at this polymorphic site. All staff who collected performance measures were blind to the genotypes.

Procedures

Participants had one 45 min practice flight in the simulator to experience the simulator's flight and landing characteristics. Additionally, participants completed five 75 min practice flights to gain familiarity with the flight scenario used throughout the study. Participants typically completed two practice flights a day during a one to 3-week period, after which they had a 3-week break before returning for the test day. During the test day, the participant flew a 75-min flight in the morning and a 75-min flight in the afternoon. Each flight was followed by a 40- to 60-min battery of cognitive tests, including CogScreen-AE (Kay 1995), a computer-administered battery of 13 tests designed to assess perceptual and cognitive abilities relevant to aircraft piloting. The entire test day lasted approximately 6 h, including a 30- to 50-min lunch break. Each flight began with the air-traffic controller's (ATC) takeoff clearance. The first ATC message was presented 3 min later, after participants had lifted off the runway and climbed to 1200 ft (365.76 m). During the flight, pilots heard 16 ATC messages, presented at the rate of one message every 3 min, directing the pilot to fly a new heading, a new altitude, dial in a new radio frequency, and in 50% of the legs, dial in a new transponder code. Participants were instructed to read back the ATC messages and execute them in order and according to FAA standards. To further increase workload, pilots were confronted with randomly presented emergency situations: engine malfunctions (carburetor icing, drop of engine oil pressure) (8 of 16 legs), and/or suddenly approaching air traffic (10 of 16 legs). Pilots were to report engine malfunctions immediately and to avoid air traffic by veering quickly yet safely in the direction diagonal to the path of the oncoming plane. Pilots flew in severe turbulence throughout the flight, and also encountered a 15-knot crosswind during approach and landing. Multiple versions of this flight scenario were presented to reduce learning of specific maneuvers and ATC messages.

Statistical analyses

For all analyses, the predictor variables were *COMT val158met* status, expertise, and *COMT val158met* genotype by expertise interaction. *COMT* genotype and expertise were coded as ordinal variables (*met/met* = 1; *met/val* = 0; *val/val* = -1; *VFR* = -1, *IFR/CFI* = 0, *CFII/ATP* = 1). The *COMT val158met* genotype by expertise interaction was calculated by multiplying the coded level of *COMT* status to the coded level of expertise for each subject. Previous work indicates that age is significantly associated with all measures of flight performance (Taylor et al. 2007; Taylor et al. 2005). Therefore, we included a measure of age (centered at median age of 57.0 years) to the model to assess the effects of *COMT val158met* status and expertise, after controlling for the effects of age. Because of extreme data points, defined as *z*-scores beyond two standard deviations of the mean, all dependent variables were ranked such that the worst score was ranked "1", the second worst score, "2," and so on; these ranked scores were used in the model.¹ PROC GLM in SAS (SAS Institute, Cary, NC) was utilized.

Results

Demographics

Table 1 lists demographic and flight experience information by *COMT val158met* allele status. No significant differences were found between *COMT* groups for any demographic or flight experience variable. The distribution of *COMT val158met* genotypes is consistent with our predominantly Caucasian population (National Center for Biotechnology Information 2010).

¹A similar pattern of results was found when the GLM was conducted with unranked dependent variables and when stepwise regression was conducted with ranked variables.

Cognitive performance

As expected, significant negative age effects were seen for all three cognitive measures (all p 's < 0.02). After controlling for the effects of age, a significant advantage was detected in executive function such that each additional *met* allele improved pilots' performance ($p = 0.017$, Effect Size (ES) = 0.19) and working memory ($p = 0.04$, ES = 0.16). No significant *COMT val158met* effects were found for speed of processing. We also note that increased levels of expertise were associated with significantly better performance on working memory ($p = 0.006$, ES = 0.21).

Flight performance

As expected from previous research, significant age and expertise effects were seen in almost all flight performance measures (all age p 's < 0.002; all expertise (except for emergencies) p 's < 0.05).

There was a nonsignificant trend for *COMT val158met* status to predict flight summary performance ($p = 0.10$, ES = 0.12). After taking into account the effect of age, a significant *COMT val158met* status by expertise interaction was found for traffic avoidance ($p = 0.026$, ES = 0.17). As shown in Fig. 1, pilots homozygous for 158*met* benefited from increased expertise on this task, whereas the other groups did not. There was a nonsignificant trend on emergencies ($p = 0.057$, ES = 0.15), in which for each additional 158*met* allele, pilots' emergency performance improved. No other significant *COMT val158met* effects were found for the flight performance. Table 2 provides results of each flight performance and cognitive variable by *COMT val158met* status by expertise level group score.

Discussion

Consistent with other studies, a significant advantage was detected in the cognitive ability measures of executive function and working memory, after controlling for the effects of age, for carriers of the *met* allele (Nagel et al. 2008; de Frias et al. 2005). These results extend previous work in that this sample is comprised of very high functioning middle-aged and older adults who have specialized training.

No significant main effects of *COMT val158met* status on flight simulator performance were detected. We did, however, find some support for one environmental influence, flight expertise, on *COMT val158met* status. Aviators with the *COMT met158met* genotype benefited from increased levels of expertise on a traffic avoidance task, whereas the other groups did not. Other researchers have suggested that people carrying the *met* allele will perform better at sustained attention tasks, whereas those carrying the *val* allele will perform better on more cognitively flexible tasks (Colzato et al. 2010; de Frias et al. 2010; Dickinson and Elvevag 2009; Houlihan et al. 2009). Our results provide some support for this idea on a real world task. Traffic avoidance requires flexibly allocating attention between scanning cockpit instruments and looking out the window. The results suggest that without highly specialized training, *met/met* carriers perform worse on real-world tasks requiring cognitive flexibility than *val/val* carriers. We conjecture that the accrual of specialized training enables those with *met/met* to overcome a possible tendency to fixate their attention on one task when the overall task, such as flying, requires flexible distribution of attention to multiple flight tasks. Future studies that incorporate eye-tracking could help determine if less experienced, *met/met* pilots are more likely than the other pilots to fixate their attention on only a subset of the relevant navigation information.

Main effects of *COMT* genotype status on flight simulator performance may have been elusive because they are more likely to occur at the neurological rather than behavioral level (de Frias et al. 2010; Dennis et al.; Dickinson and Elvevag 2009; Mier et al. 2009; Tan et al.

2007). That is, COMT influences level of dopaminergic activity which in turn, impacts performance on tasks requiring sustained or flexible cognitive ability (Robbins and Arnsten 2009). There are essentially two types of dopaminergic activations. The *met* allele is associated with relatively high levels of tonic dopaminergic activation, which has a consistent and slow firing pattern and is positively associated with sustained cognitive tasks. In contrast, the *val* allele is characterized by phasic dopaminergic activation, which occurs in strong bursts and is useful for updating pertinent novel information (de Frias et al. 2010). In a study with a sample quite similar to ours (all men, ranging in age from 50 to 65 years) (de Frias et al. 2010), no behavioral differences were found by *COMT val158met* status. However, *COMT* differences emerged at the level of brain activation required to do both sustained and cognitively flexible tasks. Specifically, *met* carriers had greater transient activation in the medial temporal lobe during a task which required updating of working memory. This result indicates the *met* carriers were less neurologically efficient than their *val* counterparts on a task requiring cognitive flexibility. The reverse pattern was found for *val* carriers, who had greater sustained activation in the prefrontal cortex (PFC) during a task in which they had to hold information in working memory. Among a sample of healthy young adults, *met* carriers were less efficient at task switching than *val/val* carriers (Colzato et al. 2010). Similarly, Dennis et al. (2010) found no *COMT val158met* differences on 19 behavioral measures in a large sample of healthy adults aged 18–84, but did find that *val* carriers had greater PFC activation during a memory encoding and retrieval task. These studies suggest a complex relationship between *COMT val158met* status, neurological activity, and behavior. It may be that factors such as age and experience help determine the circumstances in which *COMT val158met* differences emerge at the behavioral level.

Alternatively, our sample size may have been too small to detect *COMT val158met* effects due to narrow ranges of education and specialized training (Barnett et al. 2007). For example, there were trends for *COMT val158met* to predict overall flight performance and emergency performance that may have become significant with a larger sample. With a sample size of 172, we had the power to detect effect sizes of 0.16 or greater. We were able to replicate previous research showing *COMT val158met* effects on measures of executive function and working memory.

The main implication of the results is that on real world tasks requiring cognitive flexibility, *met* carriers may need additional training than *val* carriers before reaching optimal levels of performance. In the Enoch et al. (2009) study, a *COMT* × education effect was found on a broad array of cognitive abilities in a group living in a socioeconomically disadvantaged environment. Among our highly educated and specially trained participants, a genetic × environment interaction only occurred for a task requiring cognitive flexibility. This difference points to a need to more thoroughly address how demographic/environmental characteristics of the sample may influence the genetic effects on cognitive tasks.

Additionally, the *COMT* × expertise effect on aviation traffic avoidance has direct implications for driving. Driving is another complex activity that requires both sustained (steering and speed control in no or little traffic) and flexible (merging into traffic, lane changes, reacting to other drivers) cognition. Future research could investigate whether new drivers who are *met* carriers are at greater risk of traffic incidents and accidents due to problems with the cognitively flexible aspects of driving. If so, they may benefit from deliberate practice on these aspects of driving.

In summary, even in a sample with high levels of education and specialized training, an advantage on neuropsychological assessments of executive function and working memory were observed for those with the *COMT met* allele. Although main effects of *COMT val158met* status on flight simulator performance were not detected, a *COMT* by expertise

interaction on traffic avoidance suggests that *met/met* carriers benefit from increased experience on real world tasks requiring cognitive flexibility. Results indicate that examining genetic effects in real world tasks, such as aircraft navigation, can contribute to our understanding of the interplay between genes, environment, and cognition.

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References

- Adamson MM, Samarina V, Xiangyan X, Huynh V, Kennedy Q, Weiner M, Yesavage J, Taylor JL. The impact of brain size on pilot performance varies with aviation training and years of education. *J Int Neuropsychol Soc.* 2010; 16(3):412–423. doi:[10.1017/S1355617710000111](https://doi.org/10.1017/S1355617710000111). [PubMed: 20193103]
- Backman L, Nyberg L, Lindenberger 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]
- Barnett JH, Jones PB, Robbins TW, Muller U. Effects of the catechol-*O*-methyltransferase Val¹⁵⁸Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Mol Psychiatry.* 2007; 12(5):502–509. doi:[10.1038/sj.mp.4001973](https://doi.org/10.1038/sj.mp.4001973). [PubMed: 17325717]
- Bellenkes AH, Wickens CD, Kramer AF. Visual scanning and pilot expertise: the role of attentional flexibility and mental model development. *Aviat Space Environ Med.* 1997; 68(7):569–579. [PubMed: 9215461]
- Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, Goldman RS, Hoptman MJ, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Kunz M, Chakos M, Cooper TB, Lieberman JA. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biol Psychiatry.* 2002; 52(7):701–707. [PubMed: 12372660]
- Blasi G, Mattay VS, Bertolino A, Elvevag B, Callicott JH, Das S, Kolachana BS, Egan MF, Goldberg TE, Weinberger DR. Effect of catechol-*O*-methyltransferase val158met genotype on attentional control. *J Neurosci.* 2005; 25(20):5038–5045. doi:[10.1523/JNEUROSCI.0476-05.2005](https://doi.org/10.1523/JNEUROSCI.0476-05.2005). [PubMed: 15901785]
- Bruder GE, Keilp JG, Xu H, Shikhman M, Schori E, Gorman JM, Gilliam TC. Catechol-*O*-methyltransferase (COMT) genotypes and working memory: associations with differing cognitive operations. *Biol Psychiatry.* 2005; 58(11):901–907. [PubMed: 16043133]
- Colzato LS, Waszak F, Nieuwenhuis S, Posthuma D, Hommel B. The flexible mind is associated with the catechol-*O*-methyltransferase (COMT) Val158Met polymorphism: evidence for a role of dopamine in the control of task-switching. *Neuropsychologia.* 2010; 48(9):2764–2768. doi:[10.1016/j.neuropsychologia.2010.04.023](https://doi.org/10.1016/j.neuropsychologia.2010.04.023). [PubMed: 20434465]
- de Frias CM, Annerbrink K, Westburg L, Eriksson E, Adolfsson R, Nilsson L. COMT gene polymorphism is associated with declarative memory in adulthood and old age. *Behav Genet.* 2004; 34(5):533–539. [PubMed: 15319576]
- de Frias CM, Annerbrink K, Westburg L, Eriksson E, Adolfsson R, Nilsson L. Catechol *O*-Methyltransferase Val¹⁵⁸Met Polymorphism is associated with cognitive performance in nondemented adults. *J Cogn Neurosci.* 2005; 17(7):1018–1025. [PubMed: 16102234]
- de Frias CM, Marklund P, Eriksson E, Larsson A, Oman L, Annerbrink K, Backman L, Nilsson L, Nyberg L. Influence of COMT gene polymorphism on fMRI-assessed sustained and transient

- activity during a working memory task. *J Cogn Neurosci*. 2010; 22(7):1614–1622. doi:[10.1162/jocn.2009.21318](https://doi.org/10.1162/jocn.2009.21318). [PubMed: 19642882]
- Dennis NA, Need AC, LaBar KS, Waters-Metenier S, Cirulli ET, Kragel J, Goldstein DB, Cabeza R. COMT val108/158 met genotype affects neural but not cognitive processing in healthy individuals. *Cereb Cortex*. 2010; 20(3):672–683. doi:[10.1093/cercor/bhp132](https://doi.org/10.1093/cercor/bhp132). [PubMed: 19641018]
- Dickinson D, Elvevag B. Genes, cognition and brain through a COMT lens. *Neuroscience*. 2009; 164(1):72–87. doi:[10.1016/j.neuroscience.2009.05.014](https://doi.org/10.1016/j.neuroscience.2009.05.014). [PubMed: 19446012]
- Dijkstra K, Kaup B. Mechanisms of autobiographical memory retrieval in younger and older adults. *Mem Cognit*. 2005; 33(5):811–820.
- Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2001; 98(12):6917–6922. [PubMed: 11381111]
- Enoch MA, Waheed JF, Harris CR, Albaugh B, Goldman D. COMT Val158Met and cognition: main effects and interaction with educational attainment. *Genes Brain Behav*. 2009; 8(1):36–42. doi:[10.1111/j.1601-183X.2008.00441.x](https://doi.org/10.1111/j.1601-183X.2008.00441.x). [PubMed: 19076243]
- Erickson KI, Kim JS, Suever BL, Voss MW, Francis BM, Kramer AF. Genetic contributions to age-related decline in executive function: a 10-year longitudinal study of COMT and BDNF polymorphisms. *Front Hum Neurosci*. 2008; 2:11. doi:[10.3389/neuro.09.011.2008](https://doi.org/10.3389/neuro.09.011.2008). [PubMed: 18958211]
- Ericsson KA, Krampe RT, Tesch-Romer C. The role of deliberate practice in the acquisition of expert performance. *Psychol Review*. 1993; 100(3):363–406.
- Goldberg TE, Weinberger DR. Genes and the parsing of cognitive processes. *Trends Cogn Sci*. 2004; 8(7):325–335. [PubMed: 15242692]
- 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(9):889–896. [PubMed: 12963670]
- Greenwood PM. Functional plasticity in cognitive aging: review and hypothesis. *Neuropsychology*. 2007; 21(6):657–673. doi:[10.1037/0894-4105.21.6.657](https://doi.org/10.1037/0894-4105.21.6.657). [PubMed: 17983277]
- Holtzer R, Ozelius L, Xue X, Wang T, Lipton RB, Verghese J. Differential effects of COMT on gait and executive control in aging. *Neurobiol Aging*. 2008; 31(3):523–531. doi:[10.1016/j.neurobiolaging.2008.05.011](https://doi.org/10.1016/j.neurobiolaging.2008.05.011). [PubMed: 18547681]
- Houlihan LM, Harris SE, Luciano M, Gow AJ, Starr JM, Visscher PM, Deary IJ. Replication study of candidate genes for cognitive abilities: the Lothian Birth Cohort 1936. *Genes Brain Behav*. 2009; 8(2):238–247. doi:[10.1111/j.1601-183X.2008.00470.x](https://doi.org/10.1111/j.1601-183X.2008.00470.x). [PubMed: 19077115]
- 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(7):662–663. [PubMed: 12090821]
- Kay, GG. CogScreen Aeromedical edition professional manual. Odessa, FL: Psychological Assessment Resources; 1995.
- Kennedy Q, Taylor JL, Reade G, Yesavage JA. Age and expertise effects in aviation decision making and flight control in a flight simulator. *Aviat Space Environ Med*. 2010; 81(5):489–497. doi:[10.3357/ASEM.2684.2010](https://doi.org/10.3357/ASEM.2684.2010). [PubMed: 20464816]
- Luszcz MA, Bryan J, Kent P. Predicting episodic memory performance of very old men and women: contributions from age, depression, activity, cognitive ability, and speed. *Psychol Aging*. 1997; 12(2):340–351. [PubMed: 9189994]
- 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(4):652–654. [PubMed: 11925305]
- Mier D, Kirsch P, Meyer-Lindenberg A. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Mol Psychiatry*. 2009 doi:[10.1038/mp.2009.36](https://doi.org/10.1038/mp.2009.36).

- Murphy GM Jr, Taylor J, Kraemer HC, Yesavage J, Tinklenberg JR. No association between apolipoprotein E epsilon 4 allele and rate of decline in Alzheimer's disease. *Am J Psychiatry*. 1997; 154(5):603–608. [PubMed: 9137113]
- Nagel IE, Chicherio C, Li SC, von Oertzen T, Sander T, Villringer A, Heekeren HR, Backman L, Lindenberger U. Human aging magnifies genetic effects on executive functioning and working memory. *Front Hum Neurosci*. 2008; 2:1. doi:[10.3389/neuro.09.001.2008](https://doi.org/10.3389/neuro.09.001.2008). [PubMed: 18958202]
- National Center for Biotechnology Information N. [Accessed 29 March 2010] Single Nucleotide Polymorphism. 2010. http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=4680
- Parasuraman R, Greenwood PM, Sunderland T. The apolipoprotein E gene, attention, and brain function. *Neuropsychology*. 2002; 16(2):254–274. doi:[10.1037/0894-4105.16.2.254](https://doi.org/10.1037/0894-4105.16.2.254). [PubMed: 11949718]
- Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex*. 2005; 15(11):1676–1689. doi:[10.1093/cercor/bhi044](https://doi.org/10.1093/cercor/bhi044). [PubMed: 15703252]
- Raz N, Rodrigue KM, Kennedy KM, Land S. Genetic and vascular modifiers of age-sensitive cognitive skills: effects of COMT, BDNF, ApoE, and hypertension. *Neuropsychology*. 2009; 23(1):105–116. doi:[10.1037/a0013487](https://doi.org/10.1037/a0013487). [PubMed: 19210038]
- Robbins TW, Arnsten AF. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annu Rev Neurosci*. 2009; 32:267–287. doi:[10.1146/annurev.neuro.051508.135535](https://doi.org/10.1146/annurev.neuro.051508.135535). [PubMed: 19555290]
- Salhouse, T. Mechanisms of age-cognition relations in adulthood. Hillsdale, NJ: Lawrence Erlbaum Associates; 1992.
- Salhouse TA. The processing-speed theory of adult age differences in cognition. *Psychol Rev*. 1996; 103(3):403–428. [PubMed: 8759042]
- Schaie KW. Perceptual speed in adulthood: cross-sectional and longitudinal studies. *Psychol Aging*. 1989; 4(4):443–453. [PubMed: 2619951]
- Schriner AT, Morrow DG, Wickens CD, Talleur DA. Expertise differences in attentional strategies related to pilot decision making. *Hum Factors*. 2008; 50(6):864–878. [PubMed: 19292010]
- Starr JM, Fox H, Harris SE, Deary IJ, Whalley LJ. COMT genotype and cognitive ability: a longitudinal aging study. *Neurosci Lett*. 2007; 421(1):57–6. doi:[10.1016/j.neulet.2007.05.023](https://doi.org/10.1016/j.neulet.2007.05.023). [PubMed: 17548151]
- Stefanis NC, van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Stefanis CN. Effect of COMT Val158Met polymorphism on the Continuous Performance Test, Identical Pairs Version: tuning rather than improving performance. *Am J Psychiatry*. 2005; 162(9):1752–1754. [PubMed: 16135641]
- Sullivan EV, Rohlfing T, Pfefferbaum A. Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: relations to timed performance. *Neurobiol Aging*. 2010; 31(3):464–481. doi:[10.1016/j.neurobiolaging.2008.04.007](https://doi.org/10.1016/j.neurobiolaging.2008.04.007). [PubMed: 18495300]
- Tan HY, Chen Q, Sust S, Buckholtz JW, Meyers JD, Egan MF, Mattay VS, Meyer-Lindenberg A, Weinberger DR, Callicott JH. Epistasis between catechol-O-methyltransferase and type II metabotropic glutamate receptor 3 genes on working memory brain function. *Proc Natl Acad Sci U S A*. 2007; 104(30):12536–12541. [PubMed: 17636131]
- Taylor JL, O'Hara R, Mumenthaler MS, Rosen AC, Yesavage JA. Cognitive ability, expertise, and age differences in following air-traffic control instructions. *Psychol Aging*. 2005; 20(1):117–133. [PubMed: 15769218]
- Taylor JL, Kennedy Q, Noda A, Yesavage JA. Pilot age and expertise predict flight simulator performance: a 3-year longitudinal study. *Neurology*. 2007; 68(9):648–654. [PubMed: 17325270]
- Taylor J, Kennedy Q, Adamson MM, Lazzeroni LC, Noda A, Murphy GM, Yesavage J. Influences of APOE e4 and expertise on performance of older pilots. *Psychol Aging*. (in press).
- Wolk DA, Dickerson BC. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2010; 107(22):10256–10261. doi:[10.1073/pnas.1001412107](https://doi.org/10.1073/pnas.1001412107). [PubMed: 20479234]

- Yesavage JA, Taylor JL, Mumenthaler MS, Noda A, O'Hara R. Relationship of age and simulated flight performance. *J Am Geriatr Soc.* 1999; 47(7):819–823. [PubMed: 10404925]
- Yesavage JA, Mumenthaler MS, Taylor JL, Friedman L, O'Hara R, Sheikh J, Tinklenberg J, Whitehouse PJ. Donepezil and flight simulator performance: Effects on retention of complex skills. *Neurology.* 2002; 59(1):123–125. [PubMed: 12105320]

Fig. 1.
Met/met pilots benefit from increased expertise on a traffic avoidance measure

Table 1Participants' demographic and flight experience characteristics by *COMT* *val158met* status

	met/met <i>n</i> = 41	met/val <i>n</i> = 83	val/val <i>n</i> = 48
Age, mean (SD), years	57.0 (6.8)	57.0 (6.9)	56.5 (6.1)
(range, years)	(41–69)	(43–68)	(43–69)
Education, mean (SD), years	17.4 (1.8)	16.8 (1.9)	16.8 (1.8)
Women, <i>n</i> (%)	5 (12.2)	14 (16.9)	7 (14.6)
White, non-Hispanic, %	98	96	92
Aviation expertise rating, %: VFR/IFR/CFII-ATP	17/54/29	27/55/18	29/48/23
Log hours, mean (SD)	2565 (2826)	2080 (2095)	2571 (3192)
Log hours in past month, mean (SD)	10.0 (13.2)	7.9 (9.9)	10.7 (13.2)
Medical Class I, II, or III, %	14/32/54	8/34/58	2/42/56
Medical waivers, %	2.5	8.4	6.3
Cholesterol-lowering medications, %	14.6	13.3	20.8
Anti-hypertensive medications, %	14.6	19.3	18.8
Self-rated health "excellent/good/fair," %	63/34/3	55/45/0	63/37/0
Family history of dementia, %: "yes/no/not sure"	12/88/0	18/74/8	19/79/2

Note: Sample size for medical waivers is 161 and for self reported health rating, 171

Table 2Means (SD) (z-scores) of flight and cognitive variables by *COMT* *val158met* status by expertise level

	met/met		met/val			val/val			
	VFR (n = 7)	IFR (n = 22)	CFII/ATP (n = 12)	VFR (n = 22)	IFR (n = 46)	CFII/ATP (n = 15)	VFR (n = 14)	IFR (n = 23)	CFII/ATP (n = 11)
Flight variables									
Summary score	-0.27 (0.50)	0.30 (0.56)	0.35 (0.43)	-0.10 (0.55)	0.03 (0.49)	0.41 (0.38)	-0.05 (0.58)	-0.04 (0.43)	0.27 (0.48)
Communications	-0.48 (0.51)	0.35 (0.75)	0.37 (0.66)	-0.18 (0.77)	-0.13 (0.64)	0.41 (0.80)	-0.12 (0.87)	-0.13 (0.61)	0.50 (0.57)
Avoidance	-0.51 (0.91)	0.36 (0.53)	0.64 (0.62)	0.13 (0.57)	0.15 (0.65)	0.63 (0.51)	0.24 (0.75)	0.05 (0.46)	0.27 (0.60)
Emergency	-0.15 (1.37)	0.33 (0.88)	0.21 (0.67)	-0.31(1.23)	0.13 (0.78)	0.35 (0.59)	-0.23 (0.96)	-0.07(0.85)	0.12 (1.01)
Approach	0.05 (0.31)	0.18 (0.58)	0.20 (0.56)	-0.02 (0.48)	-0.02 (0.71)	0.24 (0.52)	-0.10 (0.68)	-0.02 (0.65)	0.19 (0.59)
Cognitive variables									
Executive function	0.48 (0.60)	0.33 (0.78)	-0.12 (1.08)	0.22 (0.71)	-0.11 (0.96)	0.42 (0.66)	-0.23 (1.03)	-0.31 (0.92)	0.22 (0.46)
Processing speed	-0.39 (0.82)	0.36 (0.95)	-0.20 (0.86)	0.13 (0.68)	-0.12 (0.95)	0.02 (1.03)	0.40(0.72)	-0.38 (0.63)	-0.21 (0.84)
Working memory	-0.30 (1.45)	0.21 (0.69)	0.61 (0.45)	-0.17 (0.79)	-0.06 (0.98)	0.23 (0.70)	-0.01 (0.88)	-0.18 (0.81)	0.21 (0.77)

Note: 159 participants completed the executive function measure and 170 completed the working memory measure. No significant differences in age were found in relation to the main effect of *COMT* *val158met* status or *COMT* × Expertise interaction. Thus, values are mean z-scores of each group and are not adjusted for age