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APOE-ε4 Genotype is Associated with Elevated Post-Concussion Symptoms in Military Veterans with a Remote History of Mild Traumatic Brain Injury

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Abstract

Objective: We evaluated the influence of the APOE-ε4 allele on post-concussive symptoms in military Veterans with a remote history of mild traumatic brain injury (mTBI).
Method: Participants ($N = 77$) were administered neuropsychiatric measures, on average, approximately 5 years following their most recent mTBI and provided a DNA sample for APOE genotyping. Veterans were divided into two groups based on their ε4 status ($n = 14$ ε4+, $n = 63$ ε4–). The Neurobehavioral Symptom Inventory (NSI) was the primary outcome measure, from which a total score was derived, as well as three symptom clusters (somatic, cognitive, and affective).
Results: ANCOVAs showed a significant main effect of ε4 genotype on the NSI total score and somatic symptom cluster after adjusting for posttraumatic stress symptoms and mTBI history ($p = .019$–$.028$, $\eta_p^2 = .064$–$.073$), such that ε4+ Veterans endorsed significantly greater symptoms than ε4– Veterans.
Conclusions: Our findings suggest that genetic risk may help to explain the poorer long-term outcomes often observed in this population.

Keywords: APOE gene; Genetics; Post-concussion symptoms; Neurobehavioral Symptom Inventory; Military Veterans; mTBI; Head injury

Introduction

A major challenge when studying military mild traumatic brain injury (mTBI) is disentangling the many complicating and compounding factors that influence outcome and recovery. Though full recovery is generally expected to occur within 3 months following mTBI (Boyle et al., 2014), many Veterans continue to experience post-concussion symptoms (PCS) well beyond the acute phase of injury (Schwab et al., 2017). Although poorly understood, numerous variables have been associated with prolonged neurobehavioral symptoms in Veterans, including the presence of posttraumatic stress disorder (PTSD) symptoms (Benge, Pastorek, & Thornton, 2009; Schwab et al., 2017) and number of previous TBIs (Dretsch, Silverberg, & Iverson, 2015), yet it remains to be seen the extent to which there is a genetic contribution to these enduring symptoms.

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The apolipoprotein E (APOE) gene has been implicated in both response and repair processes following neurotrauma (Horsburgh, McCarron, White, & Nicoll, 2000) and has been the most widely studied gene to date within the context of the broader TBI literature. Located on chromosome 19, the APOE gene comprises three primary alleles (ε2, ε3, and ε4), each possessing a unique structure and function (Mahley & Huang, 2012). Notably, the ε4 allele has been shown to be detrimental to neuronal recovery efforts following head injury, as it obstructs neurite outgrowth, induces mitochondrial dysfunction, alters the clearance of amyloid-β, and causes tau-mediated neurodegeneration (Horsburgh et al., 2000; Mahley & Huang, 2012). Furthermore, the APOE-ε4 allele has also been associated with poor functional and cognitive outcomes in TBI (Ariza et al., 2006; Horsburgh et al., 2000; Mahley & Huang, 2012).

Few studies have examined the effects of ε4 status on PCS following head injury and, among the studies that have characterized this relationship, the focus has primarily been on evaluating symptoms in the acute to sub-acute phase of injury (Lawrence, Comper, Hutchison, & Sharma, 2015). However, given the negative impact these symptoms have on functional status and quality of life, and the costs associated with increased service utilization (Taylor et al., 2012), it is critical to deepen our understanding of the factors that contribute to the presence of *chronic* symptoms following mTBI. Therefore, within a well-characterized sample of military Veterans with a remote history of mTBI, we aimed to investigate the relationship between APOE-ε4 status and post-concussive symptomatology. Given the deleterious effects of ε4 genotype on neuronal repair and recovery following neurotrauma, as well as previous work (Merritt et al., 2018) identifying a relationship between ε4 allele status and measures of psychiatric distress (i.e., PTSD, depression, and anxiety symptoms), we hypothesized that Veterans possessing an ε4 allele would show elevated PCS relative to Veterans without an ε4 allele.

Method

Participants and Procedures

Seventy-seven military Veterans participated in the study, the majority (94.8%) of whom served in Operation Enduring or Iraqi Freedom or Operation New Dawn. Veterans were recruited through recruitment flyers and outpatient clinics at a local Veterans Affairs hospital. All study procedures, including TBI history interviews, completion of self-report questionnaires, and collection and processing of buccal swabs, occurred within the VA setting or its affiliated university. The present study was approved by the necessary institutional review boards, and all Veterans formally consented to the research procedures.

A modified version of the VA Semi-Structured Clinical Interview for TBI was used to collect information pertaining to TBI history (dates, mechanisms of injury) as well as diagnostic details (e.g., duration of loss of consciousness [LOC], alteration of consciousness [AOC], and posttraumatic amnesia [PTA]). Additionally, the VA/DoD Clinical Practice Guidelines for Management of Concussion/Mild TBI were used, which specify the following criteria for mTBI: LOC duration may be 0–30 min, AOC duration may be up to 24 h, and PTA duration may be 0–1 day. The total number of reported events meeting mTBI diagnostic criteria was calculated, as was the time from the most recent mTBI event to the date of study enrollment/evaluation.

Exclusion criteria for the present study were: history of a severe mental illness (e.g., bipolar disorder, schizophrenia, or other psychotic disorder) as per DSM-IV-TR criteria; history of, or current, alcohol or substance abuse/dependence diagnosis as per DSM-IV-TR criteria; positive toxicology screen on day of evaluation; history of a serious medical illness or neurological condition (e.g., tumor, seizure disorder, multiple sclerosis); or history of a moderate or severe TBI as per VA/DoD criteria referenced above. In addition to having sustained at least one previous mTBI, inclusion criteria included completion of self-report questionnaires and providing a DNA sample for APOE genotyping.

Genotyping Procedures

APOE genotyping was conducted using polymerase chain reaction analysis. Briefly, DNA was collected from Veterans using buccal swabs and samples were processed and analyzed according to procedures described in Saunders and colleagues (1993). Veterans' APOE genotype was determined by using two single nucleotide polymorphism (SNP) assays for the SNPs APOE112 and APOE158 (rs429358 and rs7412, respectively). Genotyping results for the sample were: ε2/ε2 (n = 0, 0%), ε2/ε3 (n = 8, 10.4%), ε2/ε4 (n = 2, 2.6%), ε3/ε3 (n = 55, 71.4%), ε3/ε4 (n = 11, 14.3%), and ε4/ε4 (n = 1, 1.3%). Veterans were divided into two groups based on the presence or absence of the ε4 allele (n = 14 ε4+, n = 63 ε4–). Participants were not informed of their genotyping results.

Measures

The Neurobehavioral Symptom Inventory (NSI) was the primary outcome measure utilized in the study (Meterko et al., 2012). The NSI is a self-report measure assessing commonly reported PCS (e.g., headaches, feeling dizzy, difficulty making decisions, irritability, difficulty falling or staying asleep). The measure is comprised of 22 unique symptoms and participants are instructed to rate each symptom with regard to how much they have been disturbed by the symptom *since their injury.* A five-point rating scale is provided, ranging from "0" (None) to "4" (Very Severe); thus, higher scores represent more severe symptomatology. A total score was calculated for each participant by adding together the selected responses from each item (possible range: 0–88). Additionally, three symptom clusters were derived from the NSI according to a previous factor analysis (Caplan et al., 2010): (1) Somatic/Sensory (11 items; possible range: 0–44); (2) Cognitive (4 items; possible range: 0–16); and (3) Affective (7 items; possible range: 0–28). The psychometric properties of the NSI are excellent (internal consistency: $\alpha = 0.95$) in TBI samples (King et al., 2012).

The PTSD Checklist – Military Version (PCL-M) is a 17-item self-report measure assessing DSM-IV-TR Cluster B, C, and D symptoms of PTSD (Weathers, Huska, & Keane, 1991). Participants are asked to rate how much they have been bothered by each symptom *over the past month* using a rating scale ranging from "Not at all" (corresponding to a score of "1") to "Extremely" (corresponding to a score of "5"); higher scores represent more severe symptomatology. A total score was computed for each participant by summing individual responses from each item (possible range: 17–85). The PCL-M also has well established psychometric properties (Keen, Kutter, Niles, & Krinsley, 2008).

Statistical Analyses

Descriptive statistics were run on the overall sample and ε4 allele groups were compared on basic demographics and TBI characteristics using independent samples *t*-tests and chi-square analyses. Next, the distribution of the primary outcome variables (NSI Total Score and NSI symptom clusters) was evaluated using Shapiro–Wilk tests. Results indicated that the NSI Total Score was normally distributed ($W = .982$, $p = .333$), as was the Affective symptom cluster ($W = .972$, $p = .090$); however, the other two symptom clusters were not normally distributed: Somatic ($W = .962$, $p = .021$) and Cognitive ($W = .963$, $p = .023$). Data transformations did not result in any notable changes to the distribution of the data; thus, the original (non-transformed) variables were used in all analyses.

Pearson product–moment correlations (r) or Spearman's rank correlations (r_s) were run on the overall sample to examine the relationship between self-reported PCS (NSI symptom scores) and PTSD symptoms (PCL-M total score) as well as lifetime number of TBIs. Finally, one-way analyses of covariance (ANCOVAs) adjusting for PTSD symptoms (PCL-M total score) and lifetime number of TBIs were conducted to determine the effect of APOE-ε4 allele status on the NSI total score and NSI symptom clusters.

Results

Sample Characteristics

Sample characteristics are presented in Table 1 for the overall sample, as well for each allele group. As evidenced in the table, no significant differences were observed between the ε4+ and ε4– groups with respect to demographics and TBI characteristics.

Relationship between NSI Scores, PTSD Symptoms, and TBI History

The NSI total score was significantly positively associated with PTSD symptoms ($r = .776$, $p = <.001$) and lifetime number of TBIs ($r_s = .374$, $p = .001$). The somatic symptom cluster was also significantly positively associated with PTSD symptoms ($r = .671$, $p = < .001$) and lifetime number of TBIs ($r_s = .381$, $p = .001$). Similar relationships were identified between the cognitive symptom cluster and PTSD symptoms ($r = .663$, $p = <.001$), as well as between the cognitive symptom cluster and lifetime number of TBIs ($r_s = .335$, $p = .003$). Finally, the affective symptom cluster was significantly positively associated with PTSD symptoms ($r = .796$, $p = < .001$) and with lifetime number of TBIs ($r_s = .282$, $p = .013$).

Table 1. Participant demographics and injury-related variables.

Variables	Overall sample ($N = 77$)		ε4+ mTBI Veterans ($n = 14$)		ε4– mTBI Veterans ($n = 63$)		
	M	*SD*	*M*	*SD*	*M*	*SD*	p^a
Age	32.26	7.12	33.71	7.56	31.94	7.04	.402
Education (years)	13.92	1.60	13.64	1.39	13.98	1.64	.473
Lifetime # of mTBIs	2.47	1.37	1.93	1.00	2.59	1.42	.105
Time since most recent mTBI (years)	5.31	3.94	4.28	2.76	5.54	4.14	.281
CES total score*	16.51	12.11	14.92	11.87	16.88	12.25	.617
PCL-M total score	45.65	17.67	48.36	12.34	45.05	18.68	.421
	N	%	*N*	%	*N*	%	p^b
Sex							.299
Male	67	87.0	11	78.6	56	88.9	
Female	10	13.0	3	21.4	7	11.1	
Ethnicity							.232
Caucasian	33	42.9	4	28.6	29	46.0	
Non-Caucasian	44	57.1	10	71.4	34	54.0	
Mechanism of injury: blast (during most sig. TBI)							.865
Yes	26	33.8	5	35.7	21	33.3	
No	51	66.2	9	64.3	42	66.7	
LOC (during most sig. TBI)							.232
Yes	44	57.1	6	42.9	38	60.3	
No	33	42.9	8	57.1	25	39.7	
AOC (during most sig. TBI)							.232
Yes	33	42.9	8	57.1	25	39.7	
No	44	57.1	6	42.9	38	60.3	
PTA (during most sig. TBI)							.548
Yes	37	48.1	7	50.0	30	47.6	
No	35	45.5	7	50.0	28	44.4	
Unsure	5	6.5	0	0	5	7.9	

Note: mTBI = mild traumatic brain injury; CES = Combat Exposure Scale; PCL-M = Posttraumatic Stress Disorder (PTSD) Checklist – Military Version.
[a]Independent samples *t*-tests were conducted to compare ε4 allele groups on age, education, lifetime number of mTBIs, time from most recent mTBI to assessment, CES total score, and PCL-M total score.
[b]Chi-square analyses were conducted to evaluate groups on sex, ethnicity, mechanism of injury, and presence of LOC, AOC, and PTA during the most significant mTBI.
*The CES total score is based on $N = 63$ ($n = 12$ ε4+, $n = 51$ ε4–), as 14 Veterans had missing data for the CES.

APOE-ε4 Genotype & NSI Scores

A one-way ANCOVA revealed a significant effect of ε4 status on the NSI total score after controlling for PTSD symptoms and lifetime number of TBIs, $F(1, 73) = 5.01$, $p = .028$, $\eta_p^2 = .064$, such that ε4+ mTBI Veterans endorsed significantly greater symptoms than ε4– mTBI Veterans (see Fig. 1A). To determine whether particular symptoms may be driving this effect, separate ANCOVAs were conducted on the three NSI symptom clusters. When using PTSD symptoms and lifetime number of TBIs as covariates, the ε4+ and ε4– allele groups differed significantly on the somatic symptom cluster, with ε4+ participants endorsing greater symptomatology than ε4– participants ($F(1, 73) = 5.72$, $p = .019$, $\eta_p^2 = .073$; see Fig. 1B). Follow-up analyses revealed that although there was a numerical difference in the direction of more severe symptoms for ε4+ participants relative to ε4– participants for each of the 11 somatic symptom cluster items, only the items of "vision problems" and "sensitivity to light" reached statistical significance ($p < .05$). Finally, no significant differences were found for the cognitive and affective symptom clusters between ε4 allele groups after adjusting for the covariates (see Fig. 1B): $F(1, 73) = 2.21$, $p = .141$, $\eta_p^2 = .029$ and $F(1, 73) = 1.74$, $p = .191$, $\eta_p^2 = .023$, respectively.

Discussion

We evaluated the influence of APOE-ε4 genotype status on post-concussion symptom reporting in a sample of military Veterans with a remote history of mTBI. Consistent with our hypothesis, mTBI ε4+ Veterans endorsed significantly greater overall symptoms, as represented by the NSI total score, compared to mTBI ε4– Veterans. Furthermore, follow-up analyses revealed that participants with the ε4 allele reported significantly elevated somatic symptoms relative to Veterans without the

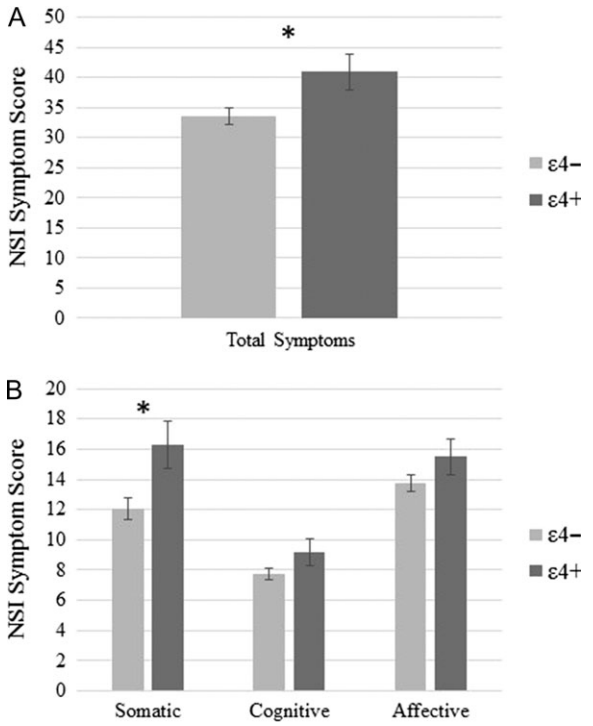

Fig. 1. Neurobehavioral Symptom Inventory (NSI) symptom scores by ε4 allele group. Adjusted mean symptom scores (± standard errors) are displayed for (A) NSI total symptom score and (B) NSI symptom clusters—somatic, cognitive, and affective. *$p < .05$.

ε4 allele, but no significant differences were found between APOE allele groups on the cognitive and affective symptom clusters, despite overall higher mean symptom scores for the ε4+ group.

A limited number of studies have evaluated the influence of ε4 genotype on post-concussion or neurobehavioral outcomes following TBI in adults and, among the published studies exploring this relationship, results have been mixed (Lawrence et al., 2015). Consistent with the present findings, a study that examined civilians with moderate-to-severe TBI 6 months post-injury found that ε4+ individuals endorsed greater PCS than ε4– individuals (Ariza et al., 2006). Similarly, in a study that examined PCS in concussed college athletes (Merritt & Arnett, 2016), ε4 carriers endorsed greater total symptoms relative to non-carriers when assessed in the acute period following injury (the majority were assessed within 1 week of injury). Nonetheless, other studies that examined symptom reporting in the acute to sub-acute phase of injury—anywhere from approximately 1–12 months post-TBI—have found no significant differences between ε4 allele groups (Chamelian, Reis, & Feinstein, 2004; Han et al., 2007; Hiekkanen, Kurki, Brandstack, Kairisto, & Tenovuo, 2009). Although our results align with some studies but contrast with others, it should be emphasized that our study focused on *chronic* PCS as opposed to symptoms assessed shortly after head injury. Thus, our study extends prior work by establishing that a relationship exists between ε4 status and PCS assessed well after injury, and suggests that genetic factors may contribute to the poorer long-term clinical outcomes that are often associated with PCS in Veterans with neurotrauma histories.

Given the high correlation between PTSD symptoms and symptom endorsement on the NSI—as well as the association between number of lifetime TBIs and NSI symptoms—we adjusted for these important variables in all analyses in order to determine the independent effect of ε4 genotype on neurobehavioral symptoms. Although many previous studies have attributed persisting PCS primarily to PTSD (Benge et al., 2009; Schwab et al., 2017) or repetitive TBIs (Dretsch et al., 2015), our findings revealed that the relationship between ε4 genotype and neurobehavioral symptoms is significant above and beyond the effects of these factors. This finding suggests a unique influence of ε4 status on PCS, particularly on somatic/sensory symptoms—that is, symptoms that are thought to be more neurologically based. Given the known deleterious effects of the ε4 genotype on neuronal repair and recovery following neurotrauma (Horsburgh et al., 2000), it is possible that those possessing an ε4 allele are slower to recover, which manifests externally in specific symptom complaints.

Taken together, our findings indicate that in Veterans with a history of mTBI, presence of an APOE-ε4 allele is associated with experiencing greater symptomatology, even after adjusting for the effects of PTSD symptoms and lifetime number of TBIs. This work advances our understanding of important factors that contribute to the enduring symptoms experienced by

many Veterans with head injury histories, and it provides evidence for a genetic contribution to these negative symptoms. Our study has a number of strengths, including a focus on *mild* head injury in a sample of well-characterized military Veterans evaluated in the chronic phase of injury. However, there are some important limitations of the present study that should be highlighted. First, our sample size was relatively small and, given the nature of our sample, our findings are not generalizable to females as well as children and older adults. Additionally, we did not have any pre-injury NSI data on the Veterans included in the study; having this data would allow us to better speak to the possible interaction between possession of an APOE-ε4 allele and history of neurotrauma. Findings should be replicated in the context of larger samples, and future research could explore whether specific symptoms are endorsed more often, or at greater severities, by ε4-allele carriers compared to those without the ε4 allele. Finally, longitudinal studies incorporating brain-based correlates are needed in order to better understand how APOE-ε4 genotype modifies neurobehavioral outcomes in the aftermath of head injury.

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Conflict of Interest

None declared.

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