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DRD2 C957T polymorphism is associated with improved 6-month verbal learning following traumatic brain injury

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Abstract

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The TRACK-TBI Investigators are listed in the Appendix in alphabetical order by last name.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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.

Traumatic brain injury (TBI) often leads to heterogeneous clinical outcomes, which may be influenced by genetic variation. A single-nucleotide polymorphism (SNP) in the dopamine D2 receptor (*DRD2*) may influence cognitive deficits following TBI. However, part of the association with *DRD2* has been attributed to genetic variability within the adjacent ankyrin repeat and kinase domain containing 1 protein (*ANKK1*). Here, we utilize the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) study to investigate whether a novel *DRD2 C957T* polymorphism (rs6277) influences outcome on a cognitive battery at 6 months following TBI—California Verbal Learning Test (CVLT-II), Wechsler Adult Intelligence Test Processing Speed Index Composite Score (WAIS-PSI), and Trail Making Test (TMT). Results in 128 Caucasian subjects show that the rs6277 T-allele associates with better verbal learning and recall on CVLT-II Trials 1–5 (T-allele carrier 52.8 ± 1.3 points, C/C 47.9 ± 1.7 points; mean increase 4.9 points, 95% confidence interval [0.9 to 8.8]; $p = 0.018$), Short-Delay Free Recall (T-carrier 10.9 ± 0.4 points, C/C 9.7 ± 0.5 points; mean increase 1.2 points [0.1 to 2.5]; $p = 0.046$), and Long-Delay Free Recall (T-carrier 11.5 ± 0.4 points, C/C 10.2 ± 0.5 points; mean increase 1.3 points [0.1 to 2.5]; $p = 0.041$) after adjusting for age, education years, Glasgow Coma Scale, presence of acute intracranial pathology on head computed tomography scan, and genotype of the *ANKK1* SNP rs1800497 using multivariable regression. No association was found between *DRD2 C947T* and non-verbal processing speed (WAIS-PSI) or mental flexibility (TMT) at 6 months. Hence, *DRD2 C947T* (rs6277) may be associated with better performance on select cognitive domains independent of *ANKK1* following TBI.

Keywords

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

Introduction

Traumatic brain injury (TBI) is a significant source of morbidity and mortality—an estimated 2.5 million cases occur annually in the USA alone [1]. Initial injury severity is commonly stratified into severe, moderate, and mild TBI categories as defined by an initial Glasgow Coma Scale (GCS) score of 8 or less, 9 to 12, and 13 to 15, respectively [2, 3]. Individuals with similar injuries often follow divergent clinical trajectories [4]. Up to 5.3 million people live with long-term disability from TBI, and numerous others experience persistent TBI-related sequelae—including cognitive deficits, changes in personality, and increased rates of post-traumatic psychiatric disorders such as depression and/or post-traumatic stress disorder [5, 6]. However, factors influencing variability in post-traumatic clinical course remain unclear and efforts are needed to better identify those at greatest risk for post-traumatic sequelae [7].

Studies have begun to suggest that genetic variability—such as single-nucleotide polymorphisms (SNPs)—may be one factor which contributes to observed clinical variance. A number of polymorphisms influencing protein structure, function, and/or availability have been identified [8–11]. In particular, SNPs arising within the dopaminergic system may influence cognition and cognitive recovery following TBI [12]. The neurotransmitter dopamine is essential for proper neuronal function of the striate nucleus linked to learning

and memory [13]. One important molecular component of dopaminergic signaling pathways is the dopamine D2 receptor (DRD2), which is highly expressed in the striatum of the subcortical forebrain. DRD2 binds to dopamine in the synaptic cleft and initiates post-synaptic secondary messenger cascades, which modulate neuronal circuits contributing to several cognitive domains, namely learning [14]. Reduced DRD2 expression has been linked to cognitive impairment and psychiatric disease [15, 16]. Furthermore, stimulation of DRD2 in the striatum has been shown to potentiate learning when treated with a D2-specific agonist [13, 17].

Given the prevalence of cognitive defects in TBI patients, there is an interest in identifying SNPs that associate with poor cognitive outcome [13, 18]. The *DRD2* gene is located on chromosome 11 q22–23 with a relatively common SNP located within exon 7 with a single-nucleotide cytosine to thymine substitution—known as the *C957T* SNP rs6277 [19, 20]. This substitution has been associated with decreased affinity of the striatal D2 receptors [21] and is associated with better learning, verbal memory, and cognitive ability in the psychiatry literature [22–24]. Initial studies report a potential connection between *DRD2 C957T* and cognitive performance following TBI [13, 15, 18]. However, this observation may be confounded by linkage effects with ankyrin repeat and kinase domain containing 1 protein (*ANKK1 TaqIA* (*rs1800497*))—a gene adjacent to and oriented tail to tail with *DRD2* on chromosome 11 [13, 25]. Therefore, a potential modulatory role of *DRD2 C957T* on cognitive performance remains unclear and warrants further investigation.

For the current analysis, we utilized data from the prospective multicenter Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Pilot study in order to explore associations between the *DRD2 C957T* SNP and cognitive outcomes post-TBI while controlling for *ANKK1 TaqIA* [26]. We demonstrate that the *DRD2 C957T* allele is associated with better performance on verbal memory but not processing speed or mental flexibility at 6 months post-TBI.

Methods

Study design

The TRACK-TBI Pilot Study is a multicenter prospective observational study conducted at three level I trauma centers in the USA—San Francisco General Hospital, University of Pittsburgh Medical Center, and University Medical Center Brackenridge (UMCB) in Austin, TX—using the National Institutes of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS) common data elements (CDEs) [26–30]. Inclusion criteria for the pilot study were adult 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. Exclusion criteria were pregnancy, comorbid life-threatening disease, incarceration, 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 association of the *DRD2 C957T* polymorphism on cognitive outcome after TBI uncomplicated by massive intracranial injury, neurosurgical intervention, or polytrauma. Therefore, our analysis was restricted to a subset of adult patients with Marshall CT Score 1–2; no acute neurosurgical intervention; no developmental delay; and no severe, critical, or

unsurvivable extracranial injuries as defined by an Abbreviated Injury Scale (AIS) score >3 in any extracranial body region. Due to the small numbers and unequal distribution of *DRD2 C957T* genotypes in other races in our sample, all selected patients were of Caucasian race.

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 [30]. 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 K₂-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 [29]. DNA was extracted from isolated leukocytes using the Wizard® Genomic DNA Purification Kit as described by the manufacturer (Promega, Madison, WI). The *DRD2 C957T* (rs6277) and *ANKK1 TaqIA* (rs1800497) polymorphisms were genotyped using the TaqMan® SNP Genotyping Assay as described by the manufacturer (Applied Biosystems, Carlsbad, CA; rs6277 Assay ID# C__11339240_10; rs1800497 Assay ID# C__7486676_10). For the purposes of evaluating a potential protective benefit of the *DRD2 C957T* T-allele, C/T and T/T individuals were combined as a single group as previously described for *DRD2 C957T* [13, 22, 23]. Therefore, for data recording and all figures, this group is referred to as *DRD2 C957T*-Present. Likewise, *ANKK1 TaqIA* genotype was dichotomized by T-allele carriers versus non-carriers as described previously [13].

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.” To evaluate for neuropsychological impairment, all participants underwent outcome assessment 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.

California Verbal Learning Test, second edition—The California Verbal Learning Test (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 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 as previously described [31, 32]. The CVLT-II Trial 1–5

raw score provides a global index of verbal learning ability [33]. Further, lower scores on the CVLT-II Short-Delay Free Recall (SDFR) indicate retroactive interference, while lower scores on the CVLT-II Long-Delay Free Recall (LDFR) indicate the occurrence of rapid forgetting. As outlined, all CVLT raw scores are adjusted for age and years of education as part of the current analysis [33].

Wechsler Adult Intelligence Scale, fourth edition, Processing Speed Index

Subscale—The Wechsler Adult Intelligence Test Processing Speed Index Composite Score (WAIS-PSI) is composed of two non-verbal tasks (symbol search and coding) which require visual attention and motor speed [34]. The composite score, normalized for age, was used in this analysis. On this test, a higher score reflects improved non-verbal processing speeds. In prior versions of this test, WAIS III, TBI has demonstrated that the WAIS-PSI predominately reflects impairment in perceptual processing speed with a small component attributable to working memory and only minimal contribution from motor speed [35]. The WAIS-PSI composite score includes adjustment for age and thus is adjusted only for years of education as part of the current analysis [34].

Trail Making Test—The Trail Making Test (TMT) is a two-part timed test (TMT-A and TMT-B). TMT-A assesses visual processing, and TMT-B assesses mental flexibility and processing speed [36]. In order to increase the accuracy of the score with respect to the flexibility and processing speed without accounting for visual processing, we subtracted the first trial from the second trial (TMT B-A) as previously described [37]. On this test, a lower score suggests improved performance. The TMT B minus A score is adjusted for age and years of education as part of the current analysis [36].

Statistical analysis

Descriptive variables are presented as means and standard deviations (SDs) for continuous variables and as proportions for categorical variables. Group differences in patient demographics and injury characteristics across *DRD2 C957T* genotypes 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 for differences in categorical variables with individual cell counts ≤ 5 . Linear regression was performed to assess the univariate association between *DRD2 C957T* genotype and each of the five outcome measures, adjusted for age and education years for CVLT measures and TMT B-A, and for education years only for WAIS-PSI, as described in the respective "Methods" section previously. Multivariable linear regression was performed to adjust for *ANKK1 TaqIA* genotype, gender, post-traumatic amnesia, emergency department admission GCS, and intracranial pathology on initial head CT scan for each outcome measure. The adjusted means and standard errors (SE) are reported for *DRD2 C957T* genotypes, and the adjusted mean differences (*B*) and their associated 95% confidence intervals (CI) are reported for predictors in each regression analysis. 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).

Results

Demographic and injury characteristics

In total, 128 subjects were included in the current analysis (Table 1). The majority were male (64%) and all self-identified as Caucasian. Mean age was 44.4 ± 16.4 years, and mean years of education were 14.3 ± 2.7 . Mechanisms of injury included fall (50%), motor vehicle accident (25%), pedestrian versus automobile (13%), assault (10%), and struck by object (2%). Mean GCS was 13.5 ± 3.2 . Injury severity by admission GCS was 85% mild, 5% moderate, and 10% severe TBI. Thirty-two percent of patients did not have post-traumatic amnesia, while 56% had positive amnesia and 12% were unknown. Thirty-eight percent of patients showed positive intracranial pathology on initial head CT. *DRD2 C947T*(rs6277) was distributed with the following *ns*: C/C = 42, C/T = 58, and T/T = 28 (C-allele frequency 0.55, T-allele frequency 0.45), conforming to the Hardy-Weinberg equilibrium ($X^2 = 0.88$, $p > 0.05$) and known Caucasian-European (CEU) HapMap distribution (C-allele frequency 0.53, T-allele frequency 0.47). No statistically significant differences were observed for any demographic or clinical descriptor across *DRD2 C957T* genotypes (Table 1). *ANKK1 TaqIA* (rs1800497) was distributed with the following *ns*: C/C = 79, C/T = 42, and T/T = 7 (C-allele frequency 0.78, T-allele frequency 0.22), conforming to the Hardy-Weinberg equilibrium ($X^2 = 0.20$, $p > 0.05$) and known CEU HapMap distribution (C-allele frequency 0.81, T-allele frequency 0.19). The *ANKK1 TaqIA* polymorphism distributed differently across *DRD2 C957T*; 26/86 (30%) of *DRD2 C957T* T-allele carriers, versus 23/42 (55%) of *DRD2 C/C* individuals, carried the *ANKK1 T*-allele ($p = 0.007$); the lower concurrent inheritance of *DRD2 C957T* T-allele and the *ANKK1 TaqIA* T-allele is consistent with prior reports [25, 38].

DRD2 C957T is associated with verbal memory but not processing speed or mental flexibility

We first sought to characterize whether the *DRD2 C957T* polymorphism was associated with global or domain-specific differences in 6-month cognitive performance. *DRD2 C957T* T-allele carriers were found to perform better on CVLT-II Trials 1–5 (mean increase 4.4 points, 95% CI [0.4 to 8.5], $p = 0.033$); a non-significant statistical trend was found for CVLT-II Short-Delay Free Recall (mean increase 1.1 points, 95% CI [−0.1 to 2.4], $p = 0.073$) and Long-Delay Free Recall (mean increase 1.1 points, 95% CI [−0.1 to 2.4], $p = 0.083$). No differences were found for TMT B-A ($B = -13.6$, 95% CI [−31.3 to 4.1], $p = 0.131$) or WAIS-PSI ($B = 1.3$, 95% CI [−4.2 to 6.8], $p = 0.639$) (Table 2). These data suggest that the *DRD2 C957T* polymorphism is not associated with a global improvement in cognitive performance, but rather a specific performance advantage with tasks of verbal learning and recall.

DRD2 C957T is associated with verbal memory after multivariable correction

We next sought to evaluate whether the association between the *DRD2 C957T* polymorphism and CVLT-II performance persisted after adjusting for known predictors of outcome after TBI. For each of the five outcome measures, *DRD2 C957T* was entered into a multivariable model including *ANKK1 TaqIA* genotype, gender, presence/absence of post-

traumatic amnesia, admission GCS, and presence/absence of intracranial pathology on CT in addition to age and education years.

On multivariable analysis of CVLT-II Trials 1–5, the *DRD2* T-allele is associated with improved performance compared to non-carriers as evidenced by a mean increase of 4.9 points (95% CI [0.9 to 8.8], $p = 0.018$) (Table 3). Male gender showed a mean decrease of 4.0 points (95% CI [−7.8 to −1.1], $p = 0.044$), and CT-positive patients had a mean decrease of 5.8 points (95% CI [−10.0 to −1.6], $p = 0.007$). *ANKK1* genotype, post-traumatic amnesia, and admission GCS did not show significant associations with CVLT-II Trials 1–5.

On multivariable analysis of CVLT-II Short-Delay Free Recall, the *DRD2* T-allele showed a significant association with improved performance (mean increase 1.2 points, 95% CI [0.1 to 2.5], $p = 0.046$). CT pathology was the only other significant multivariable predictor (mean decrease 1.7 points, 95% CI [−3.0 to −0.4], $p = 0.011$) (Table 3).

On multivariable analysis of CVLT-II Long-Delay Free Recall, the *DRD2* T-allele showed a significant association with improved performance (mean increase 1.3 points, 95% CI [0.1 to 2.5], $p = 0.041$). CT pathology was the only other significant predictor (mean decrease 2.0 points, 95% CI [−3.3 to −0.7], $p = 0.002$) (Table 3).

DRD2 C957T is not associated with processing speed or mental flexibility after multivariable correction

As previously demonstrated (Table 2), no significant differences were observed between the *DRD2* C957T polymorphism and TMT B-A or WAIS-PSI. To confirm the lack of confounder effects, we utilized a similar multivariable approach for TMT B-A and WAIS-PSI (Table 4). On multivariable analysis, a non-significant statistical trend was observed for *DRD2* C957T T-carriers on TMT B-A (mean decrease −16.2 s, 95% CI [−34.6 to 2.2], $p = 0.084$), while no other predictors showed a significant association. No significant association was observed on WAIS-PSI for *DRD2* T-allele carriers (mean increase 1.1 points, 95% CI [−4.6 to 6.9], $p = 0.700$) or any other predictor, and only admission GCS showed a non-significant statistical trend (per-unit increase of 0.8 points, 95% CI [−0.1 to 1.7], $p = 0.093$). These data confirm that the *DRD2* C957T polymorphism does not associate with 6-month performance on metrics of nonverbal processing speed or mental flexibility.

Discussion

In the present study, we investigated whether the *DRD2* C957T polymorphism was associated with cognitive performance 6 months following TBI. We show that the *DRD2* C957T polymorphism was associated with better performance on the components of the CVLT but was not the WAIS-PSI or the TMT. The CVLT assesses a patient's ability to store new information and is understood to be a gauge of verbal and working memory [33, 39]. Thus, our results suggest that the *DRD2* C957T polymorphism is *specifically* associated with better verbal and working memory post-TBI and does not offer benefit for processing speed and/or mental flexibility. The identification of a potential association with *DRD2* and cognitive outcome after TBI and the specificity of the effect for verbal and working memory are both novel insights advanced by this work.

Previous efforts to associate *DRD2* with altered cognitive performance have been promising but inconclusive. In 2005, a study found an association between *DRD2* SNPs and altered cognitive performance in a post-TBI population [18]. However, these results were confounded by the influence of a nearby gene, *ANKK1* [13]. It was not known if *DRD2* is independently associated with long-term altered cognitive performance in a post-TBI population. Here, we analyzed subjects' cognitive performance at 6 months after TBI and controlled for the effects of *ANKK1*. The 6-month time point allowed us to measure long-term cognitive outcome after TBI and not be overly influenced by transient changes in cognition that occur during the recovery period, which usually completes 3 months after injury [40, 41]. As noted previously, we found that *DRD2* genotype was associated with cognitive differences at 6 months when the *ANKK1* effects were included in the multivariate regression. Thus, these data support the idea that *DRD2 C957T* may be an independent predictor of cognitive outcome after TBI.

A recent study by Failla et al. conducted in 108 severe TBI patients investigating rs6279, a gene with considerable linkage disequilibrium with rs6277, suggests that differences attributable to the *DRD2 C957T* polymorphism may not be maintained at 12 months [42]. Our findings showing an advantage of *DRD2 C957T* at 6 months raise questions as to whether *C957T* carriers may endure an altered trajectory of recovery and experience delayed recovery sometime within the 6–12-month interval. It also may suggest that the cognitive deficits are not altogether permanent. An alternative explanation is that the severity of the injury could interact with cognitive recovery. Specifically, the work by Failla et al. focused on severe TBI subjects of all races with positive intracranial pathology on CT that received treatment from a level I trauma center, whereas our data included data from all TBI patients of Caucasian race, with a mixture of CT pathology [42]. The resolving deficit in Failla et al. could be due to the extensive treatments that this cohort offered and may not be generalizable to all TBI patients [42].

Establishing that the *DRD2* polymorphism is associated with cognitive outcome after TBI also may explain the variability in response to dopamine therapy after TBI. Indeed, there have been six randomized controlled trials examining the role of amantadine and/or bromocriptine (both dopamine-enhancing agents) in cognitive recovery after TBI; the results have not shown a consistent benefit of dopamine agents in cognitive recovery and are often discordant [43]. However, here, we show that the presence of *DRD2* polymorphisms may influence cognitive recovery after TBI, and it is very likely that the effect of dopamine agents will be heavily influenced on their presence as well as those of related polymorphisms in dopaminergic catabolic biochemical pathways—such as catechol-o-methyltransferase. Thus, we recommend that future studies examining dopamine agents as a treatment for TBI stratify patients based on the presence of the *DRD2* genotype, which may clarify the role of dopamine therapy in TBI.

Aside from establishing a potential association between *DRD2* and cognitive outcome after TBI, we also show that *DRD2 C957T* may specifically associate with improved verbal and working memory. This specificity is important because it shows that *DRD2* genotype likely does not enhance global cognitive ability, such as attention and awareness, which may covary with many different cognitive outcomes. Instead, there may be a specific link

between *DRD2* and verbal and working memory. This link can be explained by the fact that the D2 dopamine receptor has enriched expression in the basal ganglia, a region important in learning and memory [44]. Furthermore, dopaminergic neurons in the basal ganglia (substantia nigra pars compacta) project directly to the prefrontal cortex and the hippocampus, regions that have been heavily implicated in working and verbal memory, respectively [45].

Limitations

Our results provide a link between the genetic, neuroscience, and psychological markers of cognitive dysfunction after TBI. However, there are a number of caveats that should be mentioned. First, although it has been speculated that patients' genotypes can alter the magnitude dopamine expression and dopamine binding, which could change the course of their recovery [46], other studies have shown that *C957T* is associated with increased risk for some neuropsychiatric diseases [25, 47]. Therefore, it is not clear if different *DRD2* genotypes confer a baseline difference in CVLT performance or if they signify altered performance after TBI. Second, our sample consisted exclusively of Caucasian patients, and consequently, our findings may not generalize to the population as a whole. Third, we only considered patients' GCS score when producing our multivariable models. These models, therefore, did not factor in possible disparate courses of prior medications, post-injury medical treatment, or rehabilitative therapy. Furthermore, we were limited by a relatively small sample size of 128 patients without controls. While the NINDS CDE outcome domains are generally distinct, the possible overlap across cognitive symptomatology attributable to *DRD2 C957T* will benefit from a rigorous case-control study adequately powered to adjust for a range of comparisons. We were also constrained to specifications of the NINDS CDE version 1, which were limited to 6 months post-injury; as cognitive deficits following TBI may change with time after injury, an analysis tracking the trajectory of recovery for *DRD2 C957T* variants constitutes an important future direction. Lastly, the true effect of *DRD2* variants is difficult to establish due to presumed gene-gene interactions. The genetic variation in *DRD2* genes may interact with effects induced by other genes important for cognitive recovery.

Conclusions

The *DRD2 C957T* polymorphism (rs6277) is associated with verbal memory performance at 6 months following TBI independent of the *ANKK1 TaqIA* polymorphism (rs1800497), while no associations were seen on measures of non-verbal processing speed or mental flexibility, in a sample of Caucasian patients. Larger studies in more diverse populations will be necessary to confirm the influence of *DRD2 C957T* in these and other outcome domains following TBI. Whether a subgroup of patients with the *DRD2 C957T* polymorphism may benefit from closer clinical surveillance or targeted dopaminergic therapies remains to be determined and constitutes an important direction for future research.

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Appendix

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Table 1Demographic and clinical characteristics of included patients, by *DRD2 C957T* genotype

Variable	Overall (N = 128)	T-Present (N = 86)	T-Absent (N = 42)	Sig. (p)
Age (years)				
Mean, SD	44.4 ± 16.4	45.1 ± 16.7	43.1 ± 15.9	0.527
Gender				
Male	82 (64%)	57 (66%)	25 (60%)	0.455
Female	46 (36%)	29 (34%)	17 (40%)	
Education (years)				
Mean, SD	14.3 ± 2.7	14.4 ± 2.8	14.0 ± 2.7	0.460
Mechanism of injury				
Motor vehicle crash	32 (25%)	22 (26%)	10 (24%)	0.964
Pedestrian versus auto	26 (13%)	11 (13%)	5 (12%)	
Fall	64 (50%)	42 (49%)	22 (54%)	
Assault	13 (10%)	8 (9%)	5 (12%)	
Struck by	2 (2%)	2 (2%)	0 (0%)	
Post-traumatic amnesia				
No	41 (32%)	30 (35%)	11 (26%)	0.371
Yes	72 (56%)	48 (56%)	24 (57%)	
Unknown	15 (12%)	8 (9%)	7 (17%)	
ED arrival GCS				
Mean, SD	13.5 ± 3.2	13.6 ± 3.2	13.4 ± 3.3	0.756
Severe (3–8)	13 (10%)	10 (12%)	3 (7%)	
Moderate (9–12)	6 (5%)	1 (1%)	5 (12%)	
Mild (13–15)	109 (85%)	75 (87%)	34 (81%)	
CT intracranial pathology				
No	79 (62%)	54 (63%)	25 (60%)	0.721
Yes	49 (38%)	32 (37%)	17 (40%)	
<i>ANKK1 TaqIA</i> genotype				
T-Present	49 (38%)	26 (30%)	23 (55%)	0.007
T-Absent	79 (62%)	60 (70%)	19 (45%)	

All distributions are reported as column percentages

CT computed tomography, *DRD2* dopamine receptor D2, *ED* emergency department, *GCS* Glasgow Coma Scale, *SD* standard deviation

Table 2
Adjusted univariate analysis of 6-month cognitive performance, by *DRD2 C957T* genotype

Outcome measure	T-Present (N = 86)	T-Absent (N = 42)	B [95% CI]	F-ratio	Sig. (p)
CVLT-II Trials 1–5 ^a	52.1 (1.2)	47.6 (1.7)	4.4 [0.4, 8.5]	4.66	0.033
CVLT-II Short-Delay Free Recall ^a	10.8 (0.4)	9.7 (0.5)	1.1 [–0.1, 2.4]	3.27	0.073
CVLT-II Long-Delay Free Recall ^a	11.5 (0.4)	10.4 (0.5)	1.1 [–0.1, 2.4]	3.06	0.083
TMT Trail B minus A time ^b	49.5 (5.1)	63.1 (7.3)	–13.6 [–31.3, 4.1]	2.31	0.131
WAIS-PSI composite score ^a	100.5 (1.6)	99.2 (2.3)	1.3 [–4.2, 6.8]	0.22	0.639

Distributions are reported as mean ± standard error of the raw score for each cognitive measure, adjusted for age and education years for CVLT-II Trials 1–5, Short-Delay Free Recall, Long-Delay Free Recall, and TMT; WAIS-PSI composite score is adjusted for education years, as it is already normed for age

CVLT/California Verbal Learning Test, TMT/Trail Making Test, WAIS-PSI/Wechsler Adult Intelligence Scale, Fourth Edition Processing Speed Index

^aHigher scores suggest improved performance
^bLower scores suggest improved performance

Table 3
Multivariable analysis of 6-month verbal memory performance by *DRD2 C957T* genotype

Predictor	T-Present	T-Absent	B [95% CI]	F-ratio	Sig. (p)
CVLT-II Trials 1-5					
<i>DRD2 C957T</i>	52.8 ± 1.3	47.9 ± 1.7	4.9 [0.9, 8.8]	5.78	0.018
<i>ANKK1 TaqIA</i>	51.5 ± 1.6	49.3 ± 1.4	2.2 [-1.7, 6.0]	1.26	0.264
Gender (male)	-	-	-4.0 [-7.8, -1.1]	4.13	0.044
Post-traumatic amnesia (+)	-	-	-2.6 [-6.7, 1.6]	1.51	0.221
ED admission GCS (per unit)	-	-	-0.1 [-0.8, 0.5]	0.15	0.699
CT intracranial pathology (+)	-	-	-5.8 [-10.0, -1.6]	7.46	0.007
CVLT-II Short-Delay Free Recall					
<i>DRD2 C957T</i>	10.9 ± 0.4	9.6 ± 0.5	1.3 [0.1, 2.5]	4.06	0.046
<i>ANKK1 TaqIA</i>	10.6 ± 0.5	9.9 ± 0.4	0.7 [-0.5, 1.9]	1.40	0.239
Gender (male)	-	-	-0.8 [-2.0, 0.4]	1.67	0.198
Post-traumatic amnesia (+)	-	-	-0.5 [-1.8, 0.8]	0.64	0.426
ED admission GCS (per unit)	-	-	0.0 [-0.2, 0.2]	0.18	0.676
CT intracranial pathology (+)	-	-	-1.7 [-3.0, -0.4]	6.74	0.011
CVLT-II Long-Delay Free Recall					
<i>DRD2 C957T</i>	11.5 ± 0.4	10.2 ± 0.5	1.3 [0.1, 2.5]	4.29	0.041
<i>ANKK1 TaqIA</i>	11.3 ± 0.5	10.5 ± 0.5	0.8 [-0.3, 2.0]	1.97	0.163
Gender (male)	-	-	-0.8 [-2.0, 0.4]	1.70	0.195
Post-traumatic amnesia (+)	-	-	-0.2 [-1.4, 1.1]	0.05	0.817
ED admission GCS (per unit)	-	-	0.1 [-0.1, 0.2]	0.24	0.622
CT intracranial pathology (+)	-	-	-2.0 [-3.3, -0.7]	9.70	0.002

Distributions are reported as mean ± standard error of the raw score for each cognitive measure by *DRD2 C957T* and *ANKK1 TaqIA* genotypes, adjusted for age and education years. The mean difference (*B*) is presented as the increase or decrease of the denoted category from the reference category for gender (male vs. female), post-traumatic amnesia (positive vs. negative), admission GCS (per-unit increase), and CT intracranial pathology (positive vs. negative). Higher scores suggest improved performance

CT computed tomography, CVLT/California Verbal Learning Test, Second Edition, ED/emergency department, GCS/Glasgow Coma Scale

Table 4
Multivariable analysis of 6-month mental flexibility and non-verbal processing speed performance by *DRD2 C957T* genotype

Predictor	T-Present	T-Absent	B [95% CI]	F-ratio	Sig. (p)
TMT Trail B minus A					
<i>DRD2 C957T</i>	48.8 ± 6.0	65.0 ± 7.9	-16.2 [-34.6, 2.2]	3.03	0.084
<i>ANKK1 Tag1A</i>	51.8 ± 7.2	62.0 ± 6.5	-10.2 [-27.8, 7.5]	1.30	0.257
Gender (male)	-	-	-8.8 [-26.6, 9.0]	0.96	0.329
Post-traumatic amnesia (+)	-	-	-5.9 [-25.0, 13.3]	0.37	0.545
ED admission GCS (per unit)	-	-	0.5 [-2.5, 3.5]	0.12	0.733
CT intracranial pathology (+)	-	-	-7.7 [-27.0, 11.5]	0.63	0.429
WAIS-PSI composite score					
<i>DRD2 C957T</i>	100.4 ± 1.9	99.3 ± 2.4	1.1 [-4.6, 6.9]	0.15	0.700
<i>ANKK1 Tag1A</i>	99.8 ± 2.2	100.0 ± 2.0	-0.2 [-5.8, 5.3]	0.01	0.931
Gender (male)	-	-	0.7 [-4.8, 6.3]	0.07	0.792
Post-traumatic amnesia (+)	-	-	0.0 [-6.0, 5.9]	0.00	0.997
ED Admission GCS (per unit)	-	-	0.8 [-0.1, 1.7]	2.87	0.093
CT intracranial pathology (+)	-	-	0.9 [-5.0, 6.8]	0.10	0.758

Distributions are reported as mean ± standard error of the raw score for each cognitive measure by *DRD2 C957T* and *ANKK1 Tag1A* genotypes, adjusted for age and education years for TMT Trail B minus Trail A and adjusted for education years for WAIS-PSI as it is already normed for age. The mean difference (B) is presented as the increase or decrease of the denoted category from the reference category for gender (male vs. female), post-traumatic amnesia (positive vs. negative), admission GCS (per-unit increase), and CT intracranial pathology (positive vs. negative). Lower scores on TMT suggest improved performance. Higher scores on WAIS-PSI suggest improved performance

CT computed tomography, ED emergency department, GCS Glasgow Coma Scale, TMT Trail Making Test, WAIS-PSI Wechsler Adult Intelligence Scale, Fourth Edition Processing Speed Index