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COMT Val^{158}*Met* polymorphism is associated with post-traumatic stress disorder and functional outcome following mild traumatic brain injury

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Abstract

Mild traumatic brain injury (mTBI) results in variable clinical trajectories and outcomes. The source of variability remains unclear, but may involve genetic variations, such as single nucleotide polymorphisms (SNPs). A SNP in catechol-o-methyltransferase (*COMT*) is suggested to influence

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development of post-traumatic stress disorder (PTSD), but its role in TBI remains unclear. 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 is associated with PTSD and global functional outcome as measured by the PTSD Checklist – Civilian Version and Glasgow Outcome Scale Extended (GOSE), respectively. Results in 93 predominately Caucasian subjects with mTBI show that the *COMT Met*^{158} allele is associated with lower incidence of PTSD (univariate odds ratio (OR) of 0.25, 95% CI [0.09–0.69]) and higher GOSE scores (univariate OR 2.87, 95% CI [1.20–6.86]) 6-months following injury. The *COMT Val*^{158}*Met* genotype and PTSD association persists after controlling for race (multivariable OR of 0.29, 95% CI [0.10–0.83]) and pre-existing psychiatric disorders/substance abuse (multivariable OR of 0.32, 95% CI [0.11–0.97]). PTSD emerged as a strong predictor of poorer outcome on GOSE (multivariable OR 0.09, 95% CI [0.03–0.26]), which persists after controlling for age, GCS, and race. When accounting for PTSD in multivariable analysis, the association of *COMT* genotype and GOSE did not remain significant (multivariable OR 1.73, 95% CI [0.69–4.35]). Whether *COMT* genotype indirectly influences global functional outcome through PTSD remains to be determined and larger studies in more diverse populations are needed to confirm these findings.

Keywords

Traumatic brain injury; Genetic factors; PTSD; Outcome measures; Human studies

1. Introduction

Traumatic brain injury (TBI) is a common and often debilitating injury in modern societies. In the United States alone, at least 2.5 million people suffer TBIs annually which accounts for 52,000 deaths, 275,000 inpatient hospitalizations, and 1,365,000 Emergency Room visits [1]. Approximately 70–90% of all TBI is characterized as ‘mild TBI’ (mTBI) defined by a Glasgow Coma Scale score of 13–15. The vast majority of patients make a complete recovery following mTBI in the ensuing weeks to months [2,3]. However, a small but significant number of patients suffer from persistent neurologic, cognitive and/or neuropsychiatric sequelae – including headache, dizziness, fatigue, memory impairment, slowed processing speed, depression and post-traumatic stress disorder (PTSD), among others [4]. In many instances, individuals enduring similar mechanisms and magnitude of brain injury follow different clinical trajectories, and there are limited metrics to identify and/or sub-stratify those at greatest risk for persistent post-traumatic impairment [5].

The Human Genome Project has allowed the identification of single nucleotide polymorphisms (SNPs) – single nucleotide substitutions which alter amino acid sequence and protein function and/or levels of protein expression. Several SNPs are good candidates for allelic association studies aimed at explaining the divergence in outcome or in the prevalence of cognitive, behavioral and neuropsychiatric symptoms following TBI [6–8]. Catechol-*O*-methyltransferase (*COMT*; encoded by the gene *COMT* on chromosome 22q11.2) represents one such candidate gene. *COMT* enzymatically inactivates the catecholamine neurotransmitters, i.e., norepinephrine and dopamine, through 3-*O*-

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methylation of the benzene ring [9]. A common coding SNP, *Val*^{158}*Met* (*rs4680*), results in a substitution of valine (G; *Val*^{158}) for methionine (A; *Met*^{158}) at codon 158. The *Met*^{158} substitution reduces *COMT* enzymatic activity [10,11]. In areas with limited reuptake transporters, i.e., the prefrontal cortex, *COMT*-mediated inactivation is the principal mechanism of inactivation of dopaminergic signal transmission, and the *Met*^{158} variant is associated with higher catecholamine bioavailability [12–14].

Numerous studies have investigated the effects of the *COMT Val*^{158}*Met* polymorphism on human behavior and/or brain function [9,15,16]. In general, the *Met*^{158} allele confers a performance advantage in cognitive tasks – including measures of memory and attention – attributed to the higher catecholamine bioavailability in the prefrontal cortex [9,15–17]. The *Val*^{158} allele, on the other hand, may confer advantage in aversive stimulus processing [18]. Consistent with this principle, the *Met*^{158} allele has been associated with a number of anxiety disorders – including generalized anxiety disorder, panic disorder, obsessive compulsive disorder, and PTSD in some, but not all study populations [19–23]. In TBI, prior studies have shown that *Val*^{158}/*Val*^{158} homozygosity may be associated with greater impairment in certain cognitive domains, e.g., perseveration, but not others [24–27]. However, whether the *COMT Val*^{158}*Met* polymorphism influences psychiatric health following brain injury – such as TBI – has yet to be studied.

PTSD is a relatively common and often debilitating neuropsychiatric sequela of TBI with published rates ranging from of 17% to 33% of patients [28–32]. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) classifies PTSD as an anxiety disorder presenting with three concurrent symptom clusters after exposure to a traumatic event: persistent re-experiencing of the traumatic event, persistent avoidance of stimuli associated with the traumatic event, and persistent symptoms of increased arousal. The event can involve actual or perceived serious injury, a threat to one's physical integrity or the integrity of another individual, or an unexpected death or serious harm to a close family member or friend. The symptoms must be present for more than one month and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning [33]. Although PTSD may occur with any severity of TBI, the highest incidence occurs in individuals with mTBI [31,34–36]. Furthermore, symptoms of PTSD in the context of a history of mTBI is often associated with poorer outcome [37].

In this study we utilize the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) dataset, a comprehensive database of demographic history, biomarkers, neuroimaging, and neuropsychiatric and neurocognitive outcomes [38], to investigate whether the *COMT Val*^{158}*Met* polymorphism is associated with the development of symptoms meeting DSM-IV criteria of PTSD and global functional outcome following isolated and uncomplicated mild closed head injury. On the basis of the literature of anxiety disorders, we hypothesize that subjects with the *Met*^{158} allele will more frequently develop symptoms associated with PTSD and have poorer 6-month global functional outcome following mTBI.

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2. Materials and methods

2.1. Study design

The TRACK-TBI Pilot Study is a multicenter prospective observational study conducted at three Level 1 Trauma Centers in the United States – San Francisco General Hospital, University of Pittsburgh Medical Center and University Medical Center Brackenridge (UMCB) in Austin, Texas [38]. 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 re-consented, if cognitively able at later inpatient and/or outpatient follow-up assessments for continued participation in the study.

2.2. Patient selection

Inclusion criteria for the pilot study were patients presenting to a Level I trauma center with external force trauma to the head and clinically indicated head computed tomography (CT) scan within 24 h of injury. TRACK-TBI Pilot patients age ⩾16 completed outcome measures. Exclusion criteria were pregnancy, comorbid life-threatening disease, incarceration, serious psychiatric and neurologic disorders that would interfere with outcome assessment, and non-English speakers due to limitations in participation with outcome assessment. For the present study, our goal was to study the effects of *COMT* $Val^{158}Met$ in isolated and uncomplicated mTBI. Therefore, our analysis was restricted to a subset of patients with a GCS ⩾13, loss of consciousness (LOC) <30 min, post-traumatic amnesia <24 h, no skull fracture or acute intracranial pathology – defined as the absence of intraparenchymal contusions or hemorrhage, axonal injury, ventricular hemorrhage, epidural hematoma, acute subdural hematoma or traumatic subarachnoid hemorrhage – on non-contrasted head CT, and no polytrauma as defined by an Abbreviated Injury Scale (AIS) score >1 in any extracranial body region. To avoid potential confounding with measures of PTSD, patients who reported pre-injury PTSD or schizophrenia – variables known to associate with *COMT* – were excluded from the present study [39,40]. Patients with previous cerebrovascular accidents, brain tumor, and baseline developmental delay were also excluded.

2.3. Biospecimen collection and genotyping

Specimen acquisition was performed as previously described [38]. 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 [41]. DNA was extracted from isolated leukocytes using the Wizard® Genomic DNA Purification Kit as described by the manufacturer (Promega, Madison, WI). *COMT* Val158Met polymorphism (rs4680) was genotyped utilizing TaqMan®SNP Genotyping Assay as described by the manufacturer (Applied Biosystems, Carlsbad, CA). For the purposes 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

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described for *COMT* [42–45], and other genetic polymorphisms in TBI [46–48]. Therefore, for data recording and all figures this group is referred to as Met^{158}.

2.4. Neuropsychiatric assessment and outcome parameters

All participants underwent a neuropsychiatric and outcome assessment at 6 months following TBI, including the PTSD Checklist – Civilian Version (PCL-C) and the Glasgow Outcome Scale Extended (GOSE). To evaluate for the presence of PTSD, the PCL-C was utilized as previously described [49–51]. The PCL-C is a standardized self-report rating scale of 17 PTSD symptoms that can be mapped to the three required criteria for PTSD, as outlined in the DSM-IV. Respondents are asked to rate on a 5-point scale (1- “not at all” to 5-“extremely”) how much they have been bothered by each symptom in the past month. Subjects endorsing a score of ⩾3 in one or more symptoms in “Re-experiencing”, three or more symptoms in “Avoidance”, and two or more symptoms in the “Hypervigilance” categories on the PCL-C were coded as “Yes PTSD” during analysis in accordance to the DSM-IV clinical screening criteria for PTSD.

The GOSE was utilized to assess global functional outcome following TBI as previously described [52]. The GOSE provides an overall measure of disability based on information obtained through a structured interview focused on cognition, independence, employability, and social/community participation. Individuals are described by one of the eight ordinal outcome categories: 1-Dead, 2-Vegetative State, 3-Lower Severe Disability, 4-Upper Severe Disability, 5-Lower Moderate Disability, 6-Upper Moderate Disability, 7-Lower Good Recovery, and 8-Upper Good Recovery.

2.5. Statistical analysis

Group differences in baseline descriptors across *COMT* Met^{158} carriers versus Val^{158}/Val^{158} homozygotes were assessed by Pearson’s chi-squared test (χ^2) for categorical variables, and analysis of variance (ANOVA) for continuous variables. Fisher’s Exact Test was used to assess differences in categorical variables with cell counts ≤5. Predictors examined in addition to *COMT* genotype were selected on the basis of prior published reports, and limited to variables that were previously associated with the response variable and relevant within our study population of isolated, uncomplicated mTBI to help control for potential confounding in multivariable analyses. Given the constraints of our exclusion criteria, remaining variables known to associate with PTSD include the presence of a self-reported pre-existing psychiatric disorder (defined by the major categories of diagnosed depression, anxiety, sleep disorder, and bipolar disorder) and history of substance abuse [2,53–55]. For GOSE, age (per-year increase) and GCS (15 vs. 13–14) were selected as consistent predictors cited in literature [56]. Binary logistic regression was performed with PTSD as the response, and *COMT* genotype, presence of pre-existing psychiatric disorder, and illicit drug use history as predictors. Ordinal logistic regression was performed with GOSE as the response, and *COMT* genotype, age, and GCS as predictors. All multivariable regression models conformed to tests for goodness-of-fit. The Nagelkerke pseudo-R-square (NR^2) used to estimate the variance explained by the model. Race effects were independently assessed in the presence of *COMT* genotype for each response. Significance was assessed at α =

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0.05. All analyses were performed using Statistical Package for the Social Sciences (SPSS) v.21 (IBM Corporation, Chicago, IL).

3. Results

3.1. Demographic and clinical descriptors

In total, the present study included 93 subjects (Table 1). Overall, the mean age of included subjects was 40 years old, and the majority of subjects were male (60%). Subjects were predominately Caucasian (70%). Subjects also self-identified as African American (14%), Asian (7%), mixed race (7%), American Indian/Native Alaskan (2%) or Hawaiian/Pacific Islander (2%). With respect to psychiatric health, 39% of subjects had self-reported presence of one or more psychiatric conditions – including depression, anxiety, sleep disorder, or bipolar disorder – and 24% percent of subjects reported a history of substance abuse. Subjects had a multitude of different mechanisms of injury including motor vehicle or motorcycle collision, bicycle accident, pedestrian versus automobile, assault and struck by or against an object. *COMT* genotype distribution was 29% Met^{158}/Met^{158} ($n = 27$), 46% Met^{158}/Val^{158} ($n = 43$) and 25% Val^{158}/Val^{158} ($n = 23$). *COMT* allelic frequencies ($A = 0.53$, $G = 0.47$) were not found to deviate significantly from Hardy–Weinberg equilibrium ($X^2 = 0.5$, $p = 0.778$). A higher prevalence of African-Americans ($p = 0.032$) and preexisting psychiatric disorder ($p = 0.043$) were noted in the Val^{158}/Val^{158} homozygotes. 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).

3.2. COMT is associated with PTSD independent of pre-existing psychiatric disease, substance abuse and race

We first tested our hypothesis that *COMT* Met^{158} is associated with higher incidence of PTSD following mTBI. In total, 28 of 96 subjects (29%) qualified for PTSD on screening criteria. Sixteen of 73 (22%) of Met^{158} carriers and 12 of 23 (52%) of Val^{158}/Val^{158} homozygotes met qualifying screening criteria for PTSD, respectively ($X^2 = 7.75$, $p = 0.005$) (Fig. 1). *COMT* Met^{158} had a univariate odds ratio (OR) of 0.25 (95% CI [0.09–0.69], NR^2 11.0%) for the presence of PTSD (Table 2). Therefore, contrary to our initial hypothesis, *COMT* Met^{158} was associated with lower incidence of PTSD.

Given that *COMT* genotype unevenly distributed across racial subgroups, we next utilized multivariable regression for PTSD to control for the potential confounding influence of race. In the studied population, univariate analysis failed to show a statistically significant relationship between race and PTSD following mTBI ($p = 0.092$). When only the two largest racial groups were compared populations were compared (Caucasian and African American), African American race emerged as a predictor for PTSD with a univariable OR of 3.89 (95% CI [1.13–13.35]). However, only COMT genotype, but not African American racial background, remained a statistically significant predictor of PTSD when included in a multivariable model as evidenced by a multivariable OR of 0.29 (95% CI [0.10–0.83]) and 2.76 (95% CI [0.75–10.22]) for the *COMT* Met^{158} allele and African American race, respectively. Collectively, these data preliminarily suggest that the association of *COMT* and

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PTSD is not influenced by race, but larger future studies in more diverse populations are needed to confirm and/or refute these findings.

We next sought to determine whether controlling for established risk factors for PTSD, e.g., pre-existing psychiatric disease and substance abuse [2,53–55], would influence the observed association between *COMT* genotype and PTSD. Univariate analysis confirmed that pre-existing psychiatric disorder (OR 6.85, 95% CI [2.54–18.49], NR^2 22.6%) and substance abuse (OR 3.44, 95% CI [1.26–9.38], NR^2 8.6%) was associated with greater univariate odds of PTSD (Table 2). We also confirmed that there was no effect of interaction between *COMT* and preexisting psychiatric disorder on PTSD ($p = 0.195$). We then performed multivariable regression with PTSD as the response and COMT, preexisting psychiatric disorder, and substance abuse as predictors. In the multivariable model *COMT* Met^{158} remained a significant predictor of decreased odds of PTSD (OR 0.32, 95% CI [0.11–0.97]) after adjusting for pre-existing psychiatric disorder and illicit drug use. In the model, pre-existing psychiatric disorder associated with greater odds of PTSD (OR 5.17, 95% CI [1.80–14.89]) while drug use did not significantly associate with PTSD (Table 2). This model was statistically significant ($p = 8.1 \times 10^{-5}$) and explained 29.5% of the variability in PTSD – values higher than *COMT* Met^{158} or any pre-existing risk factor alone.

3.3. Functional outcome is associated with COMT and inversely related to PTSD

We next investigated whether an association exists between *COMT* Met^{158} carriers or Val^{158}/Val^{158} homozygotes and functional outcome following mTBI. For the 70 *COMT* Met^{158} carriers, 6%, 17%, 37%, and 40% were found to have GOSE scores of 5, 6, 7, 8, respectively. In comparison, 35%, 9%, 30% and 26% of the 23 *COMT* Val^{158}/Val^{158} homozygotes were found to have GOSE scores of 5, 6, 7, 8, respectively, which differed from Met^{158} carriers ($p = 0.008$) (Fig. 2). Univariate ordinal logistic regression showed that the presence of *COMT* Met^{158} allele was associated with an OR of 2.87 for higher GOSE scores (95% CI [1.20–6.86]) and explained 5.9% of the variance. Race was not a significant univariate predictor of GOSE ($p = 0.158$). After correcting for age (per-year increase: univariate OR 0.99, 95% CI [0.97–1.02]; multivariable OR 0.99, 95% CI [0.97–1.02]), and no GCS deficit (GCS 15: univariate OR 2.55 95% CI [1.00–6.57]; multivariable OR 2.68, 95% CI [1.03–6.94]), *COMT* Met^{158} remained a significant predictor of higher functional outcome on GOSE (OR 2.96, 95% CI [1.23–7.13], NR^2 6.2%).

Given the lower incidence of PTSD with *COMT* Met^{158}, we sought to determine whether the observed association between GOSE and *COMT* may in part be explained by the differences in the incidence of post-TBI PTSD between *COMT* Met^{158} carriers or Val^{158}/Val^{158} homozygotes. Overall, low GOSE scores were associated with a higher incidence of PTSD (Fig. 3A–C) Among all subjects and Met^{158} carriers a statistically significant increase in PTSD was observed with decreasing GOSE groups as reflected by *p*-values of 5.32×10^{-7} and 2.27×10^{-5}, respectively (Fig. 3A and B). Overall a similar trend was observed in Val^{158}/Val^{158} homozygotes (Fig. 3C), but this failed to reach statistical significance ($p = 0.087$). Collectively, this suggests that PTSD may influence functional outcome as previously described for other outcome metrics [57].

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To offer further support to this hypothesized relationship, we verified that PTSD is a univariate predictor of lower GOSE by ordinal logistic regression (OR 0.08, 95% CI [0.03–0.21]), and explains 30.6% of the variance in GOSE. We next performed a multivariable ordinal logistic regression with *COMT Met*^{158} and PTSD as predictors, and GOSE as the dependent variable, adjusting for age. The model was statistically significant ($p = 9.06 \times 10^{-7}$) and explained 32.8% of the variability in GOSE. Analysis confirmed that PTSD was associated with greater odds of lower GOSE score as evidenced by multivariable OR of 0.09 (95% CI [0.03–0.26]), but the association of *COMT* with global functional outcome was no longer statistically significant (multivariable OR 1.73, 95% CI [0.69–4.35]) (Table 3). These analyses suggest that PTSD is inversely associated with GOSE and may indirectly contribute to the association of COMT and GOSE following mTBI. However, the directionality of this relationship could not be conferred by the present analysis and future studies are needed to more clearly delineate the influences of PTSD on functional outcome.

4. Discussion

In the present study, we sought to investigate whether the *COMT Val*^{158}*Met* polymorphism is associated with PTSD and functional outcome following mild closed head injury in a predominately Caucasian population. We found that subjects with the *COMT Met*^{158} allele have lower rates of PTSD and better functional outcomes when compared to *Val*^{158}/*Val*^{158} homozygotes at 6-months following injury. Much of the effect on functional outcome may be related to differences in PTSD between *COMT* genotypes. How PTSD relates to outcome measures, such as GOSE, remains unclear and future studies addressing this issue are needed.

Prior reports examining the potential influence of the *COMT Val*^{158}*Met* polymorphism on long-term outcomes following TBI have been predominately restricted to measures of cognition in patients with predominantly moderate and severe TBI, with varying results [24–27]. Consistent with a potential deleterious role of *COMT Val*^{158}/ *Val*^{158} in TBI, homozygotes have been shown to have a greater number of perseverative errors following TBI [24,25]. More recently, no relationship between the *COMT Met*^{158}-*Val* genotype and cognitive performance was found; however, this study did not include measures of perseveration. The authors also failed to find an association between *COMT Val*^{158}*Met* polymorphism and functional outcome as measured by the GOSE at 12 and 24 months post-injury [27]. The source of this discrepancy with the present report is unclear. The incidence of PTSD is greatest following mTBI [31,34–36], and greater impairment of cognition or prolonged amnesia with more severe TBI may protect against development of subsequent PTSD [58]. Therefore, subjects with more severe injury as studied by Willmott et al., 2014, may not show similar outcome associations in the absence of PTSD. Whether this reflects differences in severity of injury in its entirety and/or trial design – namely interval of follow-up (6-months vs. 12- and 24-months) – or a combination thereof remains to be determined.

To the best of our knowledge, no prior reports have been published investigating the relationship between the *COMT Val*^{158}*Met* polymorphism and development of PTSD following head trauma. The rate of PTSD of 26.5% in this study is within the published range for mTBI [28–32]. The role of *COMT* in the development of PTSD following other

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forms of emotional and/or physical trauma remains unclear [21–23,59]. For example, in survivors of the Rwandan genocide, *COMT* Met^{158}/Met^{158} homozygotes demonstrated higher risk for PTSD independent of their traumatic load [21]. The *COMT* Met^{158} allele has also been associated with PTSD following urban violence [22]. However, these studies were conducted in an African and Brazilian population, respectively. It has recently been demonstrated that *COMT* $Val^{158}Met$ polymorphism exerts differential effects on risk of PTSD in children or different ethnic groups [20]; this suggests that different ethnic backgrounds and presumably heterogeneity of genetic modifiers therein modulates the effects of the *COMT* $Val^{158}Met$ polymorphism on genetic propensity for PTSD. Consistent with this principle, a study of predominately Caucasian veterans following deployment to Iraq failed to find an association between Met^{158}/Met^{158} and more prevalent PTSD, but did demonstrate that Met^{158}/Val^{158} heterozygotes developed fewer PTSD symptoms than either homozygous group [59]. Gene functions and associated phenotypic manifestations are modified through a complex interplay with environmental stimuli [6]. Therefore, whether the predominately Caucasian population, the nature and severity of traumatic event and/or combination thereof contribute to the potentially protective effect of the *COMT* Met^{158} allele following mTBI remains to be seen. We show that the association between *COMT* and PTSD following mTBI persists despite controlling for race. However, stratification of our population into racial groups showed a trend towards lower PTSD with the presence of the *COMT* Met^{158} allele in all racial groups, but failed to reach statistical significance which was in part likely the result of the small sample size of each racial group. Larger studies are therefore needed to fully delineate the potential modifying influence of ethnicity on behavioral and psychiatric associations with *COMT* $Val^{158}Met$ in the setting of head trauma.

The mechanism(s) through which *COMT* influences propensity to develop PTSD also remain unclear. In support of a potentially protective role of the *COMT* Met^{158} allele, a recent study has shown that *COMT* Val^{158}/Val^{158} homozygotes are associated with heightened reacquisition of fear from presumed alterations in reconsolidation of fearful memories [42]. Conversely, the *COMT* Met^{158} allele has been also been associated with impaired fear extinction in some, but not all studies [60,61], and may therefore increase propensity for PTSD development in other contexts. However, a detailed review of the hypothesized mechanisms is beyond the scope of the present study.

Although we designed our study with restrictive inclusion criteria, it is not without limitations. Our data was obtained for a relatively small sample size ($n = 93$) in a predominately Caucasian male population and did not conform to known HapMap Phase III subpopulations; therefore, the need for studies in larger and more diverse study populations cannot be overstated. 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 post-traumatic amnesia; thus, the generalizability of our results is limited. We pursued analyses designed to investigate a hypothesized relationship between the *COMT* $Val^{158}Met$ polymorphism and PTSD 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

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mechanisms through which the *COMT* molecular pathway may influence response and recovery to TBI.

4.1. Conclusions

The *COMT Val*^{158}*Met* polymorphism (rs4680) is associated with incidence of PTSD and functional outcome following isolated, uncomplicated mTBI. The *COMT Met*^{158} allele is associated with lower incidence of PTSD and improved functional outcome, and may exert a protective effect. However, larger studies in more diverse populations are needed to confirm the role of *COMT Met*^{158}*Val* in psychological health following mTBI. Whether *COMT Val*^{158}/*Val*^{158} homozygotes would benefit from heightened clinical surveillance and/or pharmacologic and behavior therapy targeted towards symptomatic manifestations of PTSD remain to be determined and should be the subject of future studies.

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Appendix

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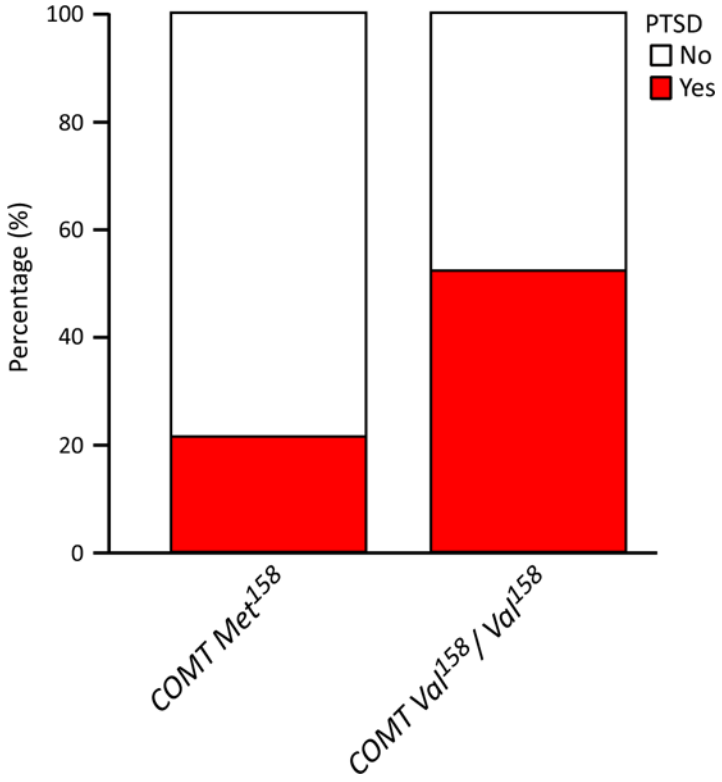

Fig. 1.

The *COMT Val*^{158}*Met* polymorphism is associated with lower prevalence of qualifying for screening criteria for post-traumatic stress disorder (PTSD) at 6-months following mild traumatic brain injury. White, did not meet PTSD qualification on screening criteria; red, met PTSD qualification on screening criteria. *COMT* = Catechol-O-Methyltransferase. red, met PTSD qualification on screening criteria.

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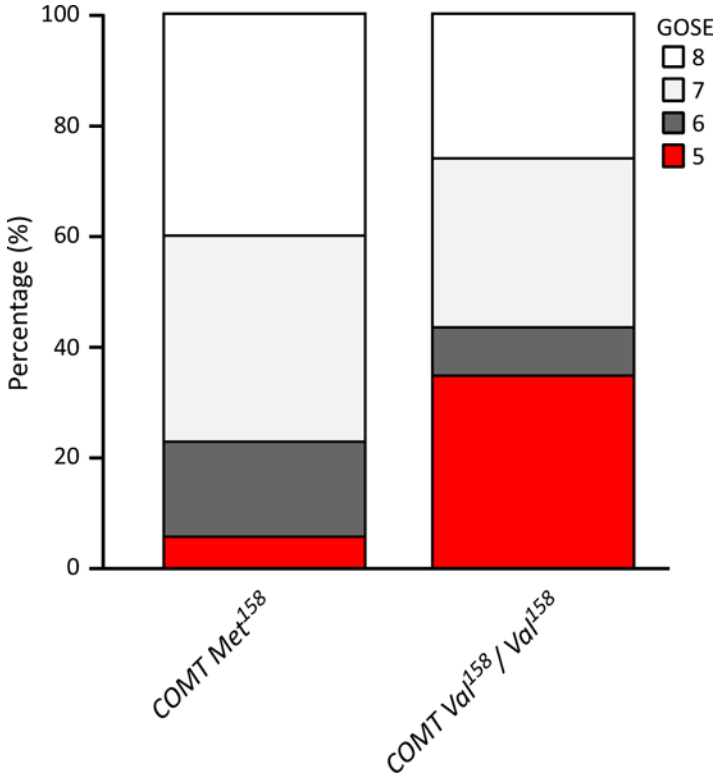

Fig. 2.

The *COMT Val*^{158}*Met* polymorphism is associated with greater global functional outcome as measured by the Glasgow Outcome Scale Extended (GOSE) at 6-months following mild traumatic brain injury. White, GOSE score of 8; light gray, GOSE score of 7; dark gray, GOSE score of 5; red, GOSE score of 5. *COMT* = Catechol-O-Methyltransferase.

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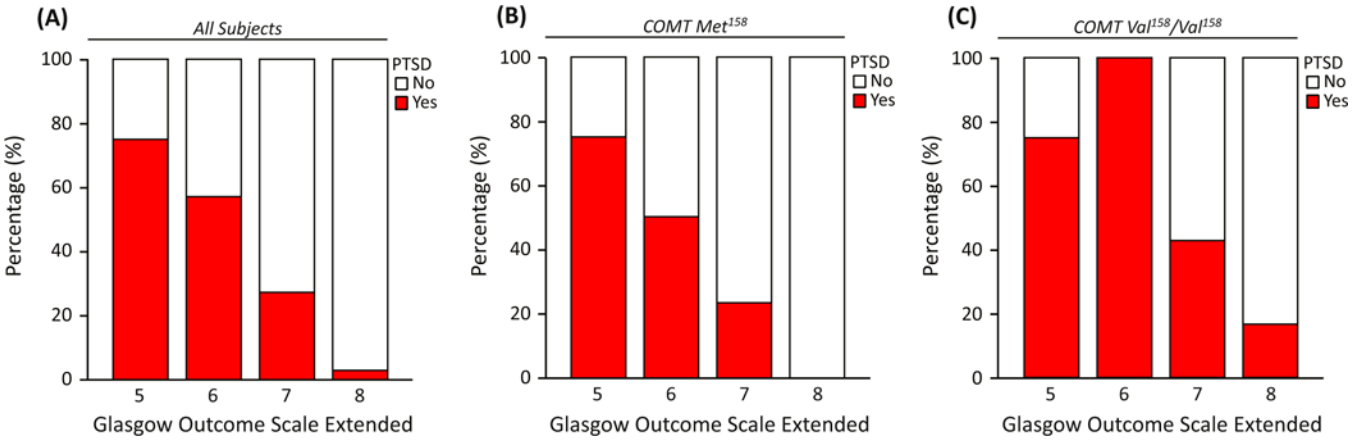

Fig. 3.

Global functional outcome is negatively associated with the presence of concomitant post-traumatic stress disorder at 6-months post-injury. (A–C) Graphs depicting proportion of individuals not meeting (white) or meeting (red) post-traumatic stress disorder (PTSD) screening criteria in all subjects (A), subjects with the *COMT Met*^{158} allele (B), and subjects with *COMT Val*^{158}*/Val*^{158} homozygosity (C). *COMT* = Catechol-O-Methyltransferase.

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Table 1

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

Variable	*Met*^{158} (*N* = 70)	*Val*^{158}/*Val*^{158} (*N* = 23)	Significance (*p*)
Age (y)			
Mean ± SD	40 ± 17	42 ± 14	0.682
Gender			
Male	42 (60%)	14 (61%)	0.941
Female	28 (40%)	9 (39%)	
Race			
Caucasian	52 (80%)	13 (20%)	0.032
African-American/African	6 (46%)	7 (54%)	
Other races	12 (80%)	3 (20%)	
Pre-existing psychiatric disorder			
No	47 (67%)	10 (44%)	0.043
Yes	23 (33%)	13 (56%)	
Substance abuse			
No	56 (80%)	15 (65%)	0.148
Yes	14 (20%)	8 (35%)	
Mechanism of injury			
Motor vehicle crash	22 (31%)	2 (9%)	0.140
Cyclist/pedestrian hit	15 (21%)	6 (26%)	
Fall	21 (30%)	8 (35%)	
Assault	8 (11%)	6 (26%)	
Struck by/against object	4 (6%)	1 (4%)	
ED arrival GCS			
13	1 (1%)	0 (0%)	0.817
14	12 (17%)	5 (22%)	
15	57 (81%)	18 (78%)	

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* = 6; *Met*^{158} = 5, *Val*^{158}/*Val*^{158} = 1), American Indian/Alaskan Native (*N* = 1; *Met*^{158} = 1), Hawaiian/Pacific Islander (*N* = 2; *Met*^{158} = 1, *Val*^{158}/*Val*^{158} = 1), and more than one race (*N* = 6; *Met*^{158} = 5, *Val*^{158}/*Val*^{158} = 1).

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Table 2

Univariate and multivariable statistical analysis of the association between the *COMT Val^{158}Met* polymorphism and a history of preexisting psychiatric disease or substance abuse with post-traumatic stress disorder (PTSD) at 6-months post-injury.

Predictor	Odds ratio (OR) [95% CI]	Predictor sig. (p)	Nagelkerke pseudo-R^2	Model sig. (p)
Univariate analysis				
COMT *Met^{158}*	0.25 [0.09–0.69]	0.006	11.0%	–
Preexisting psychiatric disorder	6.85 [2.54–18.49]	6.3×10^{-5}	22.6%	–
Substance abuse	3.44 [1.26–9.38]	0.016	8.6%	–
Multivariable analysis				
COMT *Met^{158}*	0.32 [0.11–0.97]	0.044	29.5%	8.1×10^{-5}
Preexisting psychiatric disorder	5.17 [1.80–14.89]	0.002	–	–
Substance abuse	1.88 [0.60–5.88]	0.281		

OR >1 represents greater odds of having six-month PTSD. CI = Confidence Interval; *COMT* = Catechol-O-Methyltransferase; OR = Odds Ratio; PTSD = post-traumatic stress disorder.

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Table 3

Univariate and multivariable statistical analysis of the association between the *COMT Val^{158}Met* polymorphism and post-traumatic stress disorder (PTSD) with global functional outcome (GOSE) at six months post-injury.

Predictor	Odds ratio (OR) [95% CI]	Predictor sig.(p)	Nagelkerke pseudo-R^2	Model sig. (p)
Univariate analysis				
COMT *Met^{158}*	2.87 (1.20–6.86)	0.018	5.9%	–
PTSD	0.08 [0.03–0.21]	3.62×10^{-7}	30.6%	–
Age (y)	0.99 [0.97–1.02]	0.499	0.5%	–
No GCS deficit	2.55 [1.00–6.57]	0.051	3.9%	–
Multivariable analysis				
COMT *Met^{158}*	1.73 [0.69–4.35]	0.243	32.8%	9.06×10^{-7}
PTSD	0.09 [0.03–0.26]	5.0×10^{-6}	–	–
Age (y)	1.00 [0.98–1.03]	0.723		
No GCS deficit	1.86 [0.69–5.01]	0.218		

OR >1 represents greater odds of higher six-month functional outcome score on GOSE. *COMT* = Catechol-O-Methyltransferase; CI = Confidence Interval; GOSE = Glasgow Outcome Scale Extended; OR = Odds Ratio; PTSD = post-traumatic stress disorder.