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Permalink
https://escholarship.org/uc/item/1pt0079j

Journal
Journal of Neurotrauma, 35(19)

ISSN
0897-7151

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Publication Date
2018-10-01

DOI
10.1089/neu.2017.5372

Peer reviewed

Apolipoprotein E ε4 Genotype Is Associated with Elevated Psychiatric Distress in Veterans with a History of Mild to Moderate Traumatic Brain Injury

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Abstract

As few studies have examined the relationship between the apolipoprotein E (APOE) gene and clinical outcomes after military-related traumatic brain injury (TBI), we aimed to determine whether the ε4 allele of the APOE gene influences neuropsychiatric symptoms in veterans with a history of mild-to-moderate TBI. Participants included 133 veterans (TBI = 79; military controls [MC] = 54) who underwent APOE genotyping and were divided into ε4$^+$ (TBI = 18; MC = 15) and ε4$^-$ (TBI = 61; MC = 39) groups. All participants underwent evaluation of psychological distress using the Beck Depression Inventory-II, Beck Anxiety Inventory, and PTSD Checklist-Military Version. Two-way analyses of variance were conducted to examine the effect of group (TBI vs. MC) and APOE-ε4 status (ε4$^+$ vs. ε4$^-$) across symptom measures. There was a significant main effect of group across all symptom measures (TBI > MC; all p values <0.001), no main effect of ε4 genotype ($p = 0.152$–0.222), and a significant interaction of group by ε4 genotype across all measures ($p = 0.027$–0.047). Specifically, for TBI participants, ε4$^+$ veterans demonstrated significantly higher symptom scores across all measures when compared to ε4$^-$ veterans ($p = 0.007$–0.015). For MC participants, ε4 status had no effect on the severity of psychiatric symptom scores ($p = 0.585$–0.708). Our results demonstrate that, in our well-characterized sample of veterans with history of neurotrauma, possession of the ε4 allele conveys risk for increased symptomatology (i.e., depression, anxiety, and post-traumatic stress disorder), even well outside of the acute phase of injury. Findings suggest a meaningful relationship between APOE genotype and psychiatric distress post-TBI, and they suggest that there is a brain basis for the complex neuropsychiatric presentation often observed in this vulnerable population. Future longitudinal studies are needed in order to further our understanding of how genetic factors influence response to TBI.

Keywords: APOE gene; genetics; military veterans; psychiatric distress; traumatic brain injury

Introduction

RESEARCH REGARDING CLINICAL OUTCOMES in the aftermath of traumatic brain injury (TBI) has burgeoned considerably, and it has become well established that military-related TBI is often coupled with high levels of psychiatric distress.[1–5] Post-traumatic stress disorder (PTSD) has undoubtedly been the most widely studied comorbid condition associated with TBI, but other mental health diagnoses have also been linked with TBI, including, but not limited to, depression and anxiety.[3,6–9] For example, in a study of Afghanistan and Iraq-era veterans with positive TBI screens, Carlson and colleagues[7] documented that over 80% of these service members also had at least one clinician-diagnosed psychiatric disorder. Interestingly, in this study, veterans who screened positive for TBI were 3 times more likely to have been diagnosed with PTSD

compared to those who screened negative for TBI.[7] These findings not only highlight the prevalence of psychiatric distress in this unique population, but also raise the question of why such high rates of mental health symptoms—especially PTSD—are observed in service members with a history of TBI relative to those without TBI.

A number of theories have been proposed to account for the increased rates of psychiatric distress and symptomatology in veterans who have experienced a TBI. Notably, though, the occurrence of psychiatric distress post-TBI is not specific to military-related TBI, given that civilian outcome studies have also reported high rates of mental health symptoms post-TBI.[10–12] Explanations for these observed comorbidities broadly fall within the realm of environmental versus biological contributions. Environmental considerations primarily relate to the context under which the TBI was sustained. For example, the presence or degree of combat

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exposure,[9,13] mechanism of injury (such as blast or blunt force),[14–16] and severity of the injury event[14,17] have all been hypothesized to at least partially explain the development of persisting symptoms and/or psychiatric distress post-TBI. In contrast, postulated biological mechanisms accounting for the high rates of psychiatric distress include pathophysiological changes associated with TBI,[18–20] as well as the influence of genetic predispositions.[21–23]

Our understanding of the associations between specific genetic polymorphisms and TBI susceptibility and outcome is still in its infancy. Several candidate genes have been explored thus far, but at present, the gene encoding apolipoprotein E (apoE) has been the most widely studied gene with respect to its role in recovery and outcome post-TBI.[24–26] ApoE is a lipoprotein that transports and metabolizes lipids (such as cholesterol) within the central nervous system (CNS),[27,28] and it is primarily involved in neuronal maintenance, growth, and repair.[28–30] ApoE is encoded by the apolipoprotein E (APOE) gene, located on chromosome 19, which is comprised of three alleles—APOE ε2, APOE ε3, and APOE ε4—for a total of six genotypes (three homozygous: ε2/ε2, ε3/ε3, ε4/ε4, and three heterozygous: ε2/ε3, ε2/ε4, and ε3/ε4).[31] The properties of the ε2, ε3, and ε4 alleles result in differential capacities for cell maintenance and repair/regrowth.[28,32] For instance, whereas the ε3 allele facilitates neurite outgrowth, the ε4 allele inhibits neurite outgrowth.[33–35] The ε4 allele has also been implicated in other neuropathological processes, including mitochondrial dysfunction, inflammation, increased amyloid β (Aβ) production/accumulation, and altered Aβ peptide clearance.[26,28,32] Thus, the ε4 allele is considered to be a risk factor for possible neuropathology post-CNS compromise.[24,28,36]

The APOE gene was initially studied in the context of aging, and it has consistently been found to be a risk factor for Alzheimer's disease (AD; for a review, see Verghese and colleagues[37] and Kim and colleagues[38]). More recently, there are now several lines of research suggesting that the presence of the ε4 allele is associated with unfavorable outcome post-TBI.[23–25,31] For example, TBI ε4 carriers, relative to non-ε4 carriers, have been found to demonstrate 1) worse global and functional outcomes,[39–43] 2) poorer neuropsychological performance post-injury,[44–47] and 3) increased risk for developing AD or other dementia.[48–50] However, despite rapid expansion of research related to the APOE gene and clinical outcome post-TBI, to our knowledge, no studies have examined the relationship between the APOE gene and psychiatric symptom distress in the context of military TBI. Therefore, in the present study, we aimed to determine whether the ε4 allele of the APOE gene influences neuropsychiatric symptoms in military veterans with and without mild-to-moderate TBI. We hypothesized that among veterans with a history of TBI, ε4+ participants would experience greater psychiatric symptoms relative to ε4− participants. In contrast, we hypothesized that ε4 allele status would not influence psychiatric symptoms in military controls (MCs).

Methods

Participants and procedures

Participants were 79 veterans with a history of TBI ($n = 69$ mild, $n = 10$ moderate) and 54 MCs without a history of TBI who were predominantly involved in the Iraq and Afghanistan conflicts (i.e., Operation Enduring Freedom [OEF], Operation Iraqi Freedom [OIF], and Operation New Dawn [OND]). Veterans were recruited from the VA San Diego Healthcare System (VASDHS) through outpatient clinics (e.g., a TBI specialty clinic), recruitment flyers posted within the VASDHS, and word of mouth. Participants were administered several questionnaires, which included completion of

self-report measures of psychiatric distress, as well as select modules of the Mini-International Neuropsychiatric Interview (M.I.N.I.; i.e., Major Depressive Episode and Posttraumatic Stress Disorder [PTSD]). The present study was reviewed and approved by local institutional review boards, and informed consent was obtained from all participants before research participation.

An initial screening interview was conducted to determine participant eligibility. TBI history was assessed using a clinical interview adapted from the VA Semi-Structured Clinical Interview for TBI.[51] The interview was comprised of questions pertaining to the nature of previously sustained TBIs. Specifically, the following information was gathered for each TBI reported: injury-severity characteristics (presence and duration of loss of consciousness [LOC], post-traumatic amnesia [PTA], and alteration of consciousness [AOC]), the context under which the TBI was sustained (military vs. nonmilitary event), the mechanism of injury (blast-related vs. blunt/mechanical force), and when the TBI occurred. This information was used to determine the "worst" or "most significant" TBI ever experienced by each service member, which was, in turn, used to classify injury severity for the present study. Additionally, the interview was used to determine the total number of lifetime TBIs sustained by each participant (a TBI was counted if it met criteria as defined below).

To determine whether veterans met criteria for having sustained a TBI, the VA/DoD (Department of Defense) Clinical Practice Guideline for Management of Concussion/Mild TBI[52] definition was applied; these guidelines indicate that in order for an event to be classified as a TBI, the individual must have experienced at least one of the following: 1) LOC, 2) AOC, 3) PTA, 4) neurological deficits (such as weakness, loss of balance, etc.), and 5) intracranial lesion.[52] For the purpose of this study, information pertaining to neurological deficits and intracranial lesions was not available for all participants; thus, classification of TBI was based on participant self-reported duration of LOC, AOC, and PTA. A *mild* TBI was defined as experiencing LOC <30 min, AOC up to 24 h, and/or PTA <24 h; a *moderate* TBI was defined as experiencing LOC >30 min and <24 h, AOC >24 h, and/or PTA >24 h but <7 days.[52] The interviews were conducted face to face by either post-baccalaureate research assistants or graduate students under the supervision of a neuropsychologist. If participants did not report a history of TBI (as defined above), these veterans were classified as MC participants.

Exclusion criteria for the TBI group included the following: 1) history of severe TBI (defined as LOC ≥24 h, AOC >24 h, and/or PTA ≥7 days); 2) having the "worst" or "most significant" TBI occur before the age of 18; 3) history of a neurological disorder or serious medical illness (e.g., epilepsy, multiple sclerosis, stroke, myocardial infarction, etc.); 4) history of bipolar disorder, schizophrenia, or another psychotic disorder as per *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition, Text Revision* (DSM-IV-TR) criteria[53]; 5) current (within the past 30 days) substance/alcohol abuse or dependence as per DSM-IV-TR criteria; 6) a positive toxicology screen (measured by the Rapid Response 10-drug Test Panel); and 7) suboptimal effort as determined by the Test of Memory Malingering (TOMM)[54] *or* the California Verbal Learning Test-II (CVLT-II)[55] Forced Choice Recognition subset. Exclusion criteria for the MC group included the following: 1) history of TBI (regardless of severity level) and 2) meeting criteria 3–7 as defined above for the TBI sample. Inclusion criteria for both the TBI and MC groups required that veterans provide a DNA sample that was successfully analyzed for their APOE genotype.

Laboratory procedures

Participants' DNA was collected by buccal sample; specifically, participants swabbed the inside of their cheek to obtain a saliva sample that could be used for APOE genotyping. The APOE genotype for each participant was determined by using two Taqman® single-nucleotide polymorphism (SNP) assays for the SNPs,

APOE112 (rs429358) and APOE158 (rs7412). Participants were genotyped using a method based on polymerase chain reaction identical to that of Saunders and colleagues.[56] APOE genotyping results for the overall sample were as follows: $\epsilon2/\epsilon2$ ($n=0$; 0%), $\epsilon2/\epsilon3$ ($n=12$; 9.0%), $\epsilon2/\epsilon4$ ($n=4$; 3.0%), $\epsilon3/\epsilon3$ ($n=88$; 66.2%), $\epsilon3/\epsilon4$ ($n=26$; 19.5%), and $\epsilon4/\epsilon4$ ($n=3$; 2.3%). Based on these observed frequencies, participants were divided into two groups—veterans with one or two copies of the $\epsilon4$ allele were classified as "$\epsilon4$ present" ($\epsilon4^+$) and veterans with no copies of the $\epsilon4$ allele were classified as "$\epsilon4$ absent" ($\epsilon4^-$). Veterans were not informed of their APOE genotype.

Primary outcome measures

Beck Depression Inventory-II. The Beck Depression Inventory-II (BDI-II)[57] is a 21-item self-report measure assessing depressive symptomatology. Each item on the BDI-II is comprised of four statements related to a particular symptom of depression. Participants are instructed to select the statement in each item that best describes how they have been feeling over the past 2 weeks. The statements correspond to values ranging from 0 to 3, with higher values representing more-severe depressive symptomatology. A total score was calculated by adding together the ratings for the 21 items (possible range, 0–63). The psychometric properties of the BDI-II are well established.[57,58]

Beck Anxiety Inventory. The Beck Anxiety Inventory (BAI)[59] is a 21-item self-report measure assessing generalized anxiety. Each item corresponds to a common symptom of anxiety and participants are asked to rate the extent to which they were bothered by each symptom during the past week using a 4-point rating scale ranging from 0 ("Not at all") to 3 ("Severely—I could barely stand it"). Higher scores represent more-severe anxiety. A total score was calculated by aggregating the individual responses from each item (possible range, 0–63). Similar to the BDI-II, the BAI has sound psychometric properties.[59–62]

PTSD Checklist – Military Version. The PTSD Checklist – Military Version (PCL-M)[63] is a 17-item self-report measure designed to assess DSM-IV-TR diagnostic criteria for PTSD. Each item on the PCL-M corresponds to a DSM symptom of PTSD, and participants are asked to rate the extent to which they have been bothered by each symptom over the past month using a 1–5 scale, with 1 indicating "Not at all" and 5 indicating "Extremely." Higher scores represent more-severe PTSD symptomatology. A total score was calculated by summing the selected values from each item (possible range, 17–85). The psychometric properties of the PCL-M have also been well established.[64–67]

Participants were also administered a measure of pre-morbid intellectual functioning—the Reading subtest of the Wide Range Achievement Test 4,[68] as well as measures of effort, including the TOMM[54] and the CVLT-II Forced Choice Recognition subtest.[55] As noted above, participants who demonstrated performances below clinical cut-offs on one or both of these tasks were removed from the analyses.

Statistical analyses

Descriptive statistics were run on the overall sample, and TBI and MC participants were compared to determine whether there were any differences between groups with regard to basic demographic characteristics. Independent-samples t-tests were used to evaluate continuous data, and chi-square analyses were used to evaluate categorical data. Within the TBI sample, participants were divided into mild and moderate TBI groups and were compared across demographic and injury severity characteristics. TBI participants were also divided into groups based on the presence or absence of an $\epsilon4$ allele ($\epsilon4^+$ vs. $\epsilon4^-$), and allele groups were compared across the same demographic and injury severity characteristics. Two-way analyses of variance (ANOVAs) were conducted in order to examine the effect of group (TBI vs. MC) and $\epsilon4$ status ($\epsilon4^+$ vs. $\epsilon4^-$) across self-report measures of psychiatric distress. Two-way ANOVAs were also conducted to determine whether results would differ after removal of moderate TBI participants from the analyses. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS; version 24; SPSS IBM, New York, NY).

Results

Demographic and injury-related characteristics

The overall sample included 133 military veterans (79.7% male) who were, on average, 32.35 years old (standard deviation [SD] = 7.08; median [Mdn] = 30.00; range = 21–53) and who completed 14.33 years of education (SD = 1.74; Mdn = 14.00; range = 12–18). Approximately half of the participants self-identified as white (51.1%), followed by Hispanic/Latino (27.1%), black (9.0%), Asian/Pacific Islander (8.3%), and Other (4.5%). The majority of the participants (89.5%) served in OEF/OIF/OND, and 24.8% of the overall sample had at least one $\epsilon4$ allele.

Participant demographic characteristics for the TBI ($n=79$) and MC ($n=54$) groups are presented in Table 1. Overall, groups were well matched, given that there were no differences between TBI and MC participants with respect to age, sex, marital status, employment status, branch of service, OEF/OIF/OND veteran status, and APOE $\epsilon4$ allele status. As expected, a greater proportion of participants in the TBI group (68.4%) were exposed to combat compared to the MC group (37.0%). Groups also differed on ethnicity; 66.7% of MCs identified as white compared to 40.5% of TBI participants. Finally, education significantly differed between groups ($p=0.007$), with the MC group having, on average, 0.8 more years of education than the TBI group. However, the groups did not differ on a measure of pre-morbid intellectual functioning (WRAT4 Reading subtest, $p>0.05$).

Among the TBI participants, 69 (87.3%) were classified as having a mild TBI, and 10 (12.7%) were classified as having a moderate TBI. Table 2 compares TBI participants by injury severity (mild vs. moderate TBI) across demographic variables and injury-related characteristics. The average time from injury to assessment was 76.32 months (~6 years) across the TBI sample. There were no significant differences between mild and moderate TBI groups on any of the demographic variables, and results were similar when nonparametric statistics were performed (all $p>0.05$). By definition, mild and moderate groups differed on injury severity characteristics (refer to Table 2).

Table 3 compares TBI participants by $\epsilon4$ status ($\epsilon4^+$ vs. $\epsilon4^-$) across demographic and injury-related characteristics, as well as across lifetime diagnosis of psychiatric disorders (i.e., Major Depressive Disorder [MDD], PTSD). Eighteen participants (22.8%) were classified as $\epsilon4^+$ and 61 (77.2%) were classified as $\epsilon4^-$. APOE $\epsilon4^+$ and $\epsilon4^-$ participants did not differ across any of the demographic or injury-related characteristics, nor did the groups differ on presence of psychiatric disorders.

Psychiatric distress

When examining the BDI-II total score, a main effect of group was found ($F_{(1, 129)}=59.60$; $p<0.001$; $\eta_p^2=0.316$), such that the total score was significantly greater for TBI participants (mean [M] = 20.89; SD = 12.87) than for MCs ($M=5.85$; SD = 8.65). Although the main effect of $\epsilon4$ allele status was not significant

TABLE 1. DEMOGRAPHIC CHARACTERISTICS ($N=133$)

Variables	TBI group (n=79)		MC group (n=54)		p value[a]
	M	SD	M	SD	
Age	32.43	7.05	32.22	7.19	0.869
Education (years)	13.99	1.57	14.83	1.86	0.007
WRAT4 Reading SS	100.96	10.92	103.28	9.95	0.218
	N	%	N	%	p value[b]
Sex					
Male	67	84.8	39	72.2	0.076
Female	12	15.2	15	27.8	
Ethnicity					
White	32	40.5	36	66.7	0.002
Hispanic	28	35.4	8	14.8	
Black	9	11.4	3	5.6	
Asian/Pacific Islander	9	11.4	2	3.7	
Other	1	1.3	5	9.3	
Married/cohabitating					
Yes	29	36.7	21	38.9	0.887
No	48	60.8	33	61.1	
Missing	2	2.5	0	0	
Currently employed					
Yes	36	45.6	31	57.4	0.204
No	42	53.2	23	42.6	
Missing	1	1.3	0	0	
Branch of service					
Air Force	6	7.6	5	9.3	0.731
Army	19	24.1	10	18.5	
Marines	28	35.4	16	29.6	
Navy	25	31.6	21	38.9	
Other	1	1.3	0	0	
Missing	0	0	2	3.7	
OEF/OIF/OND veteran					
Yes	74	93.7	45	83.3	0.056
No	5	6.3	9	16.7	
Combat exposure					
Yes	54	68.4	20	37.0	0.002
No	25	31.6	30	55.6	
Missing	0	0	4	7.4	
APOE ε4 allele status					
ε4 Present (ε4+)	18	22.8	15	27.8	0.513
ε4 Absent (ε4–)	61	77.2	39	72.2	

[a]Independent-samples t-tests were used to determine whether there were group differences for age, education, and WRAT4 Reading.
[b]Chi-square analyses were used to determine whether there were group differences for sex, ethnicity, marital status, employment status, military branch of service, OEF/OIF/OND status, combat exposure, and APOE ε4 allele status.
WRAT4, Wide Range Achievement Test 4; SS, standard score; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn; TBI, traumatic brain injury; MC, military control; M, mean; SD, standard deviation.

($F_{(1, 129)}=2.07$; $p=0.152$; $\eta_p^2=0.016$), the interaction between group and ε4 allele status was significant ($F_{(1, 129)}=4.01$; $p=0.047$; $\eta_p^2=0.030$). Specifically, as depicted in Figure 1, TBI-ε4+ veterans had higher BDI-II scores than TBI-ε4− veterans ($F_{(1, 142)}=6.77$; $p=0.010$; $\eta_p^2=0.050$). In contrast, there were no significant group differences by APOE-ε4 status for MCs ($F_{(1, 129)}=0.14$; $p=0.708$; $\eta_p^2=0.001$).

A main effect of group was also found for the BAI total score ($F_{(1, 129)}=40.43$; $p<0.001$; $\eta_p^2=0.239$), such that BAI scores were significantly greater for TBI participants ($M=13.43$; $SD=11.18$) than for MCs ($M=3.52$; $SD=6.79$). Additionally, although there

was no main effect of ε4 allele status ($F_{(1, 129)}=2.03$; $p=0.157$; $\eta_p^2=0.015$), the interaction between group and ε4 allele status was significant ($F_{(1, 129)}=4.99$; $p=0.027$; $\eta_p^2=0.037$). For TBI participants, ε4+ veterans had higher BAI scores than ε4− veterans ($F_{(1, 129)}=7.64$; $p=0.007$; $\eta_p^2=0.056$); for MCs, ε4 status had no effect ($F_{(1, 129)}=0.29$; $p=.590$; $\eta_p^2=0.002$; see Fig. 2).

When examining PCL-M total score, a main effect of group was found ($F_{(1, 129)}=57.43$; $p<0.001$; $\eta_p^2<0.308$). Similar to the above results, PCL-M total score was significantly greater for TBI participants ($M=43.90$; $SD=17.67$) than for MCs ($M=23.65$; $SD=11.99$). There was no main effect of ε4 allele status ($F_{(1, 129)}=$

TABLE 2. TBI PARTICIPANTS: SAMPLE CHARACTERISTICS BY TBI SEVERITY ($N=79$)

Variables	Mild TBI group (n=69)		Moderate TBI group (n=10)		
	M	SD	M	SD	p value[a]
Age	32.00	7.02	35.40	6.88	0.155
Education (years)	13.91	1.61	14.50	1.18	0.270
WRAT4 Reading SS	100.75	11.19	102.40	9.28	0.658
Time (months) from most recent TBI to testing	65.13	48.96	64.50	46.50	0.970
Time (months) from most sig. TBI to testing	75.56	51.75	81.50	57.70	0.739
Age at most sig. TBI	26.06	6.16	28.50	6.85	0.251
Lifetime number of TBIs	2.36	1.33	2.50	1.72	0.769
	N	%	N	%	p value[b]
Sex					
Male	59	85.5	8	80.0	0.650
Female	10	14.5	2	20.0	
Ethnicity					
White	29	42.0	3	30.0	0.257
Hispanic	24	34.8	4	40.0	
Black	9	13.0	0	0	
Asian/Pacific Islander	6	8.7	3	30.0	
Other	1	1.4	0	0	
Married/cohabitating					
Yes	28	40.6	1	10.0	0.053
No	39	56.5	9	90.0	
Missing	2	2.9	0	10.0	
Currently employed					
Yes	30	43.5	6	60.0	0.347
No	38	55.1	4	40.0	
Missing	1	1.4	0	0	
Branch of service					
Air Force	5	7.2	1	10.0	0.647
Army	18	26.1	1	10.0	
Marines	25	36.2	3	30.0	
Navy	20	29.0	5	50.0	
Other	1	1.4	0	0	
OEF/OIF/OND veteran					
Yes	66	95.7	8	80.0	0.057
No	3	4.3	2	20.0	
Combat exposure					
Yes	49	71.0	5	50.0	0.182
No	20	29.0	5	50.0	
LOC (most sig. TBI)					
Yes	39	56.5	10	100.0	0.008
No	30	43.5	0	0	
AOC (most sig. TBI)					
Yes	30	43.5	0	0	0.008
No	39	56.5	10	100.0	
PTA (most sig. TBI)					
Yes	33	47.8	10	100.0	0.009
No	30	43.5	0	0	
Unsure	5	7.2	0	0	
Missing	1	1.4	0	0	
APOE $\epsilon 4$ allele status					
$\epsilon 4$ Present ($\epsilon 4+$)	15	21.7	3	30.0	0.561
$\epsilon 4$ Absent ($\epsilon 4-$)	54	78.3	7	70.0	

[a]Independent-samples t-tests were used to determine whether there were group differences for age, education, WRAT4 Reading, time from most recent TBI to testing, time from most significant TBI to testing, age at most significant TBI, and lifetime number of TBIs.
[b]Chi-square analyses were used to determine whether there were group differences for sex, ethnicity, marital status, employment status, military branch of service, OEF/OIF/OND status, combat exposure, presence of LOC, presence of AOC, presence of PTA, and APOE $\epsilon 4$ allele status.
WRAT4, Wide Range Achievement Test 4; SS, standard score; TBI, traumatic brain injury; sig., significant; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn; LOC, loss of consciousness; AOC, alteration of consciousness; PTA, post-traumatic amnesia; M, mean; SD, standard deviation.

Variables	ϵ4 allele present (ϵ4+) (n=18)		ϵ4 allele absent (ϵ4–) (n=61)		
	M	SD	M	SD	p value[a]
Age	33.56	7.94	32.10	6.81	0.445
Education (years)	13.50	1.30	14.13	1.62	0.134
WRAT4 Reading SS	100.17	8.42	101.20	11.63	0.727
Months since most recent TBI	56.72	37.96	67.55	51.08	0.408
Months since most sig. TBI	67.11	42.48	79.08	54.78	0.397
Age at most sig. TBI	28.22	7.35	25.82	5.86	0.154
Number of TBIs sustained	2.17	1.34	2.44	1.39	0.457
	N	%	N	%	p value[b]
Sex					
Male	15	83.3	52	85.2	0.843
Female	3	16.7	9	14.8	
Ethnicity					
White	6	33.3	26	42.6	0.439
Hispanic	7	38.9	21	34.4	
Black	4	22.2	5	8.2	
Asian/Pacific Islander	1	5.6	8	13.1	
Other	0	0	1	1.6	
Married/cohabitating					
Yes	6	33.3	23	37.7	0.819
No	11	61.1	37	60.7	
Missing	1	5.6	1	1.6	
Currently employed					
Yes	7	38.9	29	47.5	0.481
No	11	61.1	31	50.8	
Missing	0	0	1	1.6	
Branch of service					
Air Force	0	0	6	9.8	0.277
Army	3	16.7	16	26.2	
Marines	6	33.3	22	36.1	
Navy	9	50.0	16	26.2	
Other	0	0	1	1.6	
OEF/OIF/OND veteran					
Yes	18	100.0	56	91.8	0.209
No	0	0	5	8.2	
Combat exposure					
Yes	10	55.6	44	72.1	0.184
No	8	44.4	17	27.9	
TBI severity					
Mild	15	83.3	54	88.5	0.561
Moderate	3	16.7	7	11.5	
LOC (most sig. TBI)					
Yes	9	50.0	40	65.6	0.232
No	9	50.0	21	34.4	
AOC (most sig. TBI)					
Yes	9	50.0	21	34.4	0.232
No	9	50.0	40	65.5	
PTA (most sig. TBI)					
Yes	10	55.6	33	54.1	0.423
No	8	44.4	22	36.1	
Unsure	0	0	5	8.2	
Missing	0	0	1	1.6	

(continued)

TABLE 3. (CONTINUED)

Variables	ε4 allele present (ε4+) (n=18)		ε4 allele absent (ε4−) (n=61)		p value[b]
	M	SD	M	SD	
Lifetime diagnosis: MDD[c]					
Yes	8	50.0	20	39.2	0.445
No	8	50.0	31	60.8	
Lifetime diagnosis: PTSD[c]					
Yes	8	53.3	23	45.1	0.574
No	7	46.7	28	54.9	

[a]Independent-samples *t*-tests were used to determine whether there were group differences for age, education, WRAT4 Reading, time from most recent TBI to testing, time from most significant TBI to testing, age at most significant TBI, and lifetime number of TBIs.

[b]Chi-square analyses were used to determine whether there were group differences for sex, ethnicity, marital status, employment status, military branch of service, OEF/OIF/OND status, combat exposure, TBI severity, presence of LOC, presence of AOC, presence of PTA, lifetime diagnosis of MDD, and lifetime diagnosis of PTSD.

[c]Lifetime diagnosis of MDD and PTSD were gathered through one-on-one interview using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan and colleagues, 2006). Further, M.I.N.I. data were not available for all participants; MDD diagnostic information was available for 67 of the 79 TBI participants, and PTSD diagnostic information was available for 66 of the 79 TBI participants.

WRAT4, Wide Range Achievement Test 4; SS, standard score; TBI, traumatic brain injury; sig., significant; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn; LOC, loss of consciousness; AOC, alteration of consciousness; PTA, post-traumatic amnesia; MDD, Major Depressive Disorder; PTSD, post-traumatic stress disorder; M, mean; SD, standard deviation.

1.51; $p=0.222$; $\eta_p^2=0.012$); however, the interaction between group and ε4 allele status was significant ($F_{(1, 129)}=4.20$; $p=0.042$; $\eta_p^2=0.032$). As seen in Figure 3, for TBI participants, ε4$^+$ veterans had higher PCL-M scores than ε4$^-$ veterans ($F_{(1, 129)}=6.13$; $p=0.015$; $\eta_p^2=0.045$); for MCs, ε4 status had no effect ($F_{(1, 129)}=0.30$; $p=0.585$; $\eta_p^2=0.002$).

Importantly, removal of participants with moderate TBI from the analyses revealed the same pattern of results. Specifically, there continued to be a significant main effect of group across all symptom measures (TBI > MC; all p values <0.001; $\eta_p^2=0.236–0.318$) and no main effect of ε4 genotype ($p=0.147–0.345$; $\eta_p^2=0.007–0.018$). Group by ε4 genotype interaction remained significant for the BAI total score ($p=0.024$; $\eta_p^2=0.042$) and approached significance (trend) for the BDI-II total score ($p=0.058$; $\eta_p^2=0.030$) and PCL-M total score ($p=0.083$; $\eta_p^2=0.025$). APOE-ε4$^+$ veterans with a history of mild TBI demonstrated significantly higher symptom scores on the BAI and BDI-II when compared to ε4$^-$ veterans with a history of mild TBI (BAI: $p=0.008$; $\eta_p^2=0.058$; BDI-II: $p=0.020$; $\eta_p^2=0.045$), and there was a trend in the same direction for the PCL-M ($p=0.054$;

FIG. 1. BDI-II total score across traumatic brain injury (TBI) and military control (MC) participants by ε4 genotype. Mean scores with standard errors are displayed. BDI-II, Beck Depression Inventory, Second Edition.

$\eta_p^2=0.031$). ε4 status had no effect on severity of psychiatric symptom scores for MC participants ($p=0.566–0.700$; $\eta_p^2=0.001–0.003$).

Secondary analyses

Given the observed differences in combat exposure and ethnicity between the TBI and MC samples as described above, analyses of covariance were conducted on the original sample. When controlling for combat exposure and ethnicity, a similar pattern of results was again observed—for TBI participants, ε4$^+$ veterans demonstrated significantly higher symptom scores across all measures when compared to ε4$^-$ veterans ($p=0.008–0.015$); for MC participants, ε4 status had no effect on the severity of psychiatric symptom scores ($p=0.488–0.682$).

Discussion

To our knowledge, this study represents the first to explore associations between APOE genotype status and neuropsychiatric symptoms in the context of military TBI. As expected, consistent with several previous studies showing increased rates of psychiatric symptoms in military service members with TBI histories,[1,3,4,7] our results showed that veterans with a reported history of TBI endorsed greater symptoms of depression, anxiety, and PTSD relative to MCs. Additionally, although a main effect was not found for ε4 genotype across veterans, a TBI by APOE-ε4 interaction was demonstrated, such that those with history of TBI and APOE-ε4 positivity showed the greatest level of psychiatric symptomatology across all measures administered. That is, among veterans with a history of neurotrauma, greater levels of anxiety, depression, and PTSD symptoms were found in those with an ε4 allele relative to those without an ε4 allele. Importantly, there was no effect of APOE-ε4 in those without a history of TBI. Given the proposed role of the APOE gene, and its purported mechanism of action post-CNS insult,[28,32] these findings bolster the hypothesis that, in the aftermath of neurological insult (e.g., TBI), those with an ε4 allele are at risk for more adverse outcomes relative to ε4$^-$ individuals.[24,25,31]

Although, to our knowledge, the current study represents the first to examine the relationship between the APOE gene and neuro-psychiatric sequelae in veterans with TBI, Lyons and colleagues[69]
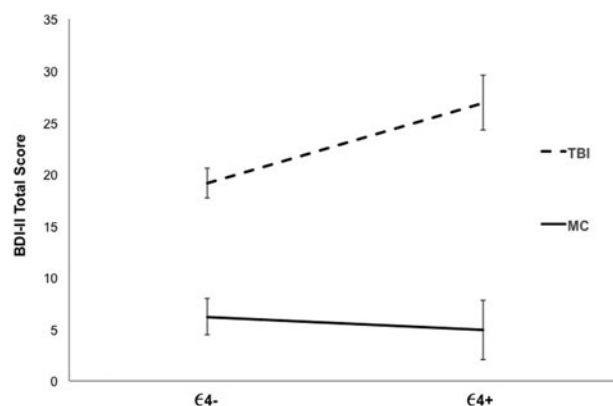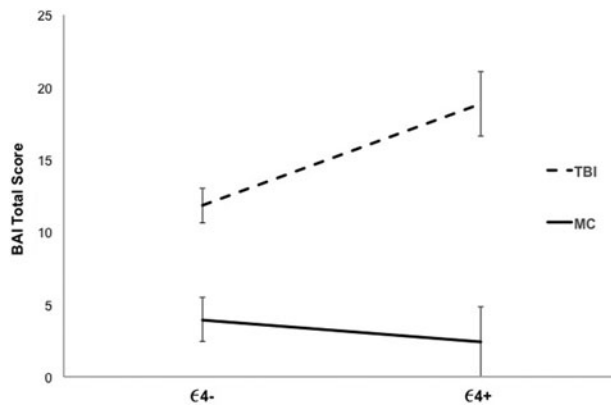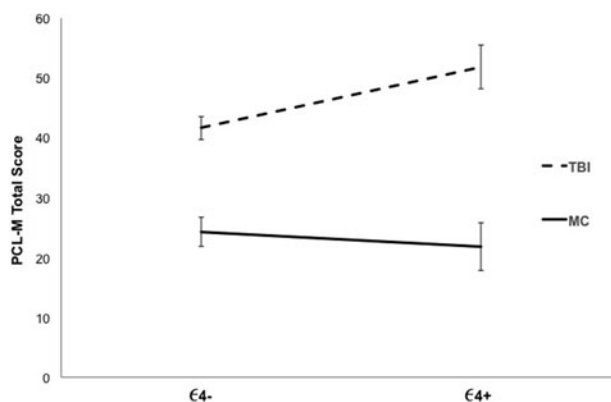
FIG. 2. BAI total score across traumatic brain injury (TBI) and military control (MC) participants by ϵ4 genotype. Mean scores with standard errors are displayed. BAI, Beck Anxiety Inventory.

demonstrated that those with a higher level of combat exposure and APOE-ϵ4 genotype status were at greatest risk for experiencing symptoms of PTSD. More recently, Kimbrel and colleagues[70] found that the influence of the ϵ4 allele differed by level of combat exposure, such that those who experienced high levels of combat and ϵ4-positivity 1) were more likely to be diagnosed with PTSD and 2) demonstrated more-severe PTSD symptoms. Interestingly, when combat exposure was low, the ϵ4 allele had no effect on psychiatric outcome. Although these findings only held in non-Hispanic blacks as compared to non-Hispanic whites, the overall findings from Lyons and colleagues[69] and Kimbrel and colleagues[70] are generally consistent with the results of our study showing that ϵ4 genotype in the context of neurotrauma (e.g., TBI or combat exposure) may predispose individuals to increased psychiatric distress (e.g., PTSD, depression, anxiety, etc.).

Beyond establishing a specific relationship between the presence of the ϵ4 allele and neuropsychiatric sequelae, the results from the present study also lend support to the broader theory that genetic factors influence psychiatric distress post-TBI. However, it is likely that still other biological and environmental contributions may impact the development of symptoms in this population.[71,72] For instance, pre-morbid levels of psychiatric distress,[14,73] degree of resilience,[73,74] personality factors,[75–77] and intellectual functioning or cognitive reserve[78,79] may also be important moderators or

mediators in this relationship. Importantly, our results show that ϵ4[+] and ϵ4[−] participants with TBI did not differ from one another with respect to either lifetime diagnosis of depression (i.e., MDD) or PTSD. Thus, our finding of an association between greater levels of self-reported psychiatric symptomatology in TBI veterans with TBI histories was not merely driven by greater overall psychiatric distress reflected by psychiatric disorder diagnoses in the ϵ4 group. The relationship between TBI and the emergence of psychiatric distress after brain injury is likely considerably complex, and the present findings provide a first attempt to better understand and elucidate a particular susceptibility gene that may be important in this multi-faceted relationship.

Although speculative, there are several potential neurobiological or brain-based mechanisms that could explain the observed interaction between neurotrauma and APOE-ϵ4 genotype on psychiatric distress. One possibility is that the ϵ4 allele may exert many of its effects through frontal subcortical regions, which are often impacted post-TBI and are heavily involved in affective states, emotion regulation, and psychiatric distress.[20] Additionally, associations between APOE ϵ4 genotype and vascular risk factors on the development of depression have been proposed, such that ϵ4 positivity enhances risk for vascular disease, thereby increasing risk for depression (for a review, see Panza and colleagues[80]). Another consideration may be that there is a link between early neurodegenerative processes and APOE ϵ4 status (e.g., promoting deposition of abnormal amyloid and tau protein species) that influences neuropsychiatric distress through limbic insult. Whereas additional brain-based mechanisms may also be at play, these theories may help to explain why we observe increased rates of psychiatric distress in many veterans with a history of neurotrauma relative to those without trauma histories. We are pursuing these questions through ongoing research in our laboratory.

Taken together, results of our study show compelling evidence that APOE-ϵ4 positivity may be more deleterious for those who have experienced neurotrauma versus those without TBI histories. Study strengths include a relatively large, well-characterized sample of veterans with a history of TBI, examination of mental health symptoms beyond PTSD to better assess the magnitude of psychiatric distress in veterans, and examination of participants who are well outside of the acute stage of injury to increase understanding of the long-term effects of APOE polymorphisms on TBI outcome. However, there are some limitations of the study that should be noted. First, although our male/female ratios are higher than many existing military TBI studies, the majority of participants were male veterans ($\sim$80%), thus reducing the generalizability to females. We also examined milder forms of TBI, and it is therefore unclear whether similar findings would be observed in individuals with more severe TBI. Additionally, longitudinal studies are needed in order to improve our understanding of the timeline associated with the detrimental effects of the ϵ4 allele (i.e., how soon after injury and for how long after injury are these effects present?). Moreover, we relied on participants' self-report to characterize TBI severity and history (e.g., timing of injuries, number of injuries sustained, etc.). A final limitation is our relatively small sample size; however, the number of participants analyzed in this study is comparable—and in some cases larger than—previously published studies examining the effect of APOE genotype in the context of TBI.[44–46,81] Nevertheless, it will be important for these findings to be replicated using larger samples. Relatedly, given the low number of participants who were homozygous for the ϵ4 allele (in the overall sample of 133, only 3 participants were ϵ4/ϵ4), concordant with its low frequency in the population, we were not

FIG. 3. PCL-M total score across traumatic brain injury (TBI) and military control (MC) participants by ϵ4 genotype. Mean scores with standard errors are displayed. PCL-M, PTSD Checklist-Military Version.

able to assess a dose-response type of influence of the $\epsilon4$ allele, although this is a future direction for our research.

In conclusion, a growing body of literature has emerged over the past several years that has established an association between TBI and symptoms of psychiatric distress. Although many studies have begun to investigate potential etiologies of this relationship, few studies have examined the relationship between genetics and the development or maintenance of neuropsychiatric sequelae post-TBI. This study is the first to show that the APOE-$\epsilon4$ allele is a risk factor for the development of neuropsychiatric symptoms in veterans with a history of TBI. Importantly, these findings do not appear to be attributed to fundamental differences in demographic or injury severity characteristics, given that groups were equivalent across these variables. Moreover, findings held even after removing veterans with moderate TBI from the analyses. Although the present study furthers our understanding of how the APOE $\epsilon4$ allele contributes to the emergence of mental health symptoms post-TBI, future longitudinal studies are necessary in order to more fully understand the association of APOE genotype status and psychiatric distress in the context of TBI.

Acknowledgments

Author Disclosure Statement

No competing financial interests exist.

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