COMT Val158Met is Associated with Domain-specific Cognitive Impairment Following Mild Traumatic Brain Injury

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Introduction

Mild TBI is a cause of cognitive impairment which may be modulated by genetic susceptibility. MTBIs account for 70-90% of all TBI [1]. Most patients are reported to recover following MTBI [2], however, ~20% of patients experience cognitive and neuropsychiatric deficits [3]. Often individuals with similar injuries will manifest different symptoms and follow divergent clinical trajectories.

A common SNP in the coding sequence at codon 158 – COMT Val158Met (rs4680) – results in substitution of a methionine for valine [4]. This substitution lessens the activity of COMT resulting in higher levels of dopamine in the prefrontal cortex (PFC) [5]. It has been shown that Val158/Val158 individuals are up to four times more efficient at catabolizing catecholamines than Met158/Met158 [6]. In turn, higher bioavailability of catecholamines in the PFC in Met158/Met158 subjects has been shown to confer a cognitive advantage over Val158 [7], and the Met158 allele is generally associated with an advantage in measures of memory, executive function and tasks requiring attention [8]. A number of prior studies have suggested that disruption or dysregulation of dopaminergic transmission in the PFC may contribute to the pathogenesis of post-traumatic cognitive impairment [9]. Conversely, it has been suggested that the dopaminergic system may be pharmacologically targeted to ameliorate persistent cognitive deficits following TBI [10].

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 [11], to evaluate whether the COMT Val158Met polymorphism influences cognitive performance six-months following MTBI on a battery of three standardized tests -- Wechsler Adult Intelligence Scale Fourth Edition Processing Speed Index subscale (WAIS PSI), Trail Making Test (TMT) and the California Verbal Learning Test Second Edition (CVLT).

Methods

TRACK-TBI Pilot is a multicenter prospective observational study conducted at three Level I Trauma Centers in the U.S. Inclusion criteria were adults presenting to one of three Level 1 Trauma Center with external force trauma to the head and clinically indicated head CT scan within 24 hours of injury. Exclusion criteria were pregnancy, life-threatening diseases, incarceration, psychiatric hold, and non-English speakers. Subjects were enrolled through convenience sampling. Informed consent was obtained for all subjects prior to enrollment in the study either by

Results

Table 1. Demographic and Clinical Characteristics

Variable	Met^{158} (N=71)	Val^{158}/Val^{158} (N=22)	Sig. (*p*)
Age (y)			
Mean ± SD	41 ± 16	42 ± 14	0.831
Gender			
Male	44 (62%)	14 (64%)	0.888
Female	27 (38%)	8 (36%)	
Race			
Caucasian	52 (81%)	12 (19%)	
African-American/African	7 (50%)	7 (50%)	0.067
Other races	12 (80%)	3 (20%)	
Education (y)			
Mean ± SD	15 ± 3	13 ± 3	0.036
Mechanism of Injury			
Motor vehicle crash	22 (31%)	2 (9%)	
Cyclist/pedestrian hit	17 (24%)	5 (23%)	
Fall	22 (31%)	9 (41%)	0.090
Assault	7 (10%)	6 (27%)	
Struck by/against object	3 (4%)	0 (0%)	
ED Arrival GCS			
13	1 (1%)	0 (0%)	
14	15 (21%)	4 (18%)	0.999
15	55 (78%)	18 (82%)	

Results in 93 isolated uncomplicated mTBI subjects showed COMT genotype distribution was 29% Met158/Met158 (n=27), 47% Met158/Val158 (n=44) and 24% Val158/Val158 (n=22). Allelic frequencies (A=0.53, G=0.47) were not found to deviate from Hardy-Weinberg equilibrium (X2=0.241, p=0.887). COMT Met158 carriers had better nonverbal processing speed on WAIS PSI compared to Val158/Val158 (103.5±12.7; 93.2±17.8). Similarly, COMT Met158 subjects demonstrated superior mental flexibility as evidenced by decreased time of difference between the two independent trails - Trail-B minus Trail-A (TMT B-A) (44.0±36.8; 65.6±55.0). COMT Val158Met did not influence verbal learning on CVLT.

Thus COMT Met158 associates with improved processing speed (mean increase 10.3 points, 95% CI [3.5 to 17.1], p=0.004) and mental flexibility (mean decrease 21.6 seconds [1.4 to 41.8], p=0.037) on WAIS-PSI and TMT, respectively, when compared to Val158/Val158.

The association between the COMT Met158 allele and WAIS-PSI persists after controlling for effects of age and education (mean increase 8.0 points [1.4 to 14.7], p=0.019). The association between the COMT Met158 allele and TMT completion times demonstrated a statistical trend after controlling for age and education (mean decrease 16.1 seconds [-34.0 to 1.8], p=0.078). Older age and decreased education associate with impairment on WAIS-PSI and TMT independent of COMT.

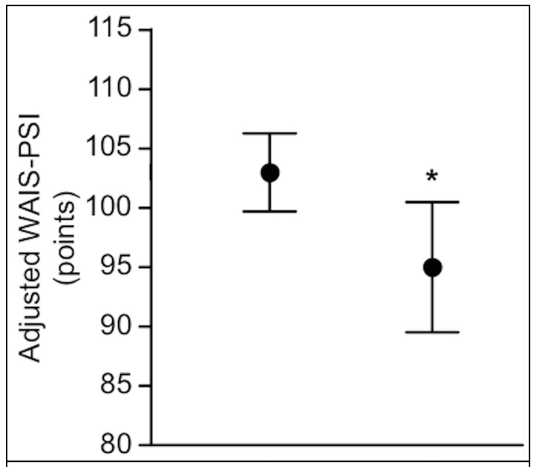
Tables and Figures

Table 2. Distribution of Outcome Measures

Outcome Measure	Met^{158} (N=71)	Val^{158}/Val^{158} (N=22)	Sig. (*p*)
WAIS Processing Speed Index†	103.5 ± 12.7	93.2 ± 17.8	0.004
TMT Trail B minus A Time‡	44.0 ± 36.8	65.6 ± 55.0	0.037
CVLT Trial 1-5 Standard Score	54.8 ± 11.2	53.2 ± 9.6	0.560

Figure 1. COMT Associates with 6-Month Processing Speed

Left: COMT Met158-carriers; Right: COMT Val158/Val158



Univariate analysis				
Predictor	***B* [95% CI]**	***F*-ratio**	**Sig. (*p*)**	**Effect Size**
COMT Met^{158}	10.3 [3.5, 17.1]	8.95	0.004	r = 0.300
Age (y)	-0.2 [-0.4, 0]	3.49	0.065	r = 0.192
Education (y)	1.8 [0.8, 2.8]	12.37	0.001	r = 0.346
Multivariable analysis				
Predictor	***B* [95% CI]**	***F*-ratio**	**Sig. (*p*)**	**Effect Size**
COMT Met^{158}	8.0 [1.4, 14.6]	5.72	0.019	$p\text{-}\eta^2$ = 0.060
Age (y)	-0.2 [-0.4, 0]	3.69	0.058	$p\text{-}\eta^2$ = 0.040
Education (y)	1.5 [0.5, 2.5]	9.11	0.003	$p\text{-}\eta^2$ = 0.093
Overall Model	---	7.66	1.3×10^{-4}	r = 0.453

Figure 2. COMT Trends with Executive Function/Flexibility

Univariate analysis				
Predictor	**B [95% CI]**	**F-ratio**	**Sig. (*p*)**	**Effect Size**
COMT Met^{158}	-21.6 [-41.8, -1.4]	4.51	0.037	r = 0.217
Age (y)	1.3 [0.8, 1.8]	25.87	2×10^{-6}	r = 0.470
Education (y)	-3.8 [-6.8, -0.8]	6.14	0.015	r = 0.251
Multivariable analysis				
Predictor	**B [95% CI]**	**F-ratio**	**Sig. (*p*)**	**Effect Size**
COMT Met^{158}	-16.1 [-34.0, 1.8]	3.18	0.078	$p\text{-}\eta^2$ = 0.035
Age (y)	1.3 [0.8, 1.8]	27.46	1×10^{-6}	$p\text{-}\eta^2$ = 0.236
Education (y)	-3.1 [-5.8, -0.4]	5.27	0.024	$p\text{-}\eta^2$ = 0.056
Overall Model	---	13.04	3.92×10^{-7}	r = 0.552

Discussion

There is physiological evidence in support of a potential modulatory role of the COMT Met158 allele in cognitive performance following TBI. The PFC is a key center for overall executive function, attention, and strategic planning [12], in which its rich dopaminergic pathways are more dependent on COMT for regulation and modulation at the synaptic cleft [4]. Prior studies have demonstrated that the COMT Val158Met SNP is associated with differences in cognitive performance in the absence of brain injury [6]. Given the absence of measures of pre-injury performance in our population, we cannot conclude whether our results reflect the maintenance of pre-existing cognitive differences between genotypes and/or an altered trajectory of recovery or impairment following MTBI.

Conclusion

The COMT Val158Met SNP (rs4680) is associated with nonverbal cognitive performance following isolated, uncomplicated MTBI. The Met158 allele is associated with improved performance in nonverbal processing speed and mental flexibility, while no associations were seen on verbal learning. Age and education are important predictors of post-traumatic cognitive performance following mild head trauma. Larger studies in similar populations will be of value to confirm the role of COMT Val158Met SNP in these domains, and to explore its effects in other cognitive domains following MTBI. Whether Val158/Val158 would benefit from heightened clinical surveillance or cognitive behavioral/pharmacologic therapy remains to be determined and may represent an important direction of future studies.

Learning Objectives

1. Identify the incidence and known risk factors of decreased cognitive performance following MTBI with an emphasis on the COMT Val158Met SNP.
2. Describe importance of a potential underlying relationship between COMT Val158Met and cognition following MTBI.
3. Discuss the specific associations between COMT Val158-Met and domains of cognitive performance following MTBI.

References

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