Missense mutation of Brain Derived Neurotrophic Factor (BDNF) alters neurocognitive performance in patients with mild traumatic brain injury: a longitudinal study

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RESEARCH ARTICLE

Missense Mutation of Brain Derived Neurotrophic Factor (BDNF) Alters Neurocognitive Performance in Patients with Mild Traumatic Brain Injury: A Longitudinal Study

Vairavan Narayanan1*, Vigneswaran Veeramuthu1*, Azlina Ahmad-Annuar2, Norlisah Ramli3, Vicknes Waran1, Karuthan Chinna4, Mark William Bondi5,6, Lisa Delano-Wood5,6, Dharmendra Ganesan1

1 Division of Neurosurgery, Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Wilayah Persekutuan, Malaysia, 2 Department of Molecular Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Wilayah Persekutuan, Malaysia, 3 University Malaya Research Imaging Centre, University of Malaya, Kuala Lumpur, Wilayah Persekutuan, Malaysia, 4 Julius Centre University Malaya, Department of Social and Preventive Medicine, University of Malaya, Kuala Lumpur, Malaysia, 5 VA San Diego Healthcare System, San Diego, California, United States of America, 6 University of California San Diego, Department of Psychiatry, San Diego, California, United States of America

These authors contributed equally to this work.
* nvairavan@um.edu.my (VN); vicveera@gmail.com (VV)

Abstract

The predictability of neurocognitive outcomes in patients with traumatic brain injury is not straightforward. The extent and nature of recovery in patients with mild traumatic brain injury (mTBI) are usually heterogeneous and not substantially explained by the commonly known demographic and injury-related prognostic factors despite having sustained similar injuries or injury severity. Hence, this study evaluated the effects and association of the Brain Derived Neurotrophic Factor (BDNF) missense mutations in relation to neurocognitive performance among patients with mTBI. 48 patients with mTBI were prospectively recruited and MRI scans of the brain were performed within an average 10.1 (SD 4.2) hours post trauma with assessment of their neuropsychological performance post full Glasgow Coma Scale (GCS) recovery. Neurocognitive assessments were repeated again at 6 months follow-up. The paired t-test, Cohen’s d effect size and repeated measure ANOVA were performed to delineate statistically significant differences between the groups [wildtype G allele (Val homozygotes) vs. minor A allele (Met carriers)] and their neuropsychological performance across the time point (T1 = baseline/ admission vs. T2 = 6th month follow-up). Minor A allele carriers in this study generally performed more poorly on neuropsychological testing in comparison wildtype G allele group at both time points. Significant mean differences were observed among the wildtype group in the domains of memory (M = -11.44, SD = 10.0, p = .01, d = 1.22), executive function (M = -11.56, SD = 11.7, p = .02, d = 1.05) and overall performance (M = -6.89 SD = 5.3, p = .00, d = 1.39), while the minor A allele carriers...
showed significant mean differences in the domains of attention ($M = -11.0$, $SD = 13.1$, $p = .00$, $d = .86$) and overall cognitive performance ($M = -5.25$, $SD = 8.1$, $p = .01$, $d = .66$). The minor A allele carriers in comparison to the wildtype G allele group, showed considerably lower scores at admission and remained impaired in most domains across the timepoints, although delayed signs of recovery were noted to be significant in the domains attention and overall cognition. In conclusion, the current study has demonstrated the role of the BDNF rs6265 Val66Met polymorphism in influencing specific neurocognitive outcomes in patients with mTBI. Findings were more detrimentally profound among Met allele carriers.

Introduction

Mild traumatic brain injury (mTBI) due to road traffic accident (RTA) is one of the most common forms of head injury, afflicting millions of people worldwide [1–3]. The complex pathophysiology of mTBI and the biochemical responses that occurs thereafter frequently results in cognitive, affective or behavioral deficits [4–6]. A wide variety of complaints and symptoms have been reported [7–11]. The predictability of these deficits are however not straightforward [12]. Crawford et al (2002) and Pruthi et al (2010) in their respective studies noted that the extent and nature of recovery in patients with mTBI are usually heterogeneous and not substantially explained by the commonly known demographic and injury-related prognostic factors [5, 13], despite having sustained similar injuries or injury severity [12, 14–15].

While there are many factors that may contribute to the outcome variability observed in mTBI, reliable genetic or imaging prognostic markers are sparse. In recent years, the expression and modulation of neurotropic genes, both normal and mutated, have been postulated as potential prognostic markers [16]. A wide range of aberrant genes including apolipoprotein E, dopamine β hydroxylase (DBH), cathecol-O-methyltransferase (COMT), calcium channel subunit gene (CACNA1A), interleukins α and β, dopamine D2 receptor (DA2) and brain derived neurotrophic factor (BDNF) has been implicated to modulate the extent of injury [12, 17–19], regulating the cascading neurochemical response to the sudden impact or trauma [12,17, 20–27], altering the natural recovery pathways [12–13, 28–38], adversely affecting the cognitive recovery processes [32, 39–46] and behavioral functions [17, 46–52]. BDNF has been implicated in many of these repair processes. It is an abundantly available neurotrophin in the brain that is activity dependent [53–55] with a widespread distribution in the cerebral cortex, hippocampus, basal forebrain, striatum and septum areas [56].

BDNF is also known to play a key role in the survival, differentiation, synaptic plasticity and outgrowth of peripheral and central neurons throughout adulthood [57–60]. Missense mutations within this gene are also known to influence both axonal and dendritic morphology where the ocular dominance column development [61–62] and initial dendritic outgrowth are altered [63–64]. While there are over 1768 missense mutations reported in BDNF [65], only two are known to influence the expression level of BDNF, rs6265 (c.196G>A, p.V66M, NM_001143814.1) [58, 66] and a dinucleotide GT microsatellite repeat designated as BDNF-linked complex polymorphic region (BDNF-LCPR) located at the 5′ UTR [58]. The rs6265 variant has been reported to affect the regulated secretion, neural activation, and neuroplastic effect of BDNF as well as neurocognitive functions in humans [29, 66–67]. It has been associated with memory and learning [29, 68–74] and as well as with aspects of executive functioning [66, 75–80], including response inhibition [75], decision making [77–78], task-switching [79], attention shifting and sequencing [80]. Meanwhile, the BDNF-LCPR variants on the other
hand have been associated with an increased risk for bipolar disorder [81]. The focus of our study, however, was limited to the broad concepts of BDNF-specific phenotype-modulated structural alteration influencing neuro-regenesis (repair and adaptive synaptic organization) [12, 51] and neurogenesis (active production of neurons, astrocytes, glia and other neural lineages) [12, 52] and its relationship with neurocognition.

Six missense mutations in BDNF [82–84], namely the rs6265, rs1048218, rs1048220, rs1048221, rs8192466 and rs139352447 were selected. The rs6265 variant has been well studied for its involvement in modulating recovery from brain injury but has yet to be investigated in the Malaysian population. The rs1048220 and rs1048221 are within the crucial protease cleavage site for proBDNF and are reported to impair proBDNF cleavage; and rs1048220 and rs104218 have been associated with Alzheimer’s disease [85–89]. However, none of these missense mutations have been explored in brain injury with the exception of rs6265 (BDNF Val66-Met) [18, 20, 32, 40, 46, 58, 66, 75]. Hence, the objective of our study was to assess the effects and association of variations within BDNF in relation to neurocognitive performance among patients with mTBI.

Materials and Methods
A total of 61 patients with mTBI who presented to the Emergency Department of University Malaya Medical Center, Kuala Lumpur between April 1st, 2013 and August 31st, 2014 were recruited prospectively. We defined mTBI as an acute head injury, consisting of non-penetrating head trauma resulting in one or more of the following: confusion/disorientation; loss of consciousness (LOC) less than 30 minutes; posttraumatic amnesia (PTA—less than 24 hours in duration); transient focal neurological signs or seizures; and Glasgow Coma Scale of 13 to 15 upon acute clinical evaluation. These patients were assessed with baseline computed tomography (CT) scans of the brain in the emergency department using a Siemens Somatom Sensation 16 CT scanner (Siemens AG, Berlin, Germany). A neuroradiologist (NR) and a neurosurgeon (VN) who were blinded to the clinical diagnosis independently evaluated the images for each patient. Patients who met the study criteria were admitted to the observation ward for 24 hours. Informed consent was obtained upon explaining the objectives of the study and as well as the research protocols/procedures as per the approved guidelines of our local Ethics Committee for the study (UM/EC/949.15). Thirteen patients were later dropped from this study as some refused screening of their genetic profiles, while others were later lost to follow-up, leaving the final sample of 48 patients with their DNA analyzed for genotyping.

Genotyping
DNA was obtained from leukocytes using the phenol-chloroform extraction method [90]. Details of the six SNPs that were examined in this study are in Fig 1. The SNPs were genotyped using Taqman® allelic discrimination assays and genotyping was carried out on a 7500 Fast Real-Time PCR machine (Applied Biosystems) using standard protocols as recommended by the manufacturer. Genotypes were confirmed by polymerase chain reaction (PCR) and Sanger sequencing in a random subset of individuals to determine the error rate for each of the Taqman SNP assays (see Fig 2 for the primer sequences).

Neurocognitive assessment
The screening module of Neuropsychological Assessment Battery (S-NAB Form 1) was used to assess the neurocognitive performance of the patients by a clinical neuropsychologist (VV). The assessments were done once the patient had recovered to a GCS score of 15 and was not under any trauma related physical or emotional distress. The S-NAB comprises a
A comprehensive set of neuropsychological tests (refer to Fig 3), with demographically corrected norms for adults between the ages of 18 to 97 years. Five cognitive domains i.e attention, memory, language, visuospatial and executive functions are evaluated through this battery. This battery consists of 12 individual tests across the five domains aforementioned. A total of 16 T scores are then derived, 14 of which contribute toward five separate Screening Index (domain-specific) scores and one Total Screening Index score [91–92]. The S-NAB Form 2 was used to

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6265</td>
<td>Val66Met</td>
<td>G to A allele</td>
<td>11</td>
<td>G= 0.533</td>
<td>A= 0.467</td>
<td>G= 0.585</td>
<td>A= 0.415</td>
<td>G= 0.529</td>
<td>A= 0.372</td>
<td>G= 0.628</td>
</tr>
<tr>
<td>rs1048218</td>
<td>Gln75His</td>
<td>G to T allele</td>
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<td>G= 0.978</td>
<td>A= 0.346</td>
<td>G= 0.979</td>
<td>A= 0.471</td>
<td>G= 1.000</td>
<td>A= 0.195</td>
<td>G= 1.000</td>
</tr>
<tr>
<td>rs1048220</td>
<td>Arg125Met</td>
<td>G to T allele</td>
<td>11</td>
<td>G= 1.000</td>
<td>G= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
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<td>T= 0.000</td>
<td>T= 0.000</td>
</tr>
<tr>
<td>rs1048221</td>
<td>Arg127Leu</td>
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<td>G= 1.000</td>
<td>G= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
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<tr>
<td>rs8192466</td>
<td>Thr211Leu</td>
<td>G to T allele</td>
<td>11</td>
<td>G= 1.000</td>
<td>G= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
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<tr>
<td>rs139352447</td>
<td>Gln75Glu</td>
<td>G to T allele</td>
<td>11</td>
<td>G= 1.000</td>
<td>G= 0.000</td>
<td>T= 0.000</td>
<td>T= 0.000</td>
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</table>


doi:10.1371/journal.pone.0158838.g001

<table>
<thead>
<tr>
<th>SNP ID</th>
<th>Forward Primer, 5’-3’</th>
<th>Reverse Primer, 5’-3’</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6265</td>
<td>GCAAACATCCGAGGACCAAGG</td>
<td>CATTGGGCCGAACCTTTCTGG</td>
</tr>
<tr>
<td>rs1048218</td>
<td>GCTTGACATCACCAAGG</td>
<td>AGAAGAGGAGGCTCCAAAGG</td>
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<td>rs1048220</td>
<td>CTCTCTCTCTCTCTCTGAG</td>
<td>ATACTGTCACACAGCTCAG</td>
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<td>rs1048221</td>
<td>TGCTCAGTAGTCAAAGTGCT</td>
<td>TGCCGTTACCTCAGTAAA</td>
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<tr>
<td>rs8192466</td>
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<td>AACTTGTCTGCGATGTTTG</td>
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<tr>
<td>rs139352447</td>
<td>CGTGCTAAGTCTGCTGCT</td>
<td>ACTCTGGAGAGGCTCAG</td>
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**Neuropsychological Assessment (S-NAB Form 1 & 2)**

<table>
<thead>
<tr>
<th>List of S-NAB Module Tests:</th>
<th>Domains Assessed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>Orientation</td>
</tr>
<tr>
<td>Digits Forward</td>
<td>Attention</td>
</tr>
<tr>
<td>Digits Backward</td>
<td>Attention/Working Memory</td>
</tr>
<tr>
<td>Numbering and Letters</td>
<td>Attention</td>
</tr>
<tr>
<td>Shape Learning Immediate Recognition</td>
<td>Memory</td>
</tr>
<tr>
<td>Story Immediate Recall</td>
<td>Memory</td>
</tr>
<tr>
<td>Delayed Shape Learning Delayed Recognition</td>
<td>Memory</td>
</tr>
<tr>
<td>Story Learning Delayed Recall</td>
<td>Memory</td>
</tr>
<tr>
<td>Auditory Comprehension (3 subtests)</td>
<td>Language</td>
</tr>
<tr>
<td>Naming</td>
<td>Language</td>
</tr>
<tr>
<td>Mazes</td>
<td>Executive Function</td>
</tr>
<tr>
<td>Word Generation</td>
<td>Executive Function/Verbal Fluency</td>
</tr>
<tr>
<td>Design Construction</td>
<td>Visuospatial</td>
</tr>
<tr>
<td>Visual Discrimination</td>
<td>Visuospatial</td>
</tr>
</tbody>
</table>

**Score Clinical Interpretation**

<table>
<thead>
<tr>
<th>Score</th>
<th>Standard Score Range</th>
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<tbody>
<tr>
<td>Very Superior</td>
<td>130-155</td>
</tr>
<tr>
<td>Superior</td>
<td>115-129</td>
</tr>
<tr>
<td>Above Average</td>
<td>107-114</td>
</tr>
<tr>
<td>Average</td>
<td>92-106</td>
</tr>
<tr>
<td>Below Average</td>
<td>85-91</td>
</tr>
<tr>
<td>Mildly Impaired</td>
<td>77-84</td>
</tr>
<tr>
<td>Mildly to Moderately Impaired</td>
<td>70-76</td>
</tr>
<tr>
<td>Moderately-Impaired</td>
<td>62-69</td>
</tr>
<tr>
<td>Moderately-to-Severely Impaired</td>
<td>55-61</td>
</tr>
<tr>
<td>Severely-Impaired</td>
<td>45-54</td>
</tr>
</tbody>
</table>

Fig 3. List S-NAB module subtests and areas of cognitive domains assessed, standard score range of individual domains in S-NAB, and clinical interpretation of the scores.

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repeat the same subtests in the screening module at 6 months by the same neuropsychologist to assess the neurocognitive performance longitudinally.
Statistical analysis

All data management and analyses were performed using the SPSS statistical software (Version 22.0). Independent t-test was used to establish the differences in demographic features of the sample, if any, based on their BDNF SNPs and allele status. The mean differences of the standard score (SS) across the time points against the allele carrier status [wildtype G allele (Val homozygotes) vs. minor A allele (Met carriers)] were then analyzed using the paired t-test for both categories. The Cohen’s d effect size (ES) was also used to measure the magnitude of the differences and a comparison of the ES was done. Repeated measure ANOVA was then performed to delineate statistically significant differences between the groups and their neuropsychological performance across the time point (T0 = baseline/admission vs. T1 = 6th month follow-up), The Bonferroni post hoc correction for both multiple comparison and confidence interval adjustment were administered. Any statistically significant (p < 0.05) major effects and interaction were then noted. To assess the association between the allele carrier status and neuropsychological performance, the Spearman correlation coefficient test was also used.

Results

Demographic Characteristics

The demographic characteristics of the study patients are presented in Fig 4. The study patients were predominantly young males (87.5%), within the age range of 18 to 53 (75.0%) with a mean age of 27.4 (SD 8.9). These patients had an average of 11.4 (SD 2.0) years of formal education. The baseline (T1) neuropsychological assessment was conducted after the full GCS recovery of the patients with an average turnaround time of 4.8 hours (SD 7.9) post trauma, while the repeat neuropsychological assessment was done at an average of 6.1 (SD 0.1) months. In order to look at clinically meaningful markers influenced by specific genotypes, we stratified the group according to the SNPs (involving only rs6265 and rs1048218 as the rest of the SNPs were monomorphic as discussed below) and their allele status. No statistically significant differences were observed within the groups except in the presence of LOC (t = -2.026, df = 46, p = 0.049), with a higher incidence among the A minor allele carriers.

Genetic results and correlation with neurocognitive performance

**Genotype distribution and minor allele frequency.** Six BDNF mutations were examined, of which four (rs1048220, rs1048221, rs8192466, rs139352447) were found to be monomorphic. Only rs6265 and rs1048218 were found to be polymorphic in our population (refer to Fig 1). Both the controls and patients conformed to the Hardy-Weinberg equilibrium for rs6265 and rs1048218. The minor allele frequency for rs6265 was 46.7% in controls compared to the patients (43.6%), but this was not significantly different (p = .380). The high MAF values is comparable to what has been reported previously [93–97] and as annotated for East Asians in the HapMap (41.8%) and 1000genomes (48.8%).

The rs1048218 variant had a low MAF in our population (2% in controls) that is also similar to what has been reported previously and in HapMap and 1000genomes. As the variant was present at a similar frequency in both the patients and controls, no further correlation analysis was performed with this variant.

**BDNF rs6265 vs. neurocognitive performance.** Individuals with the A minor allele (corresponding to Met carriers–Met homozygotes/ Met heterozygotes) generally performed more poorly on neuropsychological testing in comparison to those with the wildtype G allele (corresponding to the Val homozygotes) at both time points. Fig 5 presents the significant mean differences as observed among the group wildtype G allele in the domains of memory (M =
Further comparison of the effect size by the measurement (i.e. domain-specific SS) demonstrated that the patients with wildtype G allele were 5.86 times more likely to perform better in the domains of attention, 1.8 times in memory, 2.82 times in executive function and 2.1 times higher in overall cognition (total index score) in comparison to the A minor allele over time. Individuals with the minor allele showed considerably lower scores at admission and remained impaired in most domains across the time points, although delayed signs of recovery were noted to be significant in the domains attention and overall cognition.

ANOVA tests revealed that the different time points (T1 = admission and T2 = 6 month follow-up) produced a significant main effect on neuropsychological SS [F (6,22) = 5.786, p < 0.001, $\eta^2_p = .616$], which was largely influenced by allele status [F(6,22) = 1.997, p = 0.110,
\[ \eta_p^2 = .353 \] based on the \( \eta_p^2 \) value (Eta-squared effect size; 0.02 = small, 0.13 = moderate and 0.3 = large). Some interactions were seen in the neurocognitive domains of attention \[ F (1,27) = 1.103, p = 0.303 \], language, \( F (1,27) = 1.159, p = 0.291 \), visuospatial, \( F (1,27) = 0.935, p = 0.342 \) and executive function \( F (1,27) = 0.820, p = 0.373 \) [as seen in estimated marginal means (EMM) plot in Fig 6A, 6B, 6D and 6E]. However, only memory [Fig 6C] had a statistically significant interaction with the allele status \[ F (1,27) = 6.476, p = 0.02 \]. The overall performance showed no interaction \[ F (1,27) = 0.305, p = 0.585 \] [see Fig 6F] across the time points and allele status.

No statistically significant associations were observed across the neurocognitive domains and specific allele status with the exception of the memory SS score at 6 months (r = -0.412, \( p = 0.05 \)). The memory scores of patients with the A allele were observed to be significantly lower at six months follow-up.

**Discussion**

We explored the prevalence and possible association of six \( BDNF \) mutations with specific neurocognitive functions in patients with mTBI over time. We observed a possible protective effect of the G allele in rs6265, with better performance in the domains of attention, executive function, memory, and overall cognition among patients with mTBI. The “finer” performance by those patients with the wildtype G allele in both neurocognitive and neurobehavioral measures, have been consistently reported by other studies involving other CNS pathologies as well [32, 88, 98–99].

For example, McAllister et al (2012) demonstrated that patients with mTBI reported better performance on measures of processing speed longitudinally among the G allele homozygotes as opposed to those who were homozygote for the A allele [32]. Similarly, Chao, Kao and
Porton (2008) reported that the age of schizophrenia onset in a group of non-related African American patients (n = 42) was significantly later in G allele homozygotes [88]. Moreover, Perkovic et al. (2014) showed that patients with schizophrenia who were G allele homozygotes were better responders to pharmacotherapeutic treatment and demonstrated significant improvement of clinical symptoms, including lesser conceptual disorganization and delusions [99].

While some studies have reported increased neurocognitive vulnerability in G allele homozygotes [69, 100–102], we believe that the superior neurocognitive performance we observed in our study may be due to the possibility that the G homozygous allele is associated with increased activity dependent secretion of BDNF, increased synaptic plasticity, and better hippocampus dependent memory and cognitive performance [99]. These mechanistic processes have been well explicated in the works of Egan et al (2003) and Kauppi et al (2013) [29, 72]. The divergent influence of haplotype specific variants cannot be overlooked as well.

On the other hand, patients with the A allele in our study revealed mostly non-significant trends of impaired neurocognitive performance with some interactions seen across the time points in the domains of executive function and overall cognition. Additionally, the memory domain saw statistically significant interaction over time and was also negatively associated...
with allele status, with evidence of regressing memory function at 6 months among the patients with the G allele. Kauppi et al (2013) noted that this preferential effect on memory is in line with the role of BDNF in the molecular processes underlying memory acquisition. Mechanistically, hippocampal or para-hippocampal BDNF is secreted during neural activation [72]. The increased postsynaptic level of BDNF is known to influence the formation of new synapses in the late phase long term potentiation (LTP), a process that is crucial for the acquisition and storage of long term memories. A successful completion of this crucial molecular process is however impeded when the activity dependent secretion and intracellular trafficking of BDNF is reduced in the protein [29, 72].

Taken together, findings of the current study are the following: (1) only two non-synonymous alterations of the amino acid were present in our study population (rs6265/Val66Met and rs1048218) and the rest of the remaining variants were monomorphic in nature; (2) mTBI patients with BDNF rs6265 Val homozygous allele showed significant differences in their neurocognitive performance and were more likely to perform better than the Met carriers in the domains of attention, memory, executive function and overall performance, both acutely and over time; (3) the Met allele carriers of BDNF rs6265 had considerably low standard scores in most neurocognitive domains observed longitudinally; (4) there was a significant main effect of the time points, and the influence of specific allele status on neurocognitive performance observed; and (5) longitudinal change in memory performance with evidence of deteriorating performance among the A minor allele group (Met carriers) was observed. Strengths of the study include a relatively well characterized homogeneous group of patients in terms of injury type or severity, a short time frame from the time of injury to neurocognitive testing, detection of early neuropsychological deficits in the acute stage, and a consistent reassessment interval at 6 months post trauma. However, there are certain limitations in our study that are worth noting. First, the method of dichotomizing the patients' allele carrier status category (wildtype G allele vs. A minor allele, both the homozygous and heterozygotes) may have unequally diminished the dual allele effect of the A minor allele homozygous vs. heterozygotes (Met/Met vs. Val/Met) on the neurocognitive performance. Additionally, the sample size representing each arms of the rs6265 polymorphism was rather small and should be increased in future longitudinal studies.

Conclusion
In conclusion, the current study has demonstrated the role of the BDNF rs6265 Val66Met polymorphism in influencing specific neurocognitive outcomes in patients with mTBI. Findings were more detrimentally profound among Met allele carriers. Our results strongly suggest that the role of the Val66Met polymorphism in influencing neurostructural alterations and cognitive and behavioral changes post-mTBI should be further explored. Such investigation in future studies may have significant influence over the ways in which mTBI patients are currently managed and their outcomes predicted.

Author Contributions
Conceived and designed the experiments: VN VV AA. Performed the experiments: VN VV AA. Analyzed the data: VN VV AA KC. Contributed reagents/materials/analysis tools: AA VN NR DG. Wrote the paper: VN VV AA NR MWB LD KC VW DG.

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