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Influence of Catechol-O-methyltransferase (COMT) on Executive Functioning Longitudinally after Early Childhood Traumatic Brain Injury (TBI): Preliminary Findings

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Abstract

Objective—To elucidate the association of a functional catechol-O-methyltransferase (COMT) genotype (rs4680) with recovery of executive functions up to 18 months after early childhood traumatic brain injury (TBI) compared to an orthopedic injury (OI) group.

Setting—Outpatient

Participants—134 children with a moderate to severe TBI (n=63) or OI (n=71) between the ages of 3-6 years who were followed 18 months post-injury

Design—Case-comparison, longitudinal cohort

Main Measures—The Behavior Rating Inventory of Executive Function (BRIEF), developmental neuropsychological assessment (NEPSY) of verbal fluency (VF), and a modified Stroop Test for young children (Shape School)

Results—The low activity COMT enzyme genotype (AA) was associated with better scores on the NEPSY VF (F=3.80, p=.02) and the Shape School (F=2.89, p =.06) in all participants when controlling for injury type (TBI vs. OI) over the first 18 months after injury. Injury type (TBI vs. OI) did not significantly moderate the effect of the COMT genotypes on executive function recovery.

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Conclusion—This study provides preliminary evidence for a role of COMT genotypes in long-term recovery of executive function after pediatric TBI and OI. Larger studies are needed to determine the exact link between genetic variation in the COMT gene and TBI recovery in children.

Keywords

Brain Injury; Genetics; Pediatrics; Child; Executive Function; Recovery

Introduction

Traumatic Brain Injury (TBI) is a leading cause of morbidity and mortality for children.[1] TBI commonly results in physical and cognitive impairments. Common cognitive impairments include memory deficits, executive dysfunction, decreased concentration and attention, and language impairment.[2-13] The prognosis after TBI varies among individuals, even those with similar injuries. Such variability is likely due to environmental, injury-related, and other individual factors, including genetics. To date, a paucity of research has evaluated the association of genetics with outcomes after pediatric TBI.[14] Genetic variants associated with inflammatory cascades, neuroplasticity, cognitive functioning, and neurologic signaling pathways may influence initial biologic response and longer-term recovery after TBI.[15,16] Catecholaminergic systems are of particular interest because these systems are sensitive to TBI and play roles in neural plasticity and repair, as well as attention and memory function.[16-21]

Dopamine, epinephrine, and norepinephrine are catecholamines that are thought to play a role in recovery and functioning after TBI, given that variation in the metabolism of catechoamines after injury may influence cognitive function and recovery.[16] Because the enzyme Catechol-O-methyltransferase (COMT) primarily functions to degrade catecholinergic neurotransmitters, variations in the functioning of the enzyme may affect recovery after TBI.[22] The COMT enzyme is coded by a gene located on the long arm of chromosome 22q11.21.[22] The gene contains a common site of genetic variation that results in a methionine to valine substitution at codon 158 and leads to differing enzyme activity.[23,24] The AA genotype codes for methionine homozygotes that are associated with lower enzyme activity and the GG genotype codes for valine homozygotes that are associated with higher enzyme activity. Low COMT enzyme activity (i.e., decreased degradation of catecholamines) is associated with potentially higher levels of neurotransmitters while high activity of COMT (i.e., increased degradation of catecholamines) is associated with potentially lower levels of neurotransmitters.[23,24] Because of the biologic implications of this COMT genetic variation on catecholamine metabolism, genotypes associated with lower or higher levels of catecholamines may influence cognitive and behavioral recovery after injury.

The COMT genoyptes have been associated with performance on cognitive tasks in several populations. In healthy participants, Blasi et al. showed that the low activity COMT genotype (AA) was associated with superior attention when compared to the high activity COMT genotype (GG).[25] Kramer et al. showed that university student participants

homozygous for the high activity COMT genotype (GG) had greater prefrontal processing related to inhibitory functions.[26] Fossela et al. reported that adult subjects homozygous for the high activity COMT genotype (GG) had poorer executive attention scores than those homozygous for the low activity genotype (AA).[27] Additionally, amphetamine, a stimulant known to increase dopamine signaling, enhanced working memory task performance and efficiency of prefrontal cortex function in healthy individuals homozygous for the high activity COMT genotype (GG).[28] In adults with TBI, homozygotes for the higher activity COMT genotype (GG) showed more executive dysfunction on the Wisconsin Card Sorting Test compared to homozygotes for the lower COMT genotype (AA).[29] COMT polymorphisms have also been linked to emotion, thinking, and self-regulatory functions.[30] Specifically, they are involved in the mediation of cognitive functions related to executive functioning and self-regulating behavior.[30] In summary, this prior work indicates that these COMT genotypes may have implications for cognitive and behavioral functioning in several conditions associated with attention and executive functions; however, the association of this genetic variation with cognitive and behavioral recovery after pediatric TBI has not been explored. The aim of this study was to broaden the evaluation of the association of genetic variants with cognitive and behavioral recovery after pediatric TBI to COMT variants. Specifically, our goal was to better understand the association of the functional COMT variants (rs4680) with executive function and behavioral recovery longitudinally, up to 18 months after early childhood TBI compared to an orthopedic injury group. We predicted that the high enzyme activity genotype (GG) of the rs4680 COMT genetic variant would be associated with poorer executive functioning and that TBI would amplify these adverse effects over time.

Methods

Design

This was a prospective, longitudinal observational, case-comparison study of the association of a functional COMT variant (rs4680) with behavioral and executive function outcomes of young children with TBI and orthopedic injuries (OI).

Participants

Participants were recruited from an ongoing, prospective, long-term descriptive study evaluating children who sustained a TBI between age 3 and 7 years and a comparison group of age-matched children with orthopedic injury (OI). 213 participants who were enrolled in the original study were eligible for the current genetic study. Recruitment was from 3 children's hospitals and 1 general hospital in Ohio. Participants underwent assessments at multiple time points, including the immediate post-acute period (0-3 months after injury) and 6, 12, and 18 months post-injury. Inclusion criteria included hospitalization overnight for traumatic injury (TBI or OI) sustained between the ages of 36 and 83 months, no evidence of child abuse as the cause of the injury, no history of documented neurological problems or developmental delays pre-injury, and English as the primary language in the home. The severity of injury was characterized using the Glasgow Coma Scale (GCS). [31] Severe TBI was defined as a GCS score less than or equal to 8 as the lowest post resuscitation score. The moderate TBI group had a GCS score of 9-12 or a GCS score of

13-15 in association with abnormal brain imaging. Children with mild TBI had a GCS of 13-15 without evidence of abnormal brain imaging. The OI group included children who sustained a bone fracture (not including skull fractures), had an overnight stay in the hospital, and did not exhibit alterations in consciousness or other signs or symptoms of head trauma or brain injury.

DNA Collection

DNA was collected from saliva samples from the participants, purified using the Oragene (DNA Genotek, Ottawa, Ontario, Canada) OG-500 self-collection tubes, and analyzed using TaqMan (Applied Biosystems) assay protocols to identify the COMT rs4680 genotypes. Genotypes were AA (methionine/methionine homozygote; low COMT enzyme activity; higher catecholamine levels), GA (valine/methionine heterozygote; intermediate COMT enzyme activity, intermediate catecholamine levels) and GG (valine/valine homozygote; high COMT enzyme activity; lower catecholamine levels)

Measures

Several measures were used to ensure comprehensive assessment of behavior and executive function skills. The Behavior Rating Inventory of Executive Function (BRIEF) provides a parent rating of child executive function skills.[32-34] A developmental neuropsychological assessment (NEPSY) verbal fluency (VF) subtest measures mental flexibility or the ability to shift from one conceptual set to another.[35] The Shape School is a modified Stroop test designed to evaluate executive function skills, specifically inhibition, attentional control, and the ability to shift from one set of rules to another in pre-school aged children.[36,37] Because the BRIEF is a parent rating of executive function skills, initial ratings were based on the parent's interpretation of the child's executive function skills prior to the injury. The 6, 12, and 18 month evaluations represent the parent's ratings of the child's current executive function skills. Since the NEPSY and Shape School are measures completed by the child, they assess functioning at the time of evaluation. We used the global executive composite score on the BRIEF (BRIEF GEC) and the total score on the NEPSY VF to assess global executive function behaviors and mental flexibility respectively. For the Shape School, we used efficiency subtest scores (#correct responses minus incorrect responses/time) on tasks of inhibition, switching, and a task combining inhibition and switching as our main outcome measures. This measure evaluates selective attention, cognitive flexibility, and processing speed skills.

Analysis

Simple statistics such as means, standard deviations, and frequencies were used to summarize the data. Group comparisons (TBI and OI) were conducted using independent T-tests, Chi-Square tests, and analysis of variance (ANOVA) when appropriate. COMT genotypes were tested for Hardy-Weinberg equilibrium using JMP genomics software as part of the SAS program. Mixed model linear regression was used to analyze the relationship between executive functioning and the COMT genotypes over time, with behavior and executive functioning as the dependent variable and COMT genotypes as the independent variable. The three outcome measures or dependent variables were: BRIEF GEC, Verbal Fluency, and a measure of executive efficiency on the Shape School. Baseline

BRIEF GEC was included as a covariate in the models because it was a retrospective pre-injury rating; for verbal fluency and shape school, baseline outcomes were post-injury and were treated as dependent variable in the modeling. We included genotypes as a categorical variable. To examine the moderating effect of injury type (TBI vs. OI) on the association of genotype with the executive function outcomes over time, the triple interaction of genotype with injury type and time since injury, as well as the lower-level interaction terms were included in the model. The models also controlled for age at injury, gender, race (white versus non-white), and socioeconomic status (defined as Z-score that combined parental education and median census track income by zip code). Because of potential confounding of outcomes with race, race was retained as a covariate in all models. Additionally, because of the potential effects of socioeconomic status on outcomes, socioeconomic status was also included as a covariate. We examined multicollinearity and dropped gender from the models due to substantial collinearity with age at injury (Variance Inflation Factor ~ 10). Because standard scores for the BRIEF-GEC and VF were used, age at injury was not a significant predictor (p>.05) for the Brief GEC or VF total, and was trimmed from these models. However, because standard scores are not available for the Shape School, raw scores were used for the Shape School model and age at injury was significant in the Shape School model and was retained in this model. The interaction of injury group × genotype × time was the primary association evaluated in interaction models. Given the exploratory nature of the study, a p value of less than 0.05 was considered statistically significant and p values less than 0.1 were considered as trending toward significance. All statistical analysis was conducted using SAS 9.3©.

Results

Genetic data was collected for 134 participants. The TBI (n=63) group was 57% (n=36) male with an average age at injury of 5.2 ± 1.1 years, 30% (n=19) nonwhite, and 14% (n=9), 64% (n=40), and 22% (n=14) with mild, moderate, severe TBI, respectively. The OI group (n=71) was 52% (n=37) male with an average age at injury of 5.1±1.1 years and 24% (n=17) nonwhite. There was no difference in age, race, or gender between the TBI and OI groups (Table 1). The TBI group had significantly longer times since injury at baseline (0.12±0.07 versus 0.09±0.04 years, $p < 0.001$). There were 79 potential participants from the original cohort that were unable to be contacted or declined participation. There was no difference between groups with and without genetic data collected in terms of injury type (44.3% versus 47.0% TBI, $p = .70$), gender (64.6% versus 54.5% male, $p = .15$), race (31.7% versus 26.9% nonwhite, $p = .46$), and age at injury (4.9 versus 5.1 years, $p = .22$)

No bias was identified in the baseline data. Hardy Weinberg Equilibrium was not violated. There were no significant differences in genotype frequency between the TBI (AA = 8, GA = 32, and GG = 23) and OI (AA = 16, GA = 34, and GG = 21) groups. There were no significant differences in genotype frequency among the mild (AA = 1, GA = 4, GG = 4), moderate (AA = 4, GA = 21, GG = 15), and severe (AA = 3, GA = 7, GG = 4) TBI groups. There was no significant difference in mean injury severity score (ISS) within the OI group among the genotypes: ISS (stdv) = 6.50 (2.58), 7.21(3.04), 6.14(2.54) for AA, GA, and GG genotypes, respectively.

Main effect analyses

There was a main effect association of the low activity COMT genotype (AA) with improved scores on the NEPSY VF (F=3.80, $p = .02$, Figure 1B) and trend for an association with the Shape School (F=2.89, $p = .06$, Figure 1C) over time. There was not a main effect association of COMT genotypes with the BRIEF GEC (F=.27, $p = .76$, Figure 1A) over time.

Moderation analyses

The triple interaction term of time since injury by group by genotype was not significantly predictive of the BRIEF GEC (F= 0.83, $p = 0.44$, Figure 2), NEPSY VF (F=.32, $p = .72$, Figure 2), or Shape School (F=.92, $p = .40$, Figure 3) over time. These moderation analyses did not support the hypothesis that the high activity genotype (GG) would further exacerbate executive dysfunction, as measured by the BRIEF-GEC, NEPSY VF, and Shape School, over time after TBI. This finding is demonstrated in Figure 2 by the overall parallel nature of the plotted lines rather than a widening of a difference in outcomes over time for the BREF-GEC. In the NEPSY VF analysis (Figure 3), the plotted lines demonstrate a trend for low activity genotype (AA) in the TBI group to be associated with poorer performance over time. In the Shape School analysis (Figure 4), the plotted lines demonstrate a comparable rate of improvement over time across all groups, with the lower activity genotype (AA) in the TBI group showing the most improvement and the high activity genotype (GG) in the TBI group showing the least improvement.

Discussion

Our findings indicate that there is likely a complex association of the COMT genotypes evaluated in this study with executive function recovery after pediatric TBI and OI. When controlling for injury type (TBI versus OI), main effect analyses of the entire cohort indicated that the low activity COMT genotype (AA) was associated with improved lab-based measures of executive function, but not parent ratings of executive function as manifest in everyday behavior. The effect was not limited to the TBI group as the interaction of group by time by genotype did not achieve significance. Thus these analyses did not support the hypothesis that the high enzyme activity genotype (GG) would exacerbate executive dysfunction in the TBI group. Further work is needed to better understand the association of these functional COMT genotypes with recovery after pediatric TBI.

To our knowledge, this is the first study to evaluate the association of a functional COMT genotype with longer-term recovery after pediatric TBI and OI. The study builds on prior work that has evaluated the association of COMT and other catecholamine-related genetic variants after TBI in adults.[17,29,38,39] In prior cross-sectional work, the low COMT activity enzyme genotype (AA) was associated with better executive function.[29] In agreement with this prior work, our results indicate that the low activity COMT genotype (AA) was associated with overall better function on lab-based measures of executive functioning in the entire cohort (TBI and OI). In contrast, our study did not demonstrate a protective association of the low activity genotype (AA) with executive function in the TBI group compared to an OI group. This finding should be interpreted as exploratory, although several

potential explanations exist for these seemingly conflicting findings. First, because an individual genetic variant is likely to have a relatively small influence on outcome, larger studies are needed to definitively evaluate the relationship of these COMT genotypes with executive function outcomes. Additionally, executive function development occurs at a variable pace in children;[40,41] thus it is difficult to measure executive function with precision, especially in younger children. Furthermore, it is possible that COMT enzyme functioning may have differential effects in a population of children with pediatric TBI compared to non-injured children or adults. Finally, prior work did not evaluate association of the COMT genotypes over time and it is possible that the relationship of these COMT genotypes with executive function outcomes may be dynamic and change over time after injury. In conclusion, results of this study did not conclusively demonstrate a role of COMT genotypes in long-term recovery of executive function after pediatric TBI. However, these results raise the possibility of gene-dependent moderation of injury effects that may vary across different measures of outcome and time. Further work is needed to better understand the role of the COMT genotypes evaluated in this study and other genetic variants in moderating the effects of injury on executive functioning.

Multiple factors likely influence recovery after TBI. In pediatric TBI, the child's environment, specifically, family environment and parenting styles, is associated with neurocognitive and behavioral recovery.[42-46] There are also several examples of the interaction of environmental and genetic factors in determining disease phenotypes.[47] Specifically, dopamine receptor and dopamine pathway, serotonin transporter, and COMT genetic variants interact with environmental factors to influence cognitive and behavioral functioning in various childhood populations.[18,48-58] Although the higher activity enzyme genotype (GG) is generally associated with a reduction in executive cognition, it is also associated with better stress resiliency, indicating that stressful environmental factors may overwhelm the direct effects the COMT genotype has on cognition[59] Because a TBI often leads to increased family burden[42,60,61], the potential stress resiliency effects of the high activity genotype (GG) may outweigh the effects on executive cognition. Future studies should evaluate the interaction of genetics and environmental and other factors on recovery.

Although several previous studies have demonstrated an association of the COMT genotypes evaluated in this manuscript with cognitive and behavioral functioning, with most reporting an association of the low COMT enzyme activity genotype with improved cognitive function[25-27,29], there may be a within-gene explanation of the conflicting associations in the TBI group. One study suggests that several genetic variants within the COMT gene may contribute to the final overall activity of the enzyme;[62,63] therefore, interaction of several within-gene genotypes (i.e., a haplotype) may be better associated with overall activity. Additionally, there may be a complex interaction across several genes that may explain the genetic association with outcomes. Genes involved in other neuro-signaling, inflammatory, or neuroplasticity pathways may interact with the COMT genotypes evaluated in this manuscript to determine cognitive and behavioral recovery after pediatric TBI.

Limitations

Although this study is large relative to other studies of pediatric TBI, much larger studies and replication are needed to provide a firm understanding of the influence of COMT genotypes on cognitive and behavioral recovery after pediatric TBI. This study consisted primarily of subjects with moderate TBI, limiting the ability to perform subpopulation analyses to understand whether the COMT genotype effects are more pronounced among individuals with milder and severe TBI. Larger studies that include a broad range of injury severity are needed to better elucidate the interaction between severity and genotype. There was no examination of the interaction between environment and genotype. Future studies should take environment into consideration. Additionally, other functional polymorphisms within the COMT gene or genetic variation in other genes may influence recovery after pediatric TBI. Thus, larger studies examining the contribution of a set of genetic variants within and across genes are needed in the future.

Conclusions

Limited research has examined the effects of genetics on outcomes after pediatric TBI. This current study expands the knowledge base with a relative large sample that has been followed prospectively. The study provides preliminary evidence that genetic variation in the COMT gene may influence long-term recovery of certain executive function domains. The results indicate that the COMT genotypes evaluated may have different effects on executive function depending on domain and type of measure used to assess executive functioning. Larger studies and replication are needed to determine the exact link between genetic variation in the COMT gene and other genes with recovery after TBI in children, and how this information can be used to inform prognosis and develop individualized treatment protocols. These preliminary findings indicate that there are potential genetic influences on outcomes after pediatric TBI that warrant further investigation.

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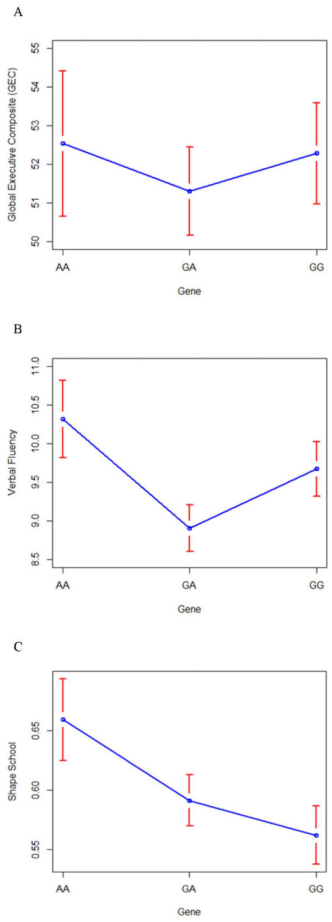

Figure 1.

Mixed model analysis and least square means for the main effect association of COMT genitive variants with executive function outcomes in all participants: (A) GEC, (B) NEPSY VF, and (C) Shape School

The primary independent variable was genetic variant (AA, GA, GG). Covariates included in the models were baseline global executive composite (GEC) score (GEC outcome only), age at injury (Shape School outcome only), race, socioeconomic status, group (TBI versus OI), time since injury. Error bars indicate standard error.

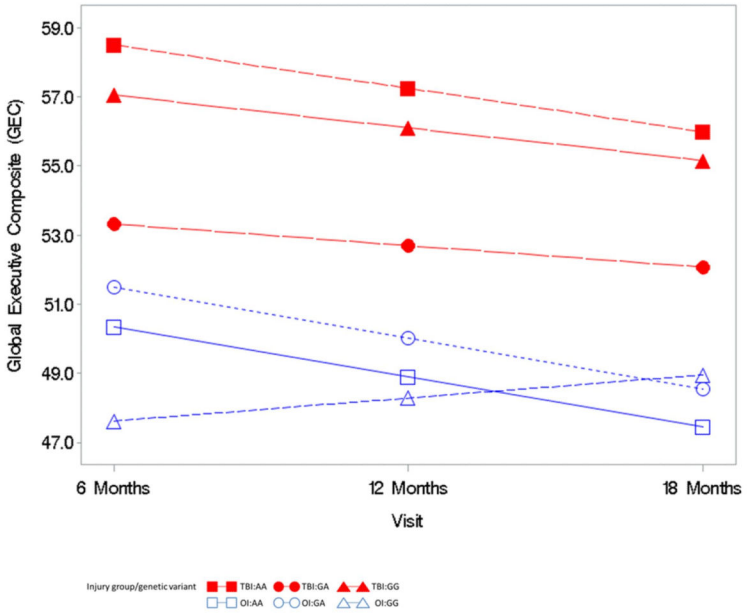

Figure 2.

Mixed model analysis of the relationship of the COMT variants with the Global Executive Composite (GEC) ratings, evaluation of the interaction of group by genetic variant by time. The primary independent variable was genetic variant (AA, GA, GG). Co-variates included in the model were baseline (i.e., pre-injury rating) GEC, race, socioeconomic status, group (TBI versus OI), time since injury, interaction terms of group by genetic variant, time since injury by genetic variant, time since injry by group, and time since injury by group by genetic variant.

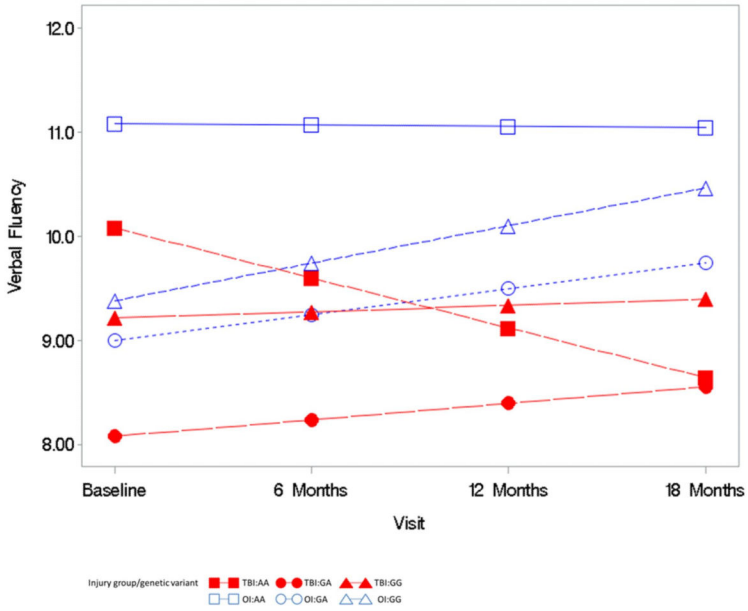

Figure 3.

Mixed model analysis of the relationship of the COMT variants with the Verbal Fluency outcome, evaluation of the interaction of group by genetic variant by time

The primary independent variable was genetic variant (AA, GA, GG). Co-variates included in the model were race, socioeconomic status, group (TBI versus OI), time since injury, interaction terms of group by genetic variant, time since injury by genetic variant, time since injry by group, and time since injury by group by genetic variant.

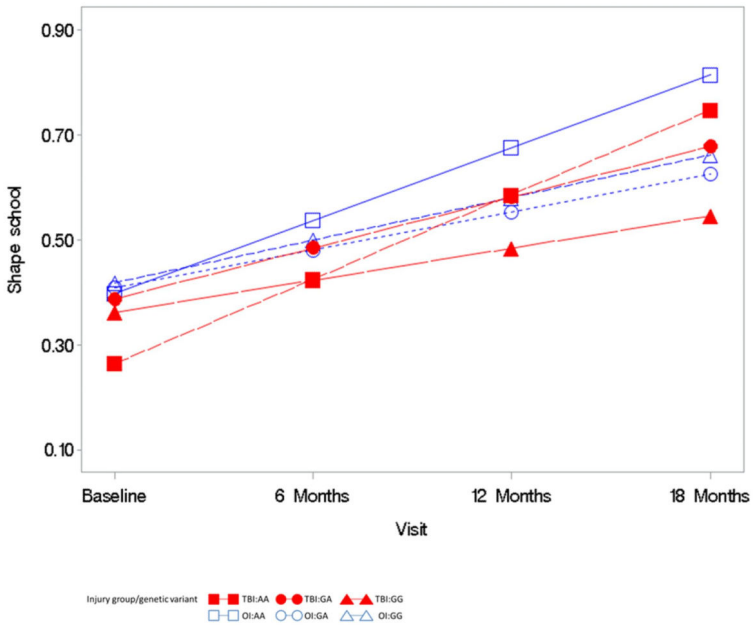

Figure 4.

Mixed model analysis of the relationship of the COMT variants with Shape School outcome, evaluation of the interaction of group by genetic variant by time

The primary independent variable was genetic variant (AA, GA, GG). Co-variates included in the model were age at injury, race, socioeconomic status, group (TBI versus OI), time since injury, interaction terms of group by genetic variant, time since injury by genetic variant, time since injry by group, and time since injury by group by genetic variant.

Table 1

Demographics of participants and outcome measures

Demographics	**OI (n=71)**	**TBI (n=63)**
Gender, n (%)		
Male	37 (52.1)	36 (57.1)
Female	34 (47.9)	27 (42.9)
Race, n (%)		
White	54 (76.1)	44 (69.8)
Non-white	11 (15.5)	14 (22.2)
Age at injury in years, mean (stdv)	5.1 (1.1)	5.2 (1.1)
Time since injury at baseline in years, mean (stdv)	0.09 (0.04) *	0.12 (0.07) *
Median family income, mean (stdv)	$60,712 (21,964)	$59,647 (23,047)
Highest Educational Attainment, n (%)		
Less than 2 years of high school	1 (1.4)	3 (4.8)
Two years of high school	5 (7.0)	7 (11.1)
High school degree	24 (33.8)	27 (42.9)
Two years of college	15 (21.1)	12 (19.1)
Four years of college	18 (25.4)	10 (15.9)
Graduate degree	8 (11.3)	4 (6.4)
Outcome Measures		
BRIEF-GEC, mean (stdv)	47.7 (12.8)	50.8 (15.2)
NEPSY: VF, mean (stdv)	9.5 (3)	8.6 (2.8)
Shape School, mean (stdv)	0.4 (0.2)	0.3 (0.2)

* indicates significant difference at p-value < .05