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# *COMT Val*$^{158}$*Met* polymorphism is associated with nonverbal cognition following mild traumatic brain injury

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## Abstract

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Ethan A. Winkler and John K. Yue contributed equally to this work.

**Compliance with ethical standards**

**Conflicts of interest** The authors declare that they have no conflicts of interest.

**Research involving human participants** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Mild traumatic brain injury (mTBI) results in variable clinical outcomes, which may be influenced by genetic variation. A single-nucleotide polymorphism in catechol-o-methyltransferase (*COMT*), an enzyme which degrades catecholamine neurotransmitters, may influence cognitive deficits following moderate and/or severe head trauma. However, this has been disputed, and its role in mTBI has not been studied. Here, we utilize the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) study to investigate whether the *COMT* $Val^{158}Met$ polymorphism influences outcome on a cognitive battery 6 months following mTBI—Wechsler Adult Intelligence Test Processing Speed Index Composite Score (WAIS-PSI), Trail Making Test (TMT) Trail B minus Trail A time, and California Verbal Learning Test, Second Edition Trial 1–5 Standard Score (CVLT-II). All patients had an emergency department Glasgow Coma Scale (GCS) of 13–15, no acute intracranial pathology on head CT, and no polytrauma as defined by an Abbreviated Injury Scale (AIS) score of ≥3 in any extracranial region. Results in 100 subjects aged 40.9 (SD 15.2) years ($COMT\ Met^{158}/Met^{158}$ 29 %, $Met^{158}/Val^{158}$ 47 %, $Val^{158}/Val^{158}$ 24 %) show that the $COMT\ Met^{158}$ allele (mean 101.6±SE 2.1) associates with higher nonverbal processing speed on the WAIS-PSI when compared to $Val^{158}/Val^{158}$ homozygotes (93.8±SE 3.0) after controlling for demographics and injury severity (mean increase 7.9 points, 95 % CI [1.4 to 14.3], $p$=0.017). The $COMT\ Val^{158}Met$ polymorphism did not associate with mental flexibility on the TMT or with verbal learning on the CVLT-II. Hence, $COMT\ Val^{158}Met$ may preferentially modulate nonverbal cognition following uncomplicated mTBI.

**Keywords**

Traumatic brain injury; Genetic factors; Cognitive function; Outcome measures; Human studies

## Introduction

Traumatic brain injury (TBI)—defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force—is a comparatively common insult with variable outcomes [1, 2]. In the USA alone, at least 2.5 million people suffer TBIs annually [3], and it has been estimated that up to 5.3 million people are currently living with TBI-related disability [4]. TBI is frequently subdivided on the basis of injury severity into severe, moderate, and mild injury categories as defined by a Glasgow Coma Scale (GCS) score of 8 or less, 9-to-12, or 13-to-15, respectively [5, 6]. Although more severe injuries may disproportionately contribute to disability, the vast majority—70 to 90 %—of all TBI is characterized as “mild TBI” (mTBI) [7]. Within mTBI, considerable variability in outcome exists across individuals. Most make a complete recovery following mTBI [8, 9]; however, up to 20 % of patients experience persistent symptoms and/or cognitive or neuropsychiatric deficits [10]. Individuals with nearly identical injuries often manifest different symptoms, follow different clinical trajectories, and/or have varied functional outcomes [11]. Efforts are therefore needed to better identify those at greatest risk for posttraumatic sequela to better prognosticate and facilitate development of tailored therapy [1].

Studies have begun to investigate relationships between genetic variants within a number of candidate genes and outcome following TBI in an effort to elucidate such variability. One

form of this variance—called single nucleotide polymorphisms (SNPs)—is comprised of single nucleotide substitutions arising within a gene's coding sequence and/or regulatory elements which may influence either protein structure/function or abundance, respectively. Numerous polymorphisms have been identified [12–14], but those arising within genes encoding important proteins underlying neurotransmission are thought to play an influential role in the preservation and/or impairment in cognition following TBI [15]. Catechol-*O*-methyltransferase (COMT; encoded by the gene *COMT* on chromosome 22q11.2) represents one such molecule [16–18] and is an enzyme which inactivates catecholamine neurotransmitters, e.g., dopamine (DA), epinephrine, and norepinephrine, through 3-*O*-methylation of the benzene ring [19]. In brain regions important to cognition, e.g., the prefrontal cortex (PFC), low expression of DA reuptake transporters makes COMT inactivation the predominant regulator of dopaminergic synaptic transmission [19–21].

A relatively common SNP arising within the coding sequence at codon 158—known as *COMT* $Val^{158}Met$ (*rs4680*)—results in substitution of a methionine for valine at this position [19]. This substitution lessens the activity of COMT resulting in higher levels of dopamine in the PFC [22], and it has been shown that $Val^{158}/Val^{158}$ individuals are up to four times more efficient at catabolizing catecholamines than $Met^{158}/Met^{158}$ homozygotes [23]. In turn, higher bioavailability of catecholamines in the PFC in $Met^{158}/Met^{158}$ subjects has been shown to confer a cognitive advantage over $Val^{158}$-carriers [24], and the $Met^{158}$ allele is generally associated with an advantage in measures of memory, executive function, and tasks requiring attention [18, 25].

Cognitive symptoms, including memory loss, inattention, and impulsivity, are relatively common in TBI and are among the most debilitating consequences of TBI and may influence functional outcome [26]. A number of prior studies have suggested that disruption and/or dysregulation of dopaminergic transmission in the PFC may contribute to the pathogenesis of posttraumatic cognitive impairment [27]. Conversely, it has been suggested in other studies that the dopaminergic system may be pharmacologically targeted to ameliorate persistent cognitive deficits following TBI [28]. Despite its importance in modulating PFC neurotransmission, studies examining the relationship between the *COMT* $Val^{158}Met$ polymorphism and cognitive deficits following TBI have largely been equivocal [16–18]. To date, these studies have been limited to more severe injury, and whether the *COMT* $Val^{158}Met$ polymorphism influences posttraumatic cognitive deficits following mTBI has yet to be studied.

Here, we utilize the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) dataset, a database of demographic history, biomarkers, neuroimaging, and neuropsychiatric and neurocognitive outcomes obtained at three clinical sites [29], to evaluate whether the *COMT* $Val^{158}Met$ polymorphism influences cognitive performance 6 months following mTBI on a battery of three standardized tests—Wechsler Adult Intelligence Scale Fourth Edition Processing Speed Index subscale, Trail Making Test, and the California Verbal Learning Test Second Edition. We hypothesized that the *COMT* $Val^{158}Met$ polymorphism is associated with improved cognitive performance following mTBI. Our data demonstrates that the *COMT* $Val^{158}Met$ polymorphism associates with

cognitive performance in select domains, e.g., nonverbal processing speed, but not others, e.g., mental flexibility or verbal learning.

## Materials and methods

### Study design

The TRACK-TBI Pilot Study is a multicenter prospective observational study conducted at three Level 1 trauma centers in USA—San Francisco General Hospital, University of Pittsburgh Medical Center, and University Medical Center Brackenridge (UMCB) in Austin, Texas [29]—using the National Institutes of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS) common data elements (CDEs) [30–33]. Inclusion criteria for the pilot study were adult patients presenting to a Level 1 trauma center with external force trauma to the head and clinically indicated head computed tomography (CT) scan within 24 h of injury. Exclusion criteria were pregnancy, comorbid life-threatening disease, incarceration, suicidal ideation/on psychiatric hold, and non-English speakers due to limitations in participation with outcome assessments. For the present study, our goal was to study the associations between *COMT Val*$^{158}$*Met* and cognition after isolated and uncomplicated mTBI. Therefore, our analysis was restricted to a subset of patients with a GCS ≥13, no skull fracture, or acute intracranial pathology—defined as the absence of intraparenchymal contusions or hemorrhage, intraventricular hemorrhage, epidural hematoma, acute subdural hematoma, or traumatic subarachnoid hemorrhage—on non-contrasted head CT within 24 h of injury, no polytrauma as defined by an Abbreviated Injury Scale (AIS) score ≥3 in any extracranial body region [34, 35], as well as no prior history of cerebrovascular accident or transient ischemic attack, brain tumor, schizophrenia, learning disability or developmental delay.

Eligible subjects were enrolled through convenience sampling at all three sites. Institutional review board approval was obtained at all participating sites. Informed consent was obtained for all subjects prior to enrollment in the study. For patients unable to provide consent due to their injury, consent was obtained from their legally authorized representative (LAR). Patients were then reconsented if cognitively able at later inpatient and/or outpatient follow-up assessments for continued participation in the study.

### Biospecimen acquisition and genotyping

Specimen acquisition was performed as previously described [29]. In brief, blood samples for DNA genotyping analysis were collected via peripheral venipuncture or existing peripheral venous indwelling catheters within 24 h of injury. Samples were collected in BD Vacutainer $K_2$-EDTA vacutainer tubes, and subsequently aliquoted and frozen in cryotubes at −80 °C within 1 h of collection in accordance with recommendations from the NIH-CDE Biomarkers Working Group [Manley 2010]. DNA was extracted from isolated leukocytes using the Wizard® Genomic DNA Purification Kit as described by the manufacturer (Promega, Madison, WI) and reported in our previous work [36]. *COMT Val158Met* polymorphism (*rs4680*) was genotyped utilizing the TaqMan®SNP Genotyping Assay as described by the manufacturer (Applied Biosystems, Carlsbad, CA, Assay ID# C_25746809_50). For the purpose of evaluating a potential protective benefit of the *Met*$^{158}$

allele, $Met^{158}/Met^{158}$ and $Met^{158}/Val^{158}$ were combined as a single group as previously described for *COMT* [37–40] and other genetic polymorphisms in TBI [41–43]. Therefore, for data reporting and all figures, this group is referred to as $Met^{158}$.

### Neuropsychiatric testing and outcome parameters

The NINDS defines measures of neuropsychological impairment as those "of neuropsychological functions, such as attention, memory, and executive function which are very sensitive to effects of TBI that affect everyday activities and social role participation [33]." To evaluate for neuropsychological impairment, all participants underwent outcome assessments at 6 months following TBI with a battery of NIH NINDS-designated "Core Measures"—those deemed most relevant and applicable across large TBI studies. For the current analysis, all three measures of the "Neuropsychological Impairment" domain of the outcome CDEs were included:

### Wechsler Adult Intelligence Scale, fourth edition Processing Speed Index Subscale

The Wechsler Adult Intelligence Scale, fourth edition Processing Speed Index Subscale (WAIS-PSI) is a summary measure of nonverbal processing speed and is comprised of two non-verbal tasks (symbol search and coding) which require visual attention and motor speed [44]. In studies of TBI, it has been shown to predominately reflect impairment in perceptual processing speed with a small component attributable to working memory and only minimal contribution from motor speed [45]. The composite score is scalar, ranging from 50 to 150 to correspond to the 0.1st to 99.9th percentile of performance across age groups. Scores of ~90, 100, and ~110 correspond to the 25th, 50th, and 75th percentiles, respectively [44].

### Trail Making Test

The Trail Making Test (TMT) is a two-part timed test (TMT-A and TMT-B), and both scores are measured in number of seconds needed for the patient to complete the task. TMT-A assesses visual processing, and TMT-B assesses mental flexibility and processing speed [46]. In order to derive a purer index of executive control and mental flexibility separate from visual processing and motor speed, we used the difference score between the Trial B and Trial A (TMT B-A) as previously described [47–49]. In this test, a lower score suggests improved performance.

### California Verbal Learning Test, second edition

The California Verbal Learning Test, second edition (CVLT-II) is a verbal learning and memory task in which five learning trials, an interference trial, an immediate recall trial, and a post-20 min recall trial are performed. The CVLT-II trials 1–5 Standard Score is a summative score of the first five learning trials normed for age and sex and provides a global index of verbal learning ability [50]. The CVLT-II was substituted for the Rey Auditory Verbal Learning Test (RAVLT) listed in the NIH NINDS outcome CDEs due to relevant revisions of the second edition and higher consistency on between-norm sets [51].

### Statistical analysis

Group differences in patient demographics and mechanism of injury across *COMT Met*$^{158}$ carriers versus *Val*$^{158}$/*Val*$^{158}$ homozygotes were assessed by Pearson's chi-squared test ($X^2$) for categorical variables and analysis of variance (ANOVA) for continuous variables. Fisher's exact test was used to assess for differences in categorical variables with group counts ≤5. Means and standard deviations are reported for continuous descriptive variables. Group differences are reported between *COMT* genotype and each outcome measure using ANOVA. Multivariable linear regression was performed for each of the three outcome measures to adjust for age and education years as recommended [44–46, 49, 50]; the WAIS-PSI Composite Score and CVLT-II trials 1–5 Standard Score are already age-normed and thus further adjusted only for education years, while the TMT B-A score was further adjusted for age and education years. As this is a study of mTBI, the GCS was used to adjust for injury severity (GCS 15 vs. less than 15). The adjusted unstandardized coefficient of regression ($B$) and associated standard error (SE) was used to quantify mean increase or decrease in the outcome measure associated with a per-unit increase in a continuous predictor or a change in the subcategory of a categorical predictor. All multivariable regression models conformed to tests for goodness-of-fit. To account for race stratification, race was entered onto the multivariable regression with three subcategories to include the two largest race categories (Caucasian, African-American/African) as well as a third category of aggregated "other races" for races with small (<5) group counts. Significance was assessed at $\alpha$=0.05. All analyses were performed using Statistical Package for the Social Sciences (SPSS) v.22 (IBM Corporation, Chicago, IL). Figures were constructed with GraphPad Prism v.6 (GraphPad Software, La Jolla, CA).

## Results

### Patient demographics and mechanisms of injury

In total, the present study included 100 subjects (Table 1). Overall, subjects had a mean age of 40.9 years (SD 15.2) and were 66 % male. The race distribution was 70 % Caucasian, 14 % African American/African, 5 % Asian, 1 % American Indian/Alaskan Native, 1 % Hawaiian/Pacific Islander, and 9 % more than one race. Subjects had a mean of 14.2 years of education (SD 2.9). Mechanisms of injury were 33 % fall, 26 % motor vehicle crash, 22 % pedestrian versus auto, 15 % assault, and 4 % struck by/against object. GCS distribution was 3, 20, and 77 % for GCS of 13, 14, and 15, respectively. Distribution of admission GCS did not change with respect to genotype. For injury severity classification, GCS of 13 and 14 were combined into a single group of "GCS less than 15″. There was also no difference in posttraumatic amnesia—another important predictor for posttraumatic cognitive impairment—across genotypes [11, 52–54]. In total, 66 subjects were discharged from the emergency department (ED), 30 were admitted to the hospital ward, and 4 were admitted to the intensive care unit (ICU). No statistically significant difference in ED disposition was observed across genotypes (Table 1).

*COMT* genotype distribution was 29 % *Met*$^{158}$/*Met*$^{158}$ ($n$= 29), 47 % *Met*$^{158}$/*Val*$^{158}$ ($n$=47), and 24 % *Val*$^{158}$/*Val*$^{158}$ ($n$= 24). *COMT* allelic frequencies (A=0.53, G=0.47) were not found to deviate significantly from Hardy-Weinberg equilibrium ($X^2$=0.33, $p$=0.566). Years

of education were higher for *Met*$^{158}$ carriers than for *Val*$^{158}$/*Val*$^{158}$ homozygotes ($p$=0.016), and a higher prevalence of *Val*$^{158}$/*Val*$^{158}$ homozygotes was noted in African-American/African subjects ($p$=0.042). No other significant differences were observed in the distribution of each demographic and clinical descriptor across *COMT Met*$^{158}$ and *Val*$^{158}$/*Val*$^{158}$ genotypes (Table 1).

## Outcome measures

We first assessed whether the *COMT Val*$^{158}$*Met* polymorphism was associated with divergent performance on three primary cognitive measures—WAIS-PSI, TMT B-A, and CVLT-II—following isolated, uncomplicated mTBI. *COMT Met*$^{158}$ carriers showed significantly higher nonverbal processing speed on WAIS-PSI when compared to *COMT Val*$^{158}$/*Val*$^{158}$ homozygotes (*Met*$^{158}$ 103.8±13.3; *Val*$^{158}$/ *Val*$^{158}$ 94.1±15.7; $p$=0.004) (Table 2). *COMT Met*$^{158}$ subjects did not associate with a task requiring mental flexibility on TMT B-A (*Met*$^{158}$ 46.6±51.5; *Val*$^{158}$/*Val*$^{158}$ 63.8±42.0, $p$=0.139) (Table 2). *COMT Val*$^{158}$*Met* polymorphism did not associate with verbal learning and fluency as measured by the CVLT-II Trial 1–5 Standard Score (*Met*$^{158}$ 54.5±11.1; *Val*$^{158}$/*Val*$^{158}$ 53.7±9.4, $p$=0.740) (Table 2).

## *COMT Val*$^{158}$*Met* is associated with nonverbal processing speed after mTBI

To further assess the association between *COMT Val*$^{158}$*Met* and nonverbal processing speed as measured by the WAIS-PSI composite score, multivariable regression was performed to control for education years, race, and injury severity (Table 3). *COMT Met*$^{158}$ carriers demonstrated higher adjusted mean scores on WAIS-PSI (101.6±2.1) compared to their *Val*$^{158}$/*Val*$^{158}$ counterparts (93.8±3.0), which corresponds to a mean increase of 7.9 points (95 % CI [1.4 to 14.3], $p$=0.017) (Fig. 1). Consistent with prior reports [55–57], education years associated with WAIS-PSI ($B$=1.4, 95 % CI [0.4 to 2.3], $p$=0.005). Greater injury severity also associated with a decrease in nonverbal processing speed (GCS 15, 101.6±1.9; GCS <15, 93.8±3.0; $B$=−7.9, 95 % CI [−14.1 to −1.7], $p$= 0.013). Race did not show a significant association with WAIS-PSI ($p$=0.539) on multivariable analysis. Further, multivariable subgroup analysis performed in the Caucasian group—the largest group—demonstrated a statistical trend between the *COMT Val*$^{158}$*Met* polymorphism and performance on WAIS-PSI ($B$=7.5, 95 % CI [−1.1 to 16.0], $p$= 0.086). Future studies are needed to confirm this finding in a larger population.

## *COMT Val*$^{158}$*Met* is not associated with mental flexibility after mTBI

To further assess the association between *COMT Val*$^{158}$*Met* and mental flexibility as measured by the TMT B-A time, multivariable regression was performed to control for education years, race, and injury severity. Since the TMT B-A has not been intrinsically adjusted for age, we further adjusted for age in the current analysis. *COMT Val*$^{158}$*Met* did not demonstrate an association with TMT B-A after adjustment (*Met*$^{158}$ 47.7±7.1; *Val*$^{158}$/*Val*$^{158}$ 58.8±10.2; $B$=−11.1, 95 % CI [−33.0 to 10.8], $p$=0.318) (Table 3). Consistent with prior reports [58, 59], both age years ($B$=1.2, 95 % CI [0.6 to 1.8], $p$<0.001) and education years ($B$=−5.2, 95 % CI [−8.4 to −2.0], $p$=0.002) associated with decreased and increased performance on mental flexibility, respectively. Injury severity did not show a significant association with TMT B-A (GCS 15 47.5±6.5; GCS <15 59.0±10.3; $B$=11.5,

95 % CI [−9.7 to 32.6], $p$=0.284). Race did not show a significant association with TMT B-A ($p$=0.492) on multivariable analysis.

### *COMT Met*$^{158}$ is not associated with verbal learning after mTBI

To further assess the association between *COMT Val*$^{158}$*Met* and verbal learning as measured by the CVLT-II, multivariable regression was performed to control for education years, race, and injury severity. *COMT Val*$^{158}$*Met* did not demonstrate an association with CVLT-II after adjustment (*Met*$^{158}$ 50.9±1.6; *Val*$^{158}$/*Val*$^{158}$ 51.6±2.4; $B$=−0.7, 95 % CI [−5.8 to 4.3], $p$=0.771) (Table 3). Consistent with prior reports [60], education years ($B$=0.6, 95 % CI [−0.1 to 1.4], $p$=0.098) showed a borderline association with verbal learning. Greater injury severity also associated with a decrease in verbal learning (GCS 15 53.7±1.5; GCS <15 48.7±2.4; $B$=−5.0, 95 % CI [−9.9 to −0.1], $p$=0.044). Race showed a borderline significant association with CVLT-II ($p$=0.068) on multivariable analysis, driven primarily by a difference between the Caucasian subgroup and the heterogeneous “other races” subgroup ($B$=−5.9 [−11.5 to −0.2], $p$=0.042).

## Discussion

In the present study, we sought to investigate whether the *COMT Val*$^{158}$*Met* polymorphism is associated with cognitive performance at 6 months following mild closed head injury in an isolated, uncomplicated mTBI population. We found that subjects with the *COMT Met*$^{158}$ allele showed higher performance on a measure of nonverbal processing speed compared to *Val*$^{158}$/*Val*$^{158}$ homozygotes at 6 months following injury independent of injury severity and race. We also demonstrate that the *COMT Val*$^{158}$*Met* polymorphism is not associated with a measure of executive control and mental flexibility or a measure of verbal learning after controlling for injury severity and race. We confirm that greater injury severity is associated with poorer nonverbal processing speed and verbal learning. Further, racial stratification was not found to significantly associate with nonverbal processing speed, mental flexibility, or verbal learning after uncomplicated mTBI in the current patient population.

In our current analysis, *COMT Met*$^{158}$ carriers showed an adjusted mean score of 101.6 on the WAIS-PSI, while *Val*$^{158}$/ *Val*$^{158}$ homozygotes showed 93.8—these scores correspond to the ~55th percentile and the ~34th percentile of nonverbal processing speed performance in the normal population, respectively [44]. We also find that the adjusted mean scores (~50 s) on the CVLT-II correspond to the general mean of the normal population for both *COMT Val*$^{158}$*Met* groups [50]. Further, the adjusted TMT B-A times for both *COMT* groups fall within the means reported in literature (~40 to ~60) for the normal/uninjured population [49, 61, 62]. Thus, it is worth noting that a subgroup of patients with isolated uncomplicated mTBI demonstrates heightened risk for decreased performance on nonverbal processing, but not verbal learning or executive function at 6 months postinjury, and this subgroup associates with the common SNP *COMT Val*$^{158}$*Met*.

It is generally accepted that acute physiologic recovery occurs by 6 months post-mTBI on imaging studies [9, 63, 64], and studies report that most cognitive symptoms resolve by within the first 3 months in mTBI [65, 66]. To our knowledge, this is the first study of the association between *COMT Val*$^{158}$*Met* and cognitive performance at an extended time point

of recovery, such as 6 months following mTBI. Prior reports examining the potential influence of the *COMT Val*$^{158}$*Met* polymorphism on TBI cognitive outcomes have been conducted during acute and subacute recovery with a mean time of collection within 2 months postinjury and have been predominately limited to patients with moderate and/or severe injuries [17, 18, 67]. For example, in a cohort of 113 TBI rehabilitation patients assessed at a mean of 2 months postinjury,[17] *Val*$^{158}$/*Val*$^{158}$ homozygotes were found to score lower on a measure of cognitive flexibility—the ability to alter a behavioral response against changing contingencies [68]—and to have a greater number of perseverative errors. In another sample of 32 moderate-to-severe TBI patients with 40 health controls, *COMT Met*$^{158}$ was found to associate with preserved strategic control of attention at 2 months postinjury [67]. In the largest study of *COMT* and moderate-to-severe TBI to date, Willmott et al. did not find an association between *COMT* and measures of cognition at roughly 1 month postinjury [18]. However, this study evaluated cognitive performance at a time point that was not standardized and closer to the time of injury (mean 29 days); the authors suggest that cognitive assessment at 6–12 months postinjury may be more likely to detect subtle group differences as demonstrated in the present report.

There is physiological evidence in support of a potential modulatory role of the *COMT Met*$^{158}$ allele in cognitive performance following TBI. The PFC is a key center for overall executive function, attention, and strategic planning [69–71], in which its rich dopaminergic pathways are more dependent on COMT for regulation and modulation at the synaptic cleft [19–21]. Prior studies have demonstrated that the *COMT Val*$^{158}$*Met* polymorphism is associated with differences in cognitive performance in the absence of brain injury [23, 72]. Given the absence of measures of baseline preinjury performance in our population or neuropsychiatric data in appropriately uninjured age-matched controls, we cannot conclude whether our results reflect the maintenance of preexisting cognitive differences between genotypes and/or an altered trajectory of recovery or impairment following mTBI.

There are also several additional limitations to the present study. Our data was obtained for a relatively small sample size ($n$=100) in a predominately Caucasian male population and did not conform to known HapMap Phase III subpopulations; therefore, there is a need for studies of confirmation in similar populations and of validation in larger and more diverse study populations. We also included patients only with isolated mTBI in the absence of intracranial findings on CT and a limited period of diminished consciousness and/or posttraumatic amnesia; thus, the generalizability of our results is limited. We also include no neuroimaging outside of 24 h or magnetic resonance imaging. Therefore, it is possible that a subset of the subjects developed delayed pathology on neuroimaging and would no longer be classified as uncomplicated. We pursued analyses designed to investigate a hypothesized relationship between the *COMT Val*$^{158}$*Met* polymorphism and cognitive outcome and did not explore the structure-function implications of *COMT* with specific brain pathology or variables important to the trajectory of recovery such as treatment and support. There is also a need to examine gene-gene interaction with other susceptibility loci in the context of mTBI to better elucidate complex interactions and mechanisms through which the *COMT* molecular pathway may influence response and recovery to TBI. Finally, all of our findings must be considered preliminary until they are formally replicated.

## Conclusions

The *COMT Val*$^{158}$*Met* polymorphism (*rs4680*) is associated with nonverbal cognitive performance following uncomplicated mTBI without polytrauma. More specifically, the *COMT Met*$^{158}$ allele is associated with increased performance in nonverbal processing speed, while no associations were seen on mental flexibility or verbal learning. Larger studies in similar populations will be of value to confirm the role of *COMT Val*$^{158}$*Met* polymorphism in these domains and to explore its effects in other cognitive domains following mTBI. Whether *COMT Val*$^{158}$/ *Val*$^{158}$ homozygotes would benefit from heightened clinical surveillance and/or pharmacologic and cognitive behavior therapy remains to be determined and may represent an important direction of future studies.

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## Appendix

## TRACK-TBI Investigators

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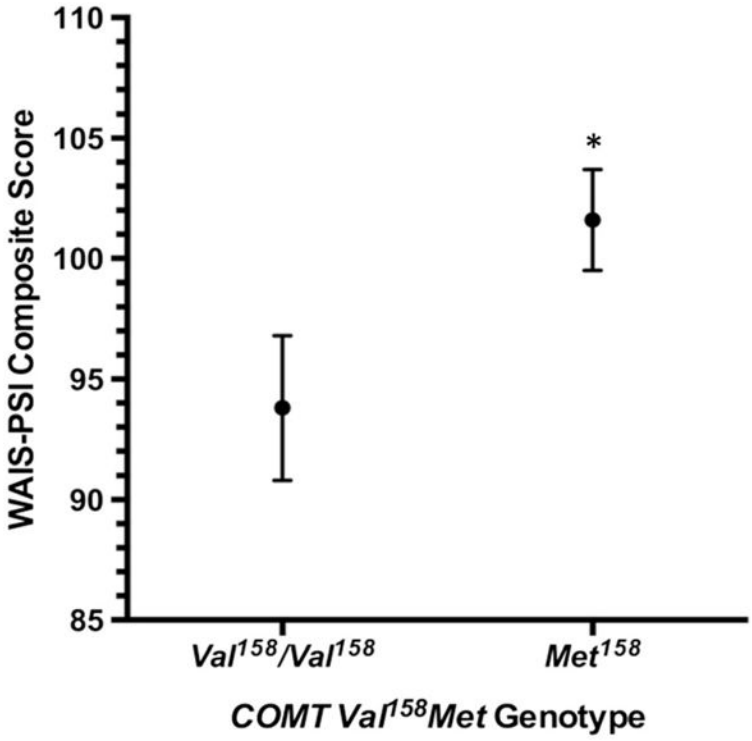


**Fig. 1.**

*COMT Val*$^{158}$*Met* and 6-month WAIS-PSI Composite Score after mild traumatic brain injury. The *COMT Val*$^{158}$*Met* polymorphism is associated with statistically greater preservation of nonverbal processing speed 6 months following mild traumatic brain injury after adjusting for race, years of education, and injury severity. Means and standard errors on the WAIS-PSI Composite Score are shown for *Met*$^{158}$ and *Val158*/*Val*$^{158}$ genotype groups. *COMT*, Catechol-O-Methyltransferase, *WAIS-PSI* Wechsler Adult Intelligence Scale Fourth Edition—Processing Speed Index. *$p$<0.05.

## Table 1

Demographic and clinical information of included subjects with mild traumatic brain injury

| Variable | *COMT Met*$^{158}$ (*N*=76) | *COMT Val*$^{158}$/*Val*$^{158}$ (*N*=24) | Sig. (*p*) |
|---|---|---|---|
| Age (years) | | | |
| Mean±SD | 40.5±15.7 | 42.2±14.1 | 0.643 |
| Gender | | | |
| Male | 49 (65 %) | 17 (71 %) | 0.566 |
| Female | 27 (35 %) | 7 (29 %) | |
| Race | | | |
| Caucasian | 57 (81 %) [a] | 13 (19 %) [a] | 0.042 |
| African-American/African | 7 (50 %) [a] | 7 (50 %) [b] | |
| Other races | 12 (75 %) [a] | 4 (25 %) [a] | |
| Education (years) | | | |
| Mean±SD | 14.6±2.7 | 13.0±3.1 | 0.015 |
| Mechanism of injury | | | |
| Motor vehicle crash | 24 (32 %) | 2 (8 %) | 0.110 |
| Pedestrian versus auto | 17 (22 %) | 5 (21 %) | |
| Fall | 23 (30 %) | 10 (42 %) | |
| Assault | 9 (12 %) | 6 (25 %) | |
| Struck by/against object | 3 (4 %) | 1 (4 %) | |
| Posttraumatic amnesia | | | |
| No | 30 (40 %) | 11 (46 %) | |
| Yes | 42 (55 %) | 10 (42 %) | 0.310 |
| Unknown | 4 (5 %) | 3 12 %) | |
| GCS—field[a] | | | |
| <15 | 21 (36 %) | 6 (35 %) | 0.982 |
| =15 | 38 (64 %) | 11 (65 %) | |
| GCS—ED arrival | | | |
| <15 | 19 (25 %) | 4 (17 %) | 0.579 |
| =15 | 57 (75 %) | 20 (83 %) | |
| ED disposition | | | |
| ED discharge | 53 (70 %) | 13 (54 %) | 0.284 |
| Hospital ward admission | 20 (26 %) | 10 (42 %) | |
| ICU admission | 3 (4 %) | 1 (4 %) | |

Race distributions are reported as row percentages. All other distributions reported as column percentages. The race subgroup “other races” was combined due to individual small sample sizes of Asian (*N*=5; *Met*$^{158}$=4, *Val*$^{158}$/*Val*$^{158}$=1), American Indian/Alaskan Native (*N*=1; *Met*$^{158}$=1), Hawaiian/Pacific Islander (*N*=1; *Met*$^{158}$=1), and more than one race (*N*=9; *Met*$^{158}$=6, *Val*$^{158}$/*Val*$^{158}$=3)

*COMT* catechol-O-methyltransferase, *ED* emergency department, *GCS* Glasgow Coma Scale, *ICU* intensive care unit, *SD* standard deviation

[a] Data for GCS—Field was only available for 76 patients

## Table 2

Distribution of performance on 6-month cognitive outcome measures following mild traumatic brain injury by *COMT* genotype

| Outcome Measure | *Met*$^{158}$ (*N*=76) | *Val*$^{158}$/*Val*$^{158}$ (*N*=24) | Sig. (*p*) |
|---|---|---|---|
| WAIS-PSI Composite Score[a] | 103.8±13.3 | 94.1±15.7 | 0.004 |
| TMT Trail B minus A Time[b] | 46.6±51.5 | 63.8±42.0 | 0.139 |
| CVLT-II Trial 1–5 Standard Score[a] | 54.5±11.1 | 53.7±9.4 | 0.740 |

Distributions are reported as mean±standard deviation

*COMT* catechol-O-methyltransferase, *CVLT-II* California Verbal Learning Test, second edition, *TMT* Trail Making Test, *WAIS-PSI* Wechsler Adult Intelligence Scale, fourth edition, Processing Speed Index

[a] Higher scores suggest improved performance

[b] Lower scores suggest improved performance

**Table 3**

Multivariable analysis of the *COMT Val*$^{158}$*Met* polymorphism and 6-month cognitive outcome following mild traumatic brain injury

| **WAIS-PSI Composite Score**[a] | **Mean±SE** | **B [95 % CI]** | **Sig. (*p*)** |
|---|---|---|---|
| *COMT Val*$^{158}$*Met* | | | 0.017 |
| *Val*$^{158}$/ *Val*$^{158}$ | 93.8±3.0 | Reference | – |
| *Met*$^{158}$ | 101.6±2.1 | 7.9 [1.4, 14.3] | |
| GCS | | | 0.013 |
| GCS=15 | 101.6±1.9 | Reference | – |
| GCS <15 | 93.8±3.0 | −7.9 [−14.1, −1.7] | |
| Race | | | 0.539 |
| Caucasian | 96.8±2.1 | Reference | – |
| African-American/African | 95.8±3.6 | −1.1 [−9.0, 6.9] | 0.790 |
| Other | 100.5±3.5 | 3.7 [−3.5, 10.9] | 0.312 |
| Education (years) | – | 1.4 [0.4, 2.3] | 0.005 |
| TMT Trail B minus A Time[b] | Mean±SE | B [95 % CI] | Sig. (*p*) |
| *COMT Val*$^{158}$*Met* | | | 0.318 |
| *Val*$^{158}$/ *Val*$^{158}$ | 58.8±10.2 | Reference | – |
| *Met*$^{158}$ | 47.7±7.1 | −11.1 [−33.0, 10.8] | |
| GCS | | | 0.284 |
| GCS=15 | 47.5±6.5 | Reference | – |
| GCS <15 | 59.0±10.3 | 11.5 [−9.7, 32.6] | |
| Race | | | 0.492 |
| Caucasian | 59.2±7.1 | Reference | – |
| African-American/African | 43.0±12.3 | −16.2 [−43.1, 10.7] | 0.235 |
| Other | 57.4±12.2 | −1.8 [−27.0, 23.4] | 0.888 |
| Education (years) | – | −5.2 [−8.4, −2.0] | 0.002 |
| Age (years) | – | 1.2 [0.6, 1.8] | <0.001 |
| CVLT-II Trial 1–5 Standard Score[a] | Mean±SE | B [95 % CI] | Sig. (*p*) |
| *COMT Val*$^{158}$*Met* | | | 0.771 |
| *Val*$^{158}$/ *Val*$^{158}$ | 51.6±2.4 | Reference | – |
| *Met*$^{158}$ | 50.9±1.6 | −0.7 [−5.8, 4.3] | |
| GCS | | | 0.044 |
| GCS =15 | 53.7±1.5 | Reference | – |
| GCS <15 | 48.7±2.4 | −5.0 [−9.9, −0.1] | |
| Race | | | 0.068 |
| Caucasian | 54.7±1.6 | Reference | – |
| African-American | 50.1±2.8 | −4.7 [−10.9, 1.5] | 0.139 |
| Other | 48.9±2.8 | −5.9 [−11.5, −0.2] | 0.042 |
| Education (years) | – | 0.6 [−0.1, 1.4] | 0.098 |

The WAIS Processing Speed Index (WAIS-PSI) Composite Score and the CVLT-II Trial 1–5 Standard Score are adjusted for education years, race (Caucasian, African-American/African, other races), and GCS (15 vs. less than 15). The TMT Trail B minus ATime is adjusted for age, education years, race, and GCS. Distributions are reported as adjusted mean±standard error. The mean difference (*B*) between *COMT* $Met^{158}$ and *COMT* $Val^{158}$ / $Val^{158}$ and associated 95 % CI is reported for each outcome measure CVLT-II, California Verbal Learning Test, Second Edition; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale, Fourth Edition.

*CI* confidence interval, *COMT* catechol-O-methyltransferase, *CVLT-II* California Verbal Learning Test, second edition, *GCS* Glasgow Coma Scale, *TMT* Trail Making Test, *WAIS* Wechsler Adult Intelligence Test

[a] Higher scores suggest improved performance

[b] Lower scores suggest improved performance