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Research Article

Brain-derived neurotrophic factor Val66Met and neuropsychological functioning after early childhood traumatic brain injury

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Abstract

Objective: The present study examined the differential effect of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism on neuropsychological functioning in children with traumatic brain injury (TBI) relative to orthopedic injury (OI).
Methods: Participants were drawn from a prospective, longitudinal study of children who sustained a TBI ($n = 69$) or OI ($n = 72$) between 3 and 7 years of age. Children completed a battery of neuropsychological measures targeting attention, memory, and executive functions at four timepoints spanning the immediate post-acute period to 18 months post-injury. Children also completed a comparable age-appropriate battery of measures approximately 7 years post-injury. Parents rated children's dysexecutive behaviors at all timepoints.
Results: Longitudinal mixed models revealed a significant allele status × injury group interaction with a medium effect size for verbal fluency. Cross-sectional models at 7 years post-injury revealed non-significant but medium effect sizes for the allele status x injury group interaction for fluid reasoning and immediate and delayed verbal memory. Post hoc stratified analyses revealed a consistent pattern of poorer neuropsychological functioning in Met carriers relative to Val/Val homozygotes in the TBI group, with small effect sizes; the opposite trend or no appreciable effect was observed in the OI group.
Conclusions: The results suggest a differential effect of the BDNF Val66Met polymorphism on verbal fluency, and possibly fluid reasoning and immediate and delayed verbal memory, in children with early TBI relative to OI. The Met allele—associated with reduced activity-dependent secretion of BDNF—may confer risk for poorer neuropsychological functioning in children with TBI.

Keywords: Clinical outcomes; Cognition; Genetics; Head injury; Pediatric; Neuroplasticity

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Introduction

Moderate to severe traumatic brain injury (TBI) in childhood is often associated with acute and chronic neuropsychological impairments, with demonstrated ramifications for adaptive, academic, and social functioning. At the group level, children with more severe injuries, younger age at injury, lower socioeconomic status (SES), poorer premorbid functioning, and less optimal family environmental contexts tend to be at greatest risk for long-term neuropsychological deficits (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005; Donders & Kim, 2019; Ewing-Cobbs et al., 1997; Max et al., 2005; Narad et al., 2016; Treble-Barna et al., 2016; Yeates et al., 2005). Despite these known predictors, there remains substantial unexplained heterogeneity in neuropsychological outcomes after pediatric TBI. Individual genetic variability is emerging as a novel additional source of heterogeneity in outcomes after TBI that may influence the brain's response to injury, including recovery and repair processes (Kurowski et al., 2019; Zeiler et al., 2018). Examination of the influence of genetic predisposition on neuropsychological recovery after pediatric TBI holds potential to move the field towards precision medicine, improving prognostic accuracy and allowing for earlier identification of children at greatest risk for long-term impairment.

The emerging literature examining genetic variation in association with clinical outcomes after TBI is focused on the effects of *apolipoprotein E (APOE)*, genes involved in expression of monoamine neurotransmitters, cytokines, and mitochondrial proteins, as well as *brain-derived neurotrophic factor* (BDNF; Zeiler et al., 2018). The *BDNF* gene is an especially promising candidate gene for examination in

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TBI because of its role in both response to injury and neurocognitive and behavioral reserve—both of which are biologic processes enriched with genetic variants implicated in clinical outcomes of TBI (Kurowski et al., 2017). BDNF is a neurotrophic growth factor that is released from pre- and post-synaptic neurons after neuronal activity. Because it is synthesized as pro-BDNF and subsequently cleaved to mature BDNF, pro-BDNF and mature BDNF function antagonistically in regulating neuroplasticity (Lee, Kermani, Teng, & Hempstead, 2001). Pro-BDNF has pro-apoptotic function, activating pathways involved in apoptosis, reduction of dendritic complexity, and neuronal long term depression (Finan, Udani, Patel, & Bailes, 2018; Teng et al., 2005; Yang et al., 2014), whereas mature BDNF has pro-survival function, activating pathways involved in cell survival, dendrite formation, and long-term potentiation (Atwal, Massie, Miller, & Kaplan, 2000; Dijkhuizen & Ghosh, 2005; Finan et al., 2018; Patterson et al., 1996). A single nucleotide polymorphism (SNP) producing a valine-to-methionine substitution at codon 66 (Val66Met; rs6265) in the *BDNF* gene is associated with reduced activity-dependent secretion of BDNF (Egan et al., 2003). While findings have been somewhat mixed (Harrisberger et al., 2014; Hong, Liou, & Tsai, 2011; Notaras, Hill, & Van Den Buuse, 2015), Val66Met allele status, and especially possession of the Met allele, has been associated with variation in brain structure and function, including smaller brain volumes (Kawasaki et al., 2021; Nemoto et al., 2006; Pezawas et al., 2004; Szeszko et al., 2005) and lower connectivity (Park et al., 2017; Ueda et al., 2020), poorer neuropsychological functioning (Kambeitz et al., 2012; Toh, Ng, Tan, Tan, & Chan, 2018), and greater risk for a multitude of psychiatric and neurological conditions, in non-brain-injured individuals (Brown, Vickers, Stuart, Cechova, & Ward, 2020; Notaras et al., 2015).

Clinical studies evaluating the role of *BDNF* genetic variation in TBI have produced mixed results, with findings appearing to be moderated by age and injury severity. In studies of adults with mild TBI, results are generally consistent with those in non-brain-injured individuals, with Met allele carriers showing poorer behavioral and neuropsychological outcomes (Gabrys, Dixon, Holahan, & Anisman, 2019; Narayanan et al., 2016; Wang et al., 2018). Studies in older adults with more severe TBI, however, have shown a protective effect of the Met allele on TBI outcomes (Barbey et al., 2014; Krueger et al., 2011), though this effect may be moderated by age (Failla, Conley, & Wagner, 2016; Failla et al., 2015). The Met allele was similarly protective in a recent cohort of children studied at 6 months after mild TBI, with carriers having fewer internalizing problems (Gagner, Tuerk, De Beaumont, Bernier, & Beauchamp, 2020) and better quality of life (Tuerk et al., 2020). In contrast, in the present cohort, we recently observed a differential effect of Val66Met allele status in children with mostly moderate to severe TBI relative to children with orthopedic injuries (OI), such that the Met allele conferred risk for poorer longitudinal behavioral adjustment in children with TBI but not in children with OI (Treble-Barna et al., 2021). To our knowledge, no studies have yet examined the influence of *BDNF* Val66Met on neuropsychological outcomes after pediatric TBI. The present study builds on our prior work in this same cohort (Treble-Barna et al., 2021) by examining performance-based measures of neuropsychological functioning and caregiver ratings of executive function rather than parent-report measures of behavioral adjustment. Prior research in pediatric TBI and other pediatric neurological conditions has shown that neuropsychological and behavioral outcomes are associated with family environmental factors to varying degrees, with behavioral outcomes often being more sensitive to such factors compared to neuropsychological outcomes (Breslau, 1995; Taylor et al., 2008; Yeates, Taylor, Walz, Stancin, & Wade, 2010). The relative sensitivity of behavioral versus neuropsychological outcomes to genetic factors is less well understood.

The primary aim of the present study was to examine the differential effect of the *BDNF* Val66Met polymorphism on neuropsychological functioning in children who sustained early childhood TBI relative to children who sustained OI but no brain injury. The inclusion of an OI comparison group is a strength of our study design that allows for differentiation of genetic effects specific to TBI recovery from potential premorbid genetic differences. We hypothesized that *BDNF* Met allele carriers would have poorer neuropsychological functioning and that this association would be moderated by injury type (e.g., TBI vs. OI), with more pronounced effects within the TBI relative to the OI group. The neuropsychological outcomes examined focus on attention, memory, and executive functions due to their vulnerability to the effects of pediatric TBI. Because executive functions are both highly vulnerable to injury and important for children's ongoing development, special emphasis was placed on measures of this domain.

Methods

Participants

Participants were drawn from the prospective, longitudinal Ohio Head Injury Outcomes (OHIO) study, which examined children who sustained a TBI or OI between 3 and 7 years of age. Participants were recruited from three tertiary care children's hospitals and one tertiary care general hospital in Ohio. Inclusion criteria were overnight hospitalization for traumatic injury (TBI or OI), no evidence of child abuse as the cause of the injury, no history of prior TBI, documented neurological problems, or developmental delays pre-injury, and English as the primary language spoken in the home. TBI severity was determined using the lowest post-resuscitation Glasgow Coma Scale (GCS) score and clinically obtained neuroimaging findings. Severe TBI was defined as a GCS score $\leq$8. Moderate TBI was defined as a GCS score of 9–12 with or without abnormal neuroimaging (moderate TBI) or a higher GCS score with abnormal neuroimaging as defined by an intracranial or parenchymal injury or depressed skull fracture (complicated mild TBI). Mild TBI was defined as a GCS score $\geq$13 without abnormal neuroimaging. Children in the OI group sustained a bone fracture (not including skull fractures), had an overnight hospitalization, and did not exhibit alterations in consciousness or other signs or symptoms of head trauma or brain injury. The study was completed in accordance with Helsinki Declaration, approved by the institutional review boards at each of the participating medical centers, and informed consent was obtained from participating caregivers.

Neuropsychological outcome measures

Participants completed research assessments at a total of six follow-up visits, including the immediate post-acute period (0–3 months after injury; visit 1); 6, 12, and 18 months post-injury (visits 2–4); and ~3.5 and ~7 years post-injury (visits 5 and 6). The same performance-based neuropsychological measures were administered at visits 1–4. The fifth visit involved only mail-in parent-report measures. Because participants were significantly older at visit 6, different age-appropriate performance-based measures of similar neuropsychological constructs were administered. Neuropsychological constructs, associated measures, and scores analyzed are shown in Table 1. Lower scores indicate poorer

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Table 1. Neuropsychological performance-based measures and scores analyzed by study visit

Construct	Visits 1–4 measure	Description	Visits 1–4 scores analyzed	Visit 6 measures	Description	Visit 6 scores analyzed
Working memory	DAS Recall of Digits	Child repeats increasingly longer strings of digits	Age-adjusted *T* score	TEA-Ch Code Transmission	Child listens to a series of single digit numbers while attempting to recall the numbers immediately preceding two consecutive "5s"	Age- and sex-adjusted scaled score
Inhibitory control	Shape School	Child names colors or shapes of cartoon "pupils" and is then asked to name the color of some pupils but not others	Efficiency scores from conditions: (1) inhibition; (2) switching; (3) both inhibition and switching	TEA-Ch Walk/ Don't Walk	Child marks footprints on a path in response to a "go" tone and inhibits marking in response to a "stop" tone	Age- and sex-adjusted scaled score
Verbal fluency	NEPSY Word Generation	Child names as many animals and foods/drinks as possible in 60 s	Semantic total age-adjusted scaled score	D-KEFS Letter Fluency condition of the Verbal Fluency test	Child says as many words beginning with a designated letter as possible in 60 s across three trials	Age-adjusted scaled score
Immediate verbal memory	WJ-III Story Recall	Child recalls a series of brief stories immediately following their presentation	Age-adjusted standard score	Verbal Paired Associates—Immediate Recall	The examiner reads 8 word pairs (4 easy word pairs and 4 hard word pairs) to the child. The child attempts to recall the words paired with the ones read by the examiner immediately following their presentation.	Raw score
Delayed verbal memory				Verbal Paired Associates—Delayed Recall	The examiner reads 8 word pairs (4 easy word pairs and 4 hard word pairs) to the child. The child attempts to recall the words paired with the ones read by the examiner after a delay.	Raw score
Attentional control				TEA-Ch Creature Counting	Child counts a series of creatures in either forward or backward order according to up or down cues	Age- and sex-adjusted scaled scores for (1) total correct; (2) timing
Planning and problem solving				TOL-DX-2	Child moves beads on his/her tower board to match the layout of the examiner's board by making the fewest number of moves possible	Total Correct age-adjusted standard score
Fluid reasoning				WASI Matrix Reasoning	Child selects visual stimuli to complete a visual matrix based on their similarity with other stimuli in the matrix	Age-adjusted *T* score

Note. A Developmental NEuroPSYchological Assessment (NEPSY; Korkman, Kirk, & Kemp, 1998); Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001); Differential Ability Scales (DAS; Elliott, 1990); Shape School (Espy, 1997); Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999); Tower of London-Drexel, Second Edition (TOL-DX-2; Culbertson & Zillmer, 1998); Verbal Paired Associates (Gonzalez, Anderson, Wood, Mitchell, & Harvey, 2007); Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999); Woodcock-Johnson Tests of Achievement, Third Edition (WJ-III; Woodcock, McGrew, & Mather, 2001).

neuropsychological function for all measures. While most measures are commonly used in pediatric neuropsychological practice, the Shape School and Verbal Paired Associates measures are described in previous papers from our group (Ganesalingam et al., 2011; Treble-Barna, Zang, et al., 2017).

In addition to performance-based measures, parents completed the age-appropriate version of the Behavior Rating Inventory of Executive Functioning (BRIEF) (Gioia, Isquith, Guy, Kenworthy, & Baron, 2000) at all visits, the first of which involved retrospective recall of the child's executive functioning prior to injury to control for pre-injury differences in child functioning. The BRIEF is a standardized rating scale on which parents report the frequency of children's dysexecutive behaviors. *T*-scores on the General Executive Composite (GEC) Scale were used as the dependent variable. Higher *T*-scores indicate more dysexecutive behaviors, with *T*-scores 65 or greater indicating clinically elevated problems.

DNA collection and genotyping

DNA was collected from saliva samples and purified using Oragene OG-500 self-collection tubes (DNA Genotek, Ottawa, Canada). The HumanExome v1.1 Bead Chip (Illumina, San Diego, CA) was used to perform genotyping using the Illumina iScan system to identify the *BDNF* rs6265 SNP. Genotypes were AA (methionine/methionine homozygote), GA (valine/methionine heterozygote), and GG (valine/valine homozygote). Consistent with prior *BDNF* val66met studies and to preserve power, we used a dominant model combining individuals with GA and AA genotypes into one group of Met allele carriers based on seminal studies demonstrating that the presence of just one copy of the *BDNF* Met allele leads to decreased activity-dependent BDNF secretion (Chen et al., 2004). Principal component analysis was employed to confirm European and African continental ancestry, which aligns with self-reported White and Black race, using 200 validated ancestry informative markers and HapMap genotypic data from individuals of known ancestry as referent groups. Concordance with self-reported race was >95%. Results of analyses were similar when including only participants of European ancestry; therefore, both ancestral groups were retained to preserve power and to be more inclusive of diverse populations (Peterson et al., 2019). Self-reported race was used as a covariate in analyses

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to control for any differences in allele frequency or linkage disequilibrium (LD) patterns relating to ancestry, as well as the association of race with neuropsychological performance (Olson & Jacobson, 2015).

Statistical analysis

All statistical analyses were conducted using SAS 9.4 (SAS, Cary, NC), except computation of conditional R^2 for mixed models, which was performed in R 4.0.2 (https://www.r-project.org). Prior to analyses, outcome scores 4 SDs above the sample mean were winsorized to 4SD ($n = 1$ score for 1 participant) to reduce the potential influence of outliers. For group comparisons, *t*-tests, chi-square, or Fisher's exact tests were employed.

Because some child outcomes were collected longitudinally and some at only one study visit (visit 6 measures), we used two approaches. For neuropsychological outcomes collected longitudinally (visits 1–4 for performance-based measures and visits 1–6 for the BRIEF), we examined genetic associations with outcome by injury group using longitudinal mixed models including all available time points while accounting for the within-subject correlation with an unstructured covariance random effect. Because longitudinal mixed models do not require complete data for all participants, participants with only a subset of study visits were retained. We examined the association of the *BDNF* rs6265 polymorphism (Met carriers vs. Val/Val homozygotes) with each score on neuropsychological measures and the moderating effect of injury group (TBI vs. OI) on these associations (e.g., allele status × injury group interaction). The three-way interaction of allele status × injury group × time was not examined due to insufficient power. Mixed models included random intercepts, slopes, and subjects. Random slopes were modeled across time. Socioeconomic status (SES; defined by averaging sample *Z* scores for maternal education and median census tract income (Yeates et al., 2010) was tested as a covariate in base models without allele status and then trimmed if $p > .10$. Time since injury was covaried in all mixed models except for the Shape School models, in which age at each visit was instead covaried because these were raw scores rather than age-adjusted scores; we did not covary both age and time since injury in the Shape School models to avoid multicollinearity. The child's pre-injury functioning as assessed at the immediate post injury visit was covaried in the BRIEF model. Self-reported race (dichotomized as White versus African) was covaried in all models. Conditional R^2 for mixed models were examined in R using function "r2_nakagawa" from the Performance package. Conditional R^2 describes the proportion of variation accounted for by both fixed and random effects (Nakagawa & Schielzeth, 2013). To understand interaction effects involving injury group, we plotted least square means for dependent variables for each group by allele status to visualize the direction of effects and conducted post-hoc stratified mixed models within each injury group.

For neuropsychological outcomes collected only at visit 6, we examined genetic associations with outcome by injury group using cross-sectional general linear models, including the allele status × injury group interaction. SES was tested as a covariate in base models without allele status and then trimmed if $p > .10$. Age was covaried in models of Verbal Paired Associates because these were raw scores rather than age-adjusted scores. Self-reported race was covaried in all models. Proportion of variance accounted for by cross-sectional models was examined using η^2.

To provide effect size estimates, we standardized all continuous variables ($M = 0, SD = 1$) other than age and time since injury prior to analyses and obtained parameter estimates based on the final model for each dependent variable. The resulting coefficients are akin to standardized regression coefficients for continuous predictors and to standardized mean differences (e.g., Cohen's *d*) for categorical variables. Because standardized regression coefficients can be scaled to correlations (Cohen, 1988), we used conventional definitions of effect size to characterize the magnitude of standardized parameter estimates for continuous predictors (i.e., 0.1 is small, 0.3 is medium, and 0.5 is large). Likewise, we used conventional definitions of effect size for mean differences to characterize the magnitude of parameter estimates for categorical predictors and any interactions involving them (i.e., 0.2 is small, 0.5 is medium, 0.8 is large).

We recognize that the number of tests performed may result in an inflated type 1 error rate in the absence of corrections for multiple testing. The Bonferroni correction, which is often used for genetic association studies, assumes that multiple tests are independent of each other. Because our outcomes are not independent, we used the Dubey/Armitage-Parmar procedure (Sankoh, Huque, & Dubey, 1997) to identify an appropriate correlation-adjusted Bonferroni correction. For longitudinal models, the overall correlation between the seven outcomes was 0.13 yielding a multiple testing threshold for statistical significance of $\alpha = 0.007$. For cross-sectional models, the overall correlation was 0.27 between the 9 models, yielding a multiple testing threshold for statistical significance of $\alpha = 0.012$. However, because the probability of detecting interaction effects in non-experimental research designs is low (McClelland & Judd, 1993) and to limit type II error in this exploratory study, we also considered results of interactions of allele status by injury group with nominal significance ($p < .05$) or at least medium effect sizes (e.g., ≥0.5 for interactions) noteworthy and further explored these in post-hoc analyses.

Results

Sample description

Of the 221 participants enrolled in the original study, 217 were eligible for the final study visit at which DNA samples were collected. We successfully re-established contact with 163 participants, 142 of whom provided DNA samples. More detailed attrition data for the total sample is reported elsewhere (Narad et al., 2019, 2016). Participants with genetic data did not differ significantly from those without genetic data in demographic characteristics or on various study measures, as previously reported (Treble-Barna, Wade, et al., 2017). Of those with genetic data, 141 of 142 participants had covariate and outcome data for at least one outcome visit to be included in the present analyses. Ten had mild TBI, 43 had complicated mild to moderate TBI, 16 had severe TBI, and 72 had OI. The TBI and OI groups were comparable in race, sex, age at injury, age at assessment, and SES, and differed by mechanism of injury (Table 2). Descriptive data for the neuropsychological measures are provided in Supplemental Table 1. Injury group comparisons between the various neuropsychological measures with appropriate covariates have been reported previously (Ganesalingam et al., 2011; Gerrard-Morris et al., 2010; Narad et al., 2017; Taylor et al., 2008; Treble-Barna, Zang, et al., 2017).

The *BDNF* rs6265 SNP did not violate Hardy–Weinberg equilibrium. No significant differences in genotype distribution or Met allele status were found between the TBI and OI groups (Table 2). TBI severity groups were also comparable for

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Table 2. Demographic, outcome, and Val66Met characteristics by injury group

		OI $n = 72$	TBI $n = 69$	p
Sex, *n* (%)				.541
	Male	35 (48.6)	30 (43.5)	
	Female	37 (51.4)	39 (56.4)	
Race, *n* (%)				.268
	White	56 (53.8)	48 (46.2)	
	Non-White	16 (43.2)	21 (56.8)	
Age at injury in years, *M* (*SD*)		5.20 (1.1)	5.22 (1.2)	.885
Mechanism of injury, *n* (%)				<.001
	Road traffic accident	11 (15.3)	28 (40.6)	
	Fall	23 (31.9)	32 (46.4)	
	Recreational	38 (52.8)	9 (13.0)	
zSES, *M* (*SD*)		0.11 (0.94)	-0.15 (0.97)	.105
Val66Met genotype				.631
	AA, *n* (%)	3 (4.2)	3 (4.3)	
	AG, *n* (%)	25 (34.7)	19 (27.5)	
	GG, *n* (%)	44 (61.1)	47 (68.1)	
Val66Met Met carriers, *n* (%)		22 (31.9)	28 (38.9)	.385

TBI = traumatic brain injury; *M* = mean; OI = orthopedic injury; *SD* = standard deviation; zSES = socioeconomic status *Z* score.

Met allele status (Fisher's exact test $p = .104$; Met allele carriers, mild = 1, moderate = 13, severe = 8).

Longitudinal mixed models

Table 3 shows results of longitudinal mixed models testing the allele status x injury group interactions. Of the seven models, the allele status x injury group interaction was statistically significant for NEPSY Word Generation with a medium effect (standardized estimate = 0.72, $p = .007$). No other allele status × injury group interactions were nominally significant or of at least medium effect size. These results suggest a differential effect of Met carrier status on longitudinal verbal fluency between the TBI and OI groups.

Figure 1 plots least square means for NEPSY Word Generation for each group by allele status and Table 4 provides results of post-hoc stratified models. Met carriers in the TBI group had poorer verbal fluency relative to Val/Val homozygotes, with a small effect (standardized estimate = −0.39, $p = .039$); whereas the opposite trend was observed in the OI group, though the effect was small and nonsignificant (standardized estimate = 0.28, $p = .162$).

Cross-sectional general linear models

Table 5 shows results of cross-sectional general linear models testing the allele status x injury group interactions for measures administered at visit 6 only. Of the nine models, the allele status x injury group interaction was not statistically or nominally significant in any model; however, models for WASI Matrix Reasoning (standardized estimate = -0.63, $p = .074$), Verbal Paired Associates—Immediate Recall (standardized estimate = −0.46, $p = .209$), and Verbal Paired Associates—Delayed Recall (standardized estimate = −0.55, $p = .131$) showed non-significant medium effects for the allele status × injury group interaction and were further explored in post-hoc analyses.

Figure 1 plots least square means for each group by allele status and Table 6 provides results of post-hoc stratified models.

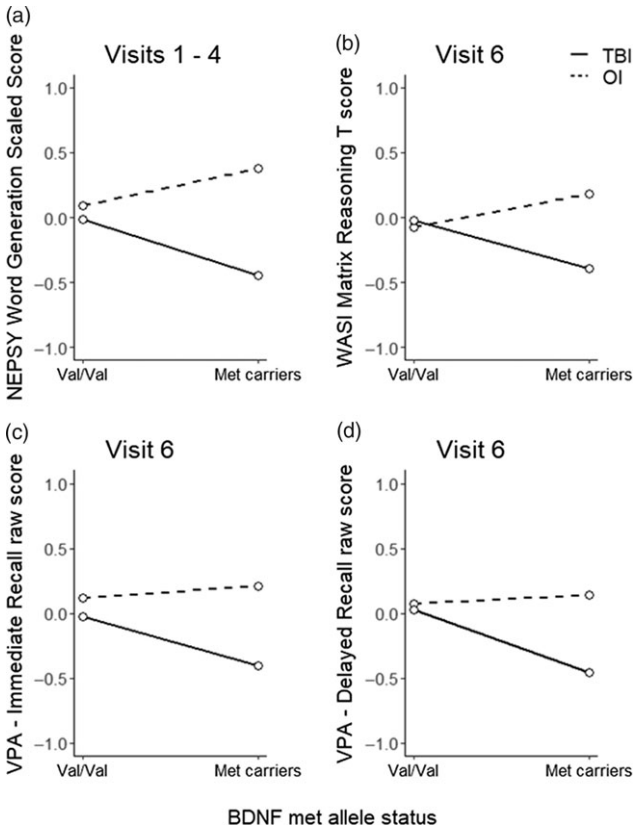

Figure 1. Least square means for dependent variables by injury group and allele status for significant and non-significant trend allele status x injury group interactions. BDNF, brain-derived neurotrophic factor; NEPSY, A Developmental NEuroPSYchological Assessment; OI, orthopedic injury; TBI, traumatic brain injury; VPA, Verbal Paired Associates; WASI, Wechsler Abbreviated Scale of Intelligence.

Although Met carriers in the TBI group tended to have poorer fluid reasoning (standardized estimate = −0.34, $p = .268$), immediate verbal memory (standardized estimate = 0.32, $p = .310$), and delayed verbal memory (standardized estimate = 0.42, $p = .198$) relative to Val/Val homozygotes, these within group effects were small and non-significant. In contrast, in the OI group, allele status had a small non-significant effect on fluid reasoning in the opposite direction relative to TBI and no effect on immediate verbal memory (standardized estimate = 0.03, $p = .899$) or delayed verbal memory (standardized estimate = 0.00, $p = .990$).

Discussion

The present study investigated the differential effect of the *BDNF* Val66Met polymorphism on neuropsychological functioning in children who sustained early TBI relative to children who sustained OI. Longitudinal mixed model analyses revealed a significant allele status × injury group interaction with a medium effect for verbal fluency, and cross-sectional models revealed medium but non-significant allele status × injury group interactions for fluid reasoning and immediate and delayed verbal memory. These effects were over and above the effects of covariates, which included race, SES, and time since injury or age, depending on the model. Post-hoc analyses of the notable interactions suggested a consistent pattern of poorer neuropsychological functioning in Met carriers relative to Val/Val homozygotes in the TBI group, with small effects that reached statistical significance for verbal fluency but not for fluid reasoning or verbal

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Table 3. Results of longitudinal mixed models testing the allele status × injury group interaction

Dependent variable	Parameter	Conditional R^2	Standardized estimate	Lower 95% CI	Upper 95% CI	*p*
DAS recall of digits		0.76				
	Race		−0.08	−0.43	0.27	.657
	zSES		0.30	0.14	0.45	<.001
	Time since injury		0.11	0.04	0.19	.003
	Allele status		0.17	−0.24	0.58	.409
	Injury group		−0.57	−1.04	−0.10	<.001
	Allele status × Injury group		−0.04	−0.63	0.54	.886
Shape school inhibition		0.57				
	Race		0.21	−0.03	0.45	.091
	zSES		0.21	0.10	0.32	<.001
	Age		0.66	0.57	0.75	<.001
	Allele status		0.16	-0.12	0.43	.268
	Injury group		-0.07	-0.31	0.16	.535
	Allele status x Injury group		−0.23	−0.63	0.16	.250
Shape school switch		0.61				
	Race		0.21	−0.06	0.48	.129
	zSES		0.15	0.03	0.27	.017
	Age		0.71	0.61	0.81	<.001
	Allele status		−0.07	−0.38	0.24	.671
	Injury group		−0.26	−0.52	0.00	.052
	Allele status × Injury group		−0.14	0.60	0.32	.547
Shape school both		0.59				
	Race		0.38	0.10	0.65	.007
	zSES		0.15	0.03	0.27	.017
	Age		0.75	0.65	0.86	<.001
	Allele status		0.03	−0.27	0.34	.832
	Injury group		−0.19	−0.45	0.07	.156
	Allele status x Injury group		0.08	−0.37	0.54	.719
NEPSY word generation		0.51				
	Race		−0.16	−0.46	0.15	.324
	zSES		0.25	0.11	0.39	<.001
	Time since injury		0.13	0.02	0.23	.022
	Allele status		−0.29	−0.65	0.07	.117
	Injury group		−0.82	−1.23	−0.41	.499
	Allele status x Injury group		***0.72***	***0.20***	***1.23***	***.007***
WJ-III story recall		0.60				
	Race		0.23	−0.10	0.55	.178
	zSES		0.24	0.10	0.39	.001
	Time since injury		0.04	−0.06	0.14	.443
	Allele status		−0.12	−0.50	0.26	.543
	Injury group		−0.56	−1.00	−0.12	.080
	Allele status × Injury group		0.27	−0.28	0.82	.332
BRIEF		0.71				
	Premorbid function		0.56	0.46	0.67	<.001
	Race		−0.27	−0.50	−0.04	.024
	Time since injury		0.03	0.01	0.04	.005
	Allele status		−0.09	−0.37	0.19	.515
	Injury group		0.34	0.11	0.58	.005
	Allele status × Injury group		0.38	−0.03	0.78	.069

TBI = traumatic brain injury; OI = orthopedic injury; zSES = socioeconomic status *Z* score.
Allele status × injury group interactions with $p < .007$ (correlation-adjusted Bonferroni correction for multiple testing threshold) are bolded.
Allele status × injury group interactions with at least medium effect sizes (*e.g.* ≥0.5) are italicized.

Table 4. Results of longitudinal mixed models post-hoc stratified analyses

Dependentvariable	Injury group	Parameter	Conditional R^2	Standardized estimate	Lower 95% CI	Upper 95% CI	*p*
NEPSY word generation	TBI		0.48				
		Race		−0.30	−0.70	0.10	.143
		zSES		0.32	0.14	0.50	.001
		Time since injury		0.10	−0.05	0.26	.178
		Allele status		**−0.40**	**−0.76**	**−0.02**	**.039**
NEPSY word generation	OI		0.5				
		Race		0.01	−0.46	0.49	.951
		zSES		0.17	−0.04	0.38	.118
		Time since injury		0.15	−0.00	0.31	.056
		Allele status		0.28	−0.11	0.67	.162

OI = orthopedic injury; TBI = traumatic brain injury; zSES = socioeconomic status *Z* score.
Allele status effects with $p < .05$ are bolded and with at least medium effect sizes (*e.g.* ≥0.5) italicized.

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Table 5. Results of cross-sectional general linear models testing the allele status × injury group interaction

Dependent variable	Parameter	η^2	Standardized estimate	Lower 95% CI	Upper 95% CI	*p*
TEA-Ch walk/do not walk		0.05				
	Race	0.00	0.03	−0.39	0.45	.905
	zSES	0.02	0.16	−0.03	0.35	.110
	Allele status	0.00	0.06	−0.43	0.56	.804
	Injury group	0.02	−0.14	−0.55	0.28	.523
	Allele status × Injury group	0.01	−0.33	−1.04	0.38	.360
D-KEFS letter fluency		0.10				
	Race	0.00	−0.23	−0.63	0.18	.270
	zSES	0.10	0.36	0.17	0.54	<.001
	Allele status	0.00	−0.12	−0.60	0.36	.623
	Injury group	0.00	−0.01	−0.41	0.39	.976
	Allele status x Injury group	0.00	0.19	−0.50	0.87	.593
Verbal paired associates—immediate recall		0.06				
	Race	0.00	−0.04	−0.44	0.36	.844
	Age	0.02	−0.14	−0.29	0.01	.844
	Allele status	0.00	0.08	−0.41	0.58	.736
	Injury group	0.02	−0.15	−0.57	0.27	.481
	Allele status x Injury group	*0.01*	*−0.46*	*−1.17*	*0.25*	*.209*
Verbal paired associates—delayed recall		0.06				
	Race	0.00	0.03	−0.37	0.44	.885
	Age	0.02	−0.13	−0.28	0.02	.099
	Allele status	0.01	0.07	−0.42	0.56	.781
	Injury group	0.01	−0.05	−0.47	0.37	.819
	Allele status x Injury group	*0.02*	*−0.55*	*−1.27*	*0.16*	*.131*
TEA-Ch creature counting, total correct		0.09				
	Race	0.05	−0.30	−0.72	0.11	.148
	zSES	0.03	0.21	0.02	0.40	.031
	Allele status	0.00	0.00	-0.48	0.49	.987
	Injury group	0.00	0.06	−0.35	0.47	.771
	Allele status x Injury group	0.00	0.21	−0.49	0.90	.563
TEA-Ch creature counting, timing		0.02				
	Race	0.01	−0.25	−0.69	0.19	.264
	Allele status	0.01	−0.10	−0.62	0.42	.710
	Injury group	0.01	0.26	−0.19	0.71	.261
	Allele status x Injury group	0.00	−0.17	−0.91	0.58	.661
TEA-Ch code transmission		0.02				
	Race	0.00	0.00	−0.41	0.41	.998
	Allele status	0.00	0.01	−0.50	0.52	.968
	Injury group	0.01	−0.07	−0.50	0.35	.731
	Allele status x Injury group	0.01	−0.32	−1.05	0.41	.388
TOL-DX-2		0.01				
	Race	0.00	−0.11	−0.51	0.30	.601
	Allele status	0.00	0.15	−0.35	0.66	.558
	Injury group	0.00	0.14	−0.28	0.57	.507
	Allele status x Injury group	0.01	−0.37	−1.09	0.35	.313
WASI matrix reasoning		0.12				
	Race	0.04	0.25	−0.15	0.65	.219
	zSES	0.05	0.24	0.05	0.42	.012
	Allele status	0.00	0.26	−0.22	0.74	.287
	Injury group	0.01	0.05	−0.35	0.45	.800
	Allele status × injury group	*0.02*	*−0.63*	*−1.31*	*0.06*	*.074*

TBI = traumatic brain injury; OI = orthopedic injury; zSES = socioeconomic status *Z* score.
Allele status × injury group interactions with $p < .05$ are bolded and with at least medium effect sizes (*e.g.* ≥0.5) italicized.

memory. In contrast, the opposite trend or no appreciable effect of allele status was observed in the OI group. The results may suggest a differential effect of the *BDNF* Val66Met polymorphism on verbal fluency, and possibly on fluid reasoning, and verbal memory, in children with early TBI relative to OI, and that the Met allele—associated with reduced activity-dependent secretion of BDNF—may confer risk for poorer neuropsychological functioning in children with TBI. Although preliminary, and requiring validation with larger and more homogeneous samples, these findings raise the potential of the Met allele serving as a marker for neuropsychological risk following pediatric TBI.

The present results add to an emerging literature showing that the role of BDNF in recovery from TBI is complex and dynamic, with effects appearing to vary by injury severity and age at injury (Barbey et al., 2014; Failla et al., 2016, 2015; Gabrys et al., 2019; Krueger et al., 2011; Narayanan et al., 2016; Wang et al., 2018). Adult studies have shown poorer outcomes in Met carriers with mild TBI (Gabrys et al., 2019; Narayanan et al., 2016; Wang et al., 2018). In adults with severe TBI, however, the Met allele appears to confer risk in younger adults but protection in older adults (Failla et al., 2016, 2015). In contrast, Met carriers have shown fewer internalizing problems (Gagner et al., 2020) and better quality of life (Tuerk et al., 2020) in a cohort of children with mild TBI. The present results are consistent with our prior report in this cohort (Treble-Barna et al., 2021), suggesting that the Met allele (associated with reduced activity-dependent secretion of BDNF) may confer risk for poorer neuroplasticity and repair mechanisms after TBI, affecting both longitudinal behavioral adjustment and neuropsychological functioning. These inconsistent findings regarding risk versus protection of the Met allele

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Table 6. Results of cross-sectional general linear models post-hoc stratified analyses

Dependent variable	Injury group	Parameter	η^2	Standardized estimate	Lower 95% CI	Upper 95% CI	*p*
WASI matrix reasoning	TBI		0.10				
		Race	0.00	−0.11	−0.74	0.52	.735
		zSES	0.08	0.34	0.05	0.62	.025
		Allele status	0.02	−0.34	−0.93	0.26	.268
	OI		0.14				
		Race	0.10	−0.42	−0.91	0.07	.097
		zSES	0.02	0.12	−0.10	0.35	.287
		Allele status	0.02	0.27	−0.15	0.68	.210
Verbal paired associates—immediate recall	TBI		0.10				
		Race	0.01	−0.32	−0.95	0.31	.322
		Age	0.07	−0.29	−0.56	−0.03	.035
		Allele status	0.02	−0.32	−0.93	0.29	.310
	OI		0.01				
		Race	0.01	0.22	−0.28	0.71	.389
		Age	0.00	−0.02	−0.23	0.18	.827
		Allele status	0.00	0.03	−0.40	0.45	.899
Verbal paired associates—delayed recall	TBI		0.11				
		Race	0.01	−0.31	−0.96	0.35	.358
		Age	0.08	−0.33	−0.60	−0.05	.024
		Allele status	0.02	−0.42	−1.06	0.21	.198
	OI		0.04				
		Race	0.03	0.34	−0.11	0.79	.149
		Age	0.00	0.03	−0.16	0.21	.756
		Allele status	0.00	0.00	−0.38	0.39	.990

OI = orthopedic injury; TBI = traumatic brain injury; zSES = socioeconomic status *Z* score.

are not unique to TBI, with similar complex and conflicting findings in other clinical conditions (Hong et al., 2011; Notaras et al., 2015), perhaps most relevantly in stroke (Rezaei, Asgari Mobarake, & Saberi, 2020; Rezaei, Mobarake, Saberi, & Keshavarz, 2020). Reviews of the effect of Val66Met in other populations have cited heterogeneity in confounders such age, sex, environmental factors, sample size, ethnicity, and phenotype assessment as likely accounting for some of the mixed findings (Hong et al., 2011; Notaras et al., 2015). In stroke, Val66Met status has shown significant interactions with age, dominant hemisphere lesions, degree of cerebral atrophy, number of lesions, recovery stage, and family history of dementia in predicting neuropsychological outcomes (Balkaya & Cho, 2019; Rezaei, Asgari Mobarake, et al., 2020; Rezaei, Mobarake, et al., 2020). Within TBI, age-related differences in the effect of the *BDNF* gene on outcomes have been suggested as potentially related to reductions in BDNF levels (Islam, Mulsant, Voineskos, & Rajji, 2017) and regional balances of BDNF pro- vs. mature receptor ratios across the lifespan (Failla et al., 2015; Finan et al., 2018; Tapia-Arancibia, Aliaga, Silhol, & Arancibia, 2008). Additional research is needed to further elucidate effects of BDNF on neurobehavioral recovery after TBI and factors moderating its complex association with outcomes.

Several study limitations should be considered in interpretation of the results. Due to the exploratory nature of the study, we corrected for multiple testing but also explored nominally significant and non-significant interaction effects with at least medium effect sizes. We found only one statistically significant allele status × injury group interaction that survived multiple testing correction and had a medium effect size, as well as three additional non-significant interactions of medium effect size. The power to detect these interactions was likely somewhat limited due to the relatively small sample size. We, therefore, urge caution in interpretation of the results. Notably, both significant and non-significant findings were consistent in the direction of effects within injury groups and consistent with our hypotheses. Nevertheless, the effect of the Val66Met allele on neuropsychological functioning after pediatric TBI appears to be modest. Modest results are not unexpected as the effects of single SNPs on complex phenotypes are often small and interact with the effects of many other potential genes and biological processes. For *BDNF* in particular, studies have shown interactive effects with *APOE*, *COMT,* serotonin transporter polymorphisms, and other neurotrophic factor genes in association with neurological and psychiatric outcomes (Chen et al., 2016; Harkness et al., 2015; Stonnington et al., 2020). Future research into the effects of the *BDNF* gene and others on TBI outcomes would benefit from the concurrent examination of multiple genes, such as through polygenic risk score and systems-biology informed gene-enrichment (Kurowski et al., 2019) approaches. In addition, the effect of the *BDNF* gene on brain structure and function has been shown to be moderated by environmental factors. Investigation is underway to examine the combined effect of childhood environmental factors and the *BDNF* gene on neurobehavioral recovery after pediatric TBI by studying *BDNF* epigenetics (Treble-Barna et al., 2020).

Another notable limitation is that our TBI group was heterogeneous. While the sample was representative of the spectrum of TBI severity, the effects we identified might be present only in a subgroup (e.g., mild or severe). Due to the relatively small sample size, we were unable to examine the moderating effects of injury severity, other injury-related medical variables, or individual background characteristics on the results, but future studies should consider such impact. Indeed, while the present cohort represents one of the largest investigations of the influence of genetic factors on pediatric TBI outcomes to date, larger sample sizes are needed to replicate the findings. Additional limitations are that the neuropsychological test battery included different tests at the earlier and final visits, precluding examination of longitudinal models across the entire study period, and the lack of performance validity testing.

The results provide preliminary evidence for the differential effect of variation in the *BDNF* Val66Met polymorphism on neuropsychological functioning in children with TBI relative to children with OI. Investigation of genetic biomarkers of pediatric TBI recovery has the potential to advance the field of pediatric TBI toward precision medicine, improving prognostic accuracy and providing earlier identification of children at greatest risk for

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long-term impairment to provide intervention. A better understanding of the role of BDNF in recovery from TBI may enable translation of pharmacological and non-pharmacological interventions targeting the BDNF pathway that have improved cognitive outcomes in experimental models of TBI.

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