PAPER

Apolipoprotein E and traumatic brain injury in a military population: evidence of a neuropsychological compensatory mechanism?

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Objective: Although research has implicated the apolipoprotein E (APOE) epsilon-4 genotype as having a negative effect on neuropsychological outcomes following traumatic brain injury (TBI), the potentially negative role of the ϵ4 allele on TBI outcomes has recently been challenged. In light of this debate, the present study served to examine the role of APOE genotype on neuropsychological outcomes approximately 1 month following mild to moderate TBI in a military population. Because of the well documented role of the APOE-ϵ4 allele in increasing the risk of Alzheimer's disease, we predicted that persons with the APOE-ϵ4 genotype would display relatively greater deficits in cognition than their non-ϵ4 counterparts.

Methods: 78 participants were consecutively recruited following a mild to moderate TBI and were divided into two groups based on the presence or absence of an APOE ϵ4 allele. Groups were comparable on demographic characteristics and psychosocial outcomes. Participants were administered a comprehensive neuropsychological battery.

Results: Analyses revealed comparable performances on most neuropsychological measures and better performances by ϵ4 carriers on select measures of attention, executive functioning and episodic memory encoding. Furthermore, differences remained after accounting for the effects of TBI severity.

Conclusions: Evidence from these analyses supports current literature refuting the notion of relatively poorer neuropsychological functioning associated with the APOE-ϵ4 genotype among young adult participants shortly following mild or moderate brain injury. Neuropsychological performance differences by APOE genotype following TBI are discussed in terms of the importance of considering severity of injury, timing of postinjury assessment and possible neurocognitive compensatory mechanisms.

Traumatic brain injury (TBI) represents one of the most significant health risks related to military duty. Previous work has demonstrated that memory, attention and executive functions can be significantly impaired following TBI.[1 2] Specifically, patients with TBI often have problems learning and recalling recent information, attending to multiple pieces of information simultaneously, manipulating information mentally and solving novel problems.[1 3 4] In addition to their cognitive impairments, TBI patients can also experience dramatic changes in emotionality and personality, which include depression, anxiety, irritability, euphoria and decreased motivation,[5] which may further impact cognitive functioning negatively. Moreover, the cognitive impairments of TBI have been associated with a decrease in quality of life.[6]

The potentially negative consequences of TBI highlight the need for predicting which patients will have a poorer outcome. A recent advancement has been the finding that there could be a genetic predisposition to poorer outcome following TBI, and one such candidate gene is the apolipoprotein E (APOE) gene. Located on chromosome 19, the APOE gene is responsible for the production of apolipoprotein, a protein that is produced in response to central nervous system insult and is involved in regulating the redistribution of cholesterol during the production of cell membranes.[7] There is now strong evidence indicating that individuals with an ϵ4 allele of APOE (APOE-ϵ4) have a greater likelihood of developing Alzheimer's disease (AD).[8 9] The mechanism of the involvement of the gene in this disease is believed to be in its role of binding to amyloid beta peptide, which results in accumulation of this peptide and eventual development of the neuritic plaques characteristic of AD. Other work implicates the APOE-ϵ4 allele in the formation of neurofibrillary tangles,[10 11] a direct neurotoxic role in hippocampal cell death,[12] as well as a reduced ability for central nervous system plastic response.[13]

Past work has found indirect evidence of a relationship between the effects of TBI and the presence of the APOE-ϵ4 allele. For example, Mayeux and colleagues[14] found that patients with at least one APOE-ϵ4 allele were approximately 10 times more likely to develop AD following a head injury. Other groups have also identified head injury as a risk factor for developing AD in individuals with the APOE-ϵ4 genotype.[15–17] Furthermore, the APOE-ϵ4 genotype is associated with greater neurological impairment in some boxers.[18] Graham and colleagues[19] found that 30% of individuals who died from a TBI displayed deposition of the β-amyloid, and a significantly larger proportion of those individuals were APOE-ϵ4 carriers. Other studies have also found an increased risk for fatal TBI in individuals with the APOE-ϵ4 genotype.[20 21] It also appears that possession of the APOE-ϵ4 genotype results in a greater risk of prolonged coma following TBI.[22]

To date, there have been few studies that have compared outcome in TBI in individuals with and without the APOE-ϵ4 genotype. A study by Teasdale and colleagues[23] found that TBI

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CVLT-II, California Verbal Learning Test-second edition; D-KEFS, Delis–Kaplan Executive Functions System; DVBIC, Defense and Veterans Brain Injury Center; GOS, Glasgow Outcome Scale; TBI, traumatic brain injury; WAIS-III, Wechsler Adult Intelligence Scale-third edition; WMS-III, Wechsler Memory Scale-third edition

patients with this genotype had a poorer outcome, as measured by the Glasgow Outcome Scale (GOS), 6 months postinjury. Friedman and colleagues[24] also found that patients with the APOE-ϵ4 genotype had a greater likelihood of a poorer score on the Glasgow Coma Scale as well as loss of consciousness greater than 7 days. Taken together, these studies suggest that the presence of the APOE-ϵ4 genotype is a risk factor for poorer outcome following TBI when compared with those individuals without a copy of the ϵ4 allele. However, this association has also been contested by other studies. Chamelian and colleagues,[25] for example, presented evidence that not only failed to support an association between the APOE-ϵ4 genotype and poorer neuropsychological outcomes following mild to moderate TBI, but also produced data revealing better (although not statistically significant) performances by ϵ4 subjects on various cognitive measures. In fact, there is growing evidence to suggest that normal young adult participants who are APOE-ϵ4 positive may perform better than non-ϵ4 subjects on a number of neuropsychological measures, regardless of a CNS insult. Papassotiropoulos and colleagues[26] found that the APOE-ϵ4 allele was associated in a dose dependent manner with better memory performances among 340 healthy young adults. Hubacek and colleagues[27] found that among 366 participants, those with an ϵ4 allele generally achieved a higher level of education than those with an ϵ2 allele. Keltikangas-Jarvinen and colleagues[28] found that possession of an ϵ4 allele correlated with increased ''mental vitality'' (ie, more active, energetic and alert), ''socialability'' (ie, responsivity) and ''positive emotionality'' (ie, a tendency to be happy and friendly) among 1577 randomly selected healthy children, adolescents and young adults.

This apparent discrepancy in the literature regarding APOE-ϵ4 association with poorer outcomes after mild–moderate TBI may be explained, at least in part, by the limitations of previous studies. Firstly, many of these studies used relatively narrow measures of outcome (eg, the GOS), which may not necessarily specify important characteristics of a patient's neuropsychological functioning following TBI. Furthermore, recent studies have indicated that the cognitive deficits observed in severe TBI patients can best be identified using measures that examine multiple specific components of a particular cognitive domain.[29 30] Using participant groups equated on demographic and psychosocial functioning variables, the present study served to address this apparent discrepancy and provide evidence in support of an association between APOE-ϵ4 status, TBI severity and neuropsychological functioning among young participants approximately 1 month following TBI.

METHODS

Subjects

Active duty personnel with a recent history of mild to moderate traumatic brain injury were enrolled in the study using standard informed consent procedures approved by the Naval Medical Center San Diego and the Veterans Administration. Mild TBI was defined as an initial loss of consciousness of less than 15 min, an initial Glasgow Coma Scale score between 13 and 15 and post-traumatic amnesia of less than 24 h; moderate TBI was defined as an initial loss of consciousness of less than 24 h but greater than 15 min, an initial Glasgow Coma Scale of 8–12 and post-traumatic amnesia greater than 24 h but less than 7 days. Any participant with any of the qualifying criteria for ''moderate TBI'' was characterised as a ''moderate TBI'' case. TBI participants were referred to the Defense and Veterans Brain Injury Center (DVBIC) from two primary sources: Balboa Naval Medical Center San Diego and Marine Corps Base Camp Pendleton. The DVBIC has been conducting a comprehensive programme to educate providers on the signs, symptoms and treatments of TBI. The goal of the DVBIC is to be referred any possible case of TBI ranging from mild to severe when TBI is suspected by a health care provider, even if TBI is not the original reason for seeking treatment. As a standard of care, the DVBIC provides a comprehensive evaluation of all referred TBI patients. This evaluation served as a pre-screen to determine a patient's eligibility to participate in this protocol. Eligible candidates were offered the opportunity to participate and informed consent was obtained. Exclusion criteria included a history of severe or repeated head injuries; past or current substance or alcohol abuse according to DSM-IV criteria; a history of metabolic or other diseases known to affect the CNS; or a history of axis I psychiatric disorders according to DSM-IV (see Dikmen and colleagues[1] for similar criteria). Some examples of reported aetiologies of head trauma included motor vehicle accidents, falling from moving vehicles or from heights, assaults and detonation of nearby explosive devices.

Materials and procedure

Subjects were enrolled and tested, on average, within 4–5 weeks of the date of their injury (range 15–65 days) and tested on a battery of psychosocial and neuropsychological measures. Psychosocial measures included sections A, D and E of the Frontal Lobe Personality Scale,[31] which provides a self-rated evaluation of various aspects of personality associated with frontal lobe pathology; the Glasgow Assessment Schedule,[32] which is a 40 item examiner rated evaluation of six areas of functioning, including personality change, subjective complaints, occupational functioning, cognitive functioning, physical examination and activities of daily living; the Kennedy-Johnson Post-Concussion Scale,[33] which was developed to assess postconcussive symptoms; the Beck Depression Inventory; the Beck Anxiety Inventory; and the Rand SF-36 Item Health Survey,[34] which consists of 36 questions assessing various aspects of functioning following illness or injury and has been used extensively following TBI. Neuropsychological measures of attentional skills and psychomotor speed included the Digit Span and Digit Symbol subtests from the Wechsler Adult Intelligence Scale-third edition (WAIS-III) and the Paced Auditory Serial Addition Test.[4]. Neuropsychological measures of visuoconstructional skills and executive functioning included the Block Design and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI), and Verbal Fluency, Design Fluency, Colour–Word Interference, Sorting Test and Trail-Making subtests from the Delis–Kaplan Executive Functions System (D-KEFS[35]). Neuropsychological measures of memory included the Logical Memory subtest from the Wechsler Memory Scale-third edition (WMS-III) and the California Verbal Learning Test-second edition (CVLT-II[36]). The American National Adult Reading Test[37] was administered as an estimate of verbal IQ. Cheek buccal swabbing for APOE genotyping took place either at the time of the initial consent or in the same session as the psychosocial or neuropsychological battery. All participants were genotyped for APOE allele type using a PCR based method identical to that of Saunders and colleagues.[38]

Statistical analysis

Independent sample t tests, χ^2 tests and non-parametric Mann–Whitney tests were performed on the data. Levene's test was used to assess data for equality of variances between groups. Assuming equality of variance, two tailed Student's t tests were performed on demographic, psychosocial and neuropsychological outcomes. Given the exploratory nature of the current study, a balance was struck between statistical conservatism and the reduction of possible type II errors. In order to account for multiple comparisons among neuropsychological outcomes, values observed at a 1% level of significance or lower were

Table 1 Demographic and psychosocial information for participants

	APOE genotype			
	ε4	Non-ε4	t or (χ^2)	p Value
Demographic information				
n	16	62		
Age (y)	22.56 (3.76)	25.26 (5.776)	−1.769	0.081
Sex (M/F)	13/3	59/2	(2.774)	0.096
Education	12.50 (1.09)	12.93 (1.91)	−0.807	0.422
Rank	3.53 (1.13)	3.95 (1.42)	−1.037	0.303
Days from injury	38.73 (13.80)	37.58 (11.94)	0.325	0.746
Psychosocial measures				
GAS total score	9.13 (7.86)	9.62 (6.71)	−0.239	0.812
Job status	2.63 (1.50)	2.62 (1.47)	0.016	0.987
Beck Depression Inventory	8.64 (6.58)	11.76 (9.51)	−1.149	0.255
Beck Anxiety Inventory	8.13 (7.37)	10.84 (10.70)	−0.914	0.364
Rand 36 Item Health Survey	103.40 (6.15)	103.14 (8.99)	0.103	0.918
Kennedy-Johnson Post-concussion Scale	20.00 (13.15)	24.67 (20.70)	−0.820	0.415
FLOPS A before/after	24.47 (7.58)/30.27 (10.20)	23.10 (5.71)/33.16 (9.54)	0.748/−1.013	0.457/0.315
FLOPS D before/after	29.13 (8.25)/31.07 (8.22)	27.96 (8.58)/31.27 (8.21)	0.468/−0.082	0.642/0.935
FLOPS E before/after	32.67 (10.44)/37.07 (11.32)	31.24 (8.99)/40.29 (12.78)	0.516/−0.875	0.608/0.385

APOE, apolipoprotein E; FLOPS, Frontal Lobe Personality Scale; GAS, Glasgow Assessment Schedule.
Student's t tests were two tailed.

considered ''significant'' and values that were between 1% and 5% level of significance were considered ''near significant''. Whenever equal variance assumptions were not met, non-parametric Mann–Whitney tests were conducted. Effects sizes were calculated for the psychosocial and neuropsychological variables and reported in the form of partial eta-squared statistics. The χ^2 tests were performed to identify any interaction between APOE genotype and the demographic variable of gender as well as TBI severity. Finally, because it is possible that active military personnel are granted more ''leave'' time based on the severity of their injury, and given possible differences in TBI severity by APOE genotype, we were concerned that any observed APOE effect might have been caused by extended recovery time. To account for this possible explicatory factor, we numerically balanced APOE genotype groups by TBI severity through random selection and reanalysed the neuropsychological data. In other words, we reanalysed between group genetic differences using groups with equal numbers of mild and moderate cases represented. The SPSS statistical software program (SPSS Inc., Chicago, Illinois, USA) was used to compute all statistical output and for the latter random selection procedure.

Table 2 Neuropsychological functioning by APOE genotype

	APOE genotype				
Neuropsychological measures	ε4	Non-ε4	t (or z)	p Value	η_p^2
ANART IQ	107.75 (7.95)	108.02 (7.86)	−0.120	0.905	0.00
PASAT Total T Score	41.20 (10.35)	35.44 (13.91)	1.493	0.140	0.03
Digit Span Age SS (WAIS-III)	9.50 (1.51)	9.57 (2.71)	[−0.038]	0.970	0.00
Digit Symbol Age SS (WAIS-III)	10.38 (2.85)	8.87 (2.51)	2.079	0.041*	0.06
Block Design T Score (WASI)	54.81 (7.79)	55.07 (7.18)	−0.123	0.902	0.00
Matrix Reasoning T Score (WASI)	54.94 (5.95)	52.33 (9.06)	1.089	0.280	0.01
Verbal Fluency Switch Responses SS (D-KEFS)	10.25 (2.89)	9.54 (3.13)	0.818	0.416	0.01
Verbal Fluency Number of Switches SS (D-KEFS)	10.69 (2.39)	9.97 (2.94)	0.903	0.370	0.01
Design Fluency Switching SS (D-KEFS)	11.13 (2.92)	10.79 (2.72)	0.435	0.665	0.00
Colour–Word Interference Inhibition SS (D-KEFS)	9.88 (2.87)	10.15 (5.84)	−0.182	0.856	0.00
Colour–Word Interference Inhibition/Switching SS (D-KEFS)	10.38 (1.93)	8.88 (3.40)	[−1.450]	0.147	0.03
Sorting Test Correct Sorts SS (D-KEFS)	10.75 (1.48)	10.08 (2.45)	1.038	0.303	0.01
Sorting Test Recognition Description SS (D-KEFS)	9.63 (2.60)	8.89 (2.90)	0.925	0.358	0.01
Trail Making Number–Letter Switching SS (D-KEFS)	10.53 (1.85)	8.85 (3.42)	1.835	0.070	0.04
Logical Memory I Age SS (WMS-III)	10.13 (2.06)	9.54 (3.13)	0.706	0.483	0.01
Logical Memory II Age SS (WMS-III)	10.69 (2.55)	9.46 (3.29)	1.384	0.170	0.03
CVLT-II List A, Trials 1–5 Total T Score	46.19 (10.85)	38.75 (9.46)	2.714	0.008**	0.14
CVLT-II Short Delay Free Recall z Score	−0.53 (1.16)	−0.96 (1.00)	1.501	0.137	0.03
CVLT-II Short Delay Cued Recall z Score	−0.56 (1.25)	−1.14 (0.95)	2.020	0.047*	0.07
CVLT-II Long Delay Free Recall z Score	−0.78 (1.13)	−0.85 (1.05)	1.661	0.101	0.04
CVLT-II Long Delay Cued Recall z Score	−0.81 (1.29)	−1.32 (1.11)	1.572	0.120	0.04

ANART, American National Adult Reading Test; APOE, apolipoprotein E; CVLT-II, California Verbal Learning Test-second edition; D-KEFS, Delis–Kaplan Executive Functions System; PASAT, Paced Auditory Serial Addition Test; SS, scaled score; WAIS-III, Wechsler Adult Intelligence Scale-third edition; WMS-III, Wechsler Memory Scale-third edition
Student's t tests were two tailed and α was adjusted to reflect multiple comparisons at 1% significance.
[Parentheses] denote unequal variance according to Levene's test and subsequent use of the Mann–Whitney non-parametric test.
*Near-significant values ($p<0.05$); **significant values ($p<0.01$).

RESULTS

Demographic and psychosocial characteristics

Of the 78 participants enrolled in the study, 16 had an APOE genotype with at least one ϵ4 allele (1 ϵ2/ϵ4, 13 ϵ3/ϵ4, 2 ϵ4/ϵ4) and 62 did not (0 ϵ2/ϵ2, 10 ϵ2/ϵ3, 51 ϵ3/ϵ3). APOE-ϵ4 and non-ϵ4 groups did not differ significantly with respect to age, gender, years of education, attained rank, days from injury or any of the psychosocial measures (table 1).

TBI severity

Of the ϵ4 group, eight participants had injuries that qualified as ''mild'' and eight that qualified as ''moderate''. Of the non-ϵ4 group, 43 had injuries that qualified as ''mild'' and 19 that qualified as ''moderate''. χ^2 analyses testing the association between APOE genotype and TBI severity yielded no significant difference between groups ($\chi^2 = 1.24$, $p = 0.27$).

Neuropsychological performances

Analyses revealed a significant difference between groups for CVLT-II List A Trials 1–5 Total Learning T score ($p = 0.01$), and a near-significant difference in WAIS-III Digit Symbol Age scaled score ($p = 0.04$) and CVLT-II Short Delay Free Recall z score ($p = 0.05$) such that ϵ4 participants performed better than their non-ϵ4 counterparts (table 2).

Secondary analyses controlling for possible differences in the proportion of TBI severity between APOE genotype groups revealed a near-significant difference between groups for WAIS-III Digit Symbol Age subscale ($p = 0.03$), D-KEFS Colour–Word Interference Inhibition/Switching subscale ($p = 0.02$) and CVLT-II List A Trials 1–5 Total Learning T score ($p = 0.04$). Again, all near-significant differences indicated better performance by ϵ4 participants (table 3).

DISCUSSION

Participants with an APOE-ϵ4 allele performed significantly or marginally better on select neuropsychological measures than their non-ϵ4 counterparts, and these differences persisted regardless of TBI severity. The distinction between mild and moderate injury was taken into account as a result of the extended leave given to more moderate than mild head injury cases. In order to account for any benefit of this extended leave, we analysed the data according to the most conservative delineation between mild and moderate cases. We consequently coded as ''moderate'' any case that had any one marker of head injury in the upper limit. Given the low numbers of subjects that qualified for a ''moderate'' TBI designation using this system, we believe this approach to be the most conservative in order to adjust for any beneficial influence of extended leave. As the analysis of neuropsychological outcomes according to mild–moderate type remained very similar in result to the analysis of outcomes with mild and moderate cases grouped together, we feel confident that the influence of TBI type (mild vs moderate) is negligible on the present findings. The present findings support previous studies refuting an association between the APOE-ϵ4 genotype and poorer neuropsychological outcome following mild to moderate TBI,[25] and counter previous studies supporting such an association.[23 39–43] A number of discrepancies exist between the current study and previous studies that have supported an association between the APOE-ϵ4 genotype and poorer neuropsychological outcome, including TBI severity distinctions, differing measurement strategies and patient characteristics. For example, Teasdale and colleagues[23] found an association between APOE-ϵ4 genotype and poorer outcome on the GOS, but their assessment was conducted 6 months after injury as opposed to 1 month in the current study. The earlier time frame of our study and our discrepant findings may suggest that a dynamic temporal model may exist between APOE genotype and neuropsychological outcomes following mild–moderate TBI. In a follow up study, Teasdale and colleagues[39] found evidence for an interaction between age and APOE genotype such that possession of the ϵ4 allele reduced favourable outcome in children and young adults. The authors likened this effect to the equivalent of ageing by 25 years in those TBI participants less than 15 years old, despite no overall statistical association found between APOE and outcome measures in their study. Although their study considered all types of TBI severity and a dichotomous outcome measure (a ''favourable'' vs ''unfavourable'' distinction), we had a subject pool approximately a decade older than their age group, utilised sensitive measurement tools for neurocognition, and conservatively limited consideration to only mild and moderate cases controlled for demographic and psychosocial characteristics, as older age and greater severity TBI may automatically predispose patients to worse outcomes. Crawford and colleagues[40] presented evidence in support of an association between ϵ4 and poorer memory performance among active duty military who sustained a head injury, but their participants were approximately a decade older and sustained head injuries much more severe than those in the current study. Liberman and colleagues[41] showed an association between APOE-ϵ4 genotype and poorer neuropsychological outcomes 3 weeks after mild TBI; however, their participants were almost two decades older than participants in the present study. Ariza and colleagues[42] also presented support for an association between the APOE-ϵ4 genotype and poorer neuropsychological outcomes 6 months after injury. In addition to differences in follow-up time interval between their study and the present study, differences in the age range of participants can also be identified.

What mechanisms might possibly explain better memory, executive functioning or attention performance by young adult ϵ4 participants despite sustaining a mild to moderate TBI? One

Table 3 Significantly (or near significantly) different neuropsychological performances by APOE genotype using groups balanced by TBI severity

Neuropsychological measures controlled for TBI severity	APOE GENOTYPE		t (or z)	p Value	η_p^2
	ϵ4	Non-ϵ4			
Digit Symbol Age SS (WAIS-III)	10.38 (2.85)	8.72 (2.32)	2.206	0.032*	0.10
Colour–Word Interference Inhibition/Switching SS (D-KEFS)	10.38 (1.93)	8.31 (3.16)	2.404	0.020*	0.10
Trail Making Number–Letter Switching SS (D-KEFS)	10.53 (1.85)	8.69 (3.50)	[−1.752]	0.080	0.06
CVLT-II List A, Trials 1–5 Total T Score	46.19 (10.85)	39.53 (10.35)	2.111	0.040*	0.13

APOE, apolipoprotein E; CVLT-II, California Verbal Learning Test-second edition; D-KEFS, Delis–Kaplan Executive Functions System; SS, scaled score; TBI, traumatic brain injury; WAIS-III, Wechsler Adult Intelligence Scale-third edition.
Student's t tests were two tailed and α was adjusted to reflect multiple comparisons at 1% significance.
[Parentheses] denote unequal variance according to Levene's test and subsequent use of the Mann–Whitney non-parametric test.
*Near-significant values ($p<0.05$).

possible explanation is based on a compensatory hypothesis, which suggests that the brain compensates in multiple ways for neural damage sustained in an effort to function optimally. In those at risk for AD, the compensatory hypothesis posits that middle-age to elderly subjects with an APOE-ϵ4 allele show greater activity in task related brain regions than their non-ϵ4 counterparts despite equivalent behavioural performances on memory.[44–46] These increases in brain activity are thought to represent an overactivation of relevant brain networks to compensate for greater underlying neuropathological accumulations among older ϵ4 persons. If there is indeed a compensatory effect for older ϵ4 subjects, it is possible that there may be similar mechanisms for younger ϵ4 subjects following an insult to the brain and thus may be related to improvement in cognition in the short term. Eventually, however, these compensatory mechanisms become exhausted and result in poorer outcome in the long term and also give way to a greater propensity to develop AD in later life.[14–17]

In fact, among healthy APOE-ϵ4 persons, individuals show stronger performances than non-ϵ4 persons on a number of cognitive measures in early life.[26–28] Taken together, studies of both neurological and non-neurological samples suggest an alternate model whereby APOE-ϵ4 subjects may simply show better aptitude in various cognitive abilities when compared with non-ϵ4 subjects early in the ageing process and regardless of CNS injury. However, this early benefit may consequently predispose APOE-ϵ4 subjects to greater cognitive deficits in post-TBI long term recovery or as the ageing process extends into later life and against the backdrop of AD related neuropathological accumulations. The findings of Teasdale and colleagues[39] are consistent with this notion.

Recent studies have already identified APOE related brain activation differences among young participants.[47 48] Using positron emission tomography, Scarmeas and colleagues[47] showed brain regions where ϵ4 carriers were higher or lower in activity than non-ϵ4 carriers. One interpretation offered by the authors of the discrepant pattern of activation was that it represented a predisposition to brain disease later in life. Reiman and colleagues[48] identified lower rates of glucose metabolism among young adult ϵ4 carriers in the bilateral posterior cingulate, parietal, temporal and prefrontal cortex despite equivalent neuropsychological performances between ϵ4 and non-ϵ4 carriers. Again, the interpretation offered by Scarmeas *et al* is consistent with the results of Reimen *et al*. A clear implication of both of these studies is that APOE genetic distinctions in brain activation are identifiable early in the life span, which may or may not correlate with neurocognitive performance at later stages of life. Consequently, these studies may be considered indirect evidence for a comprehensive model of APOE phenotypes that dynamically change across the age spectrum and also in response to CNS insult.

There are a number of limitations to note when considering the present findings. Firstly, the present study sample, active duty military personnel, is not generalisable to a non-military population as a whole. This population was chosen for its increased risk of head injury as well as for its well established system of monitoring TBI patients. Other selection characteristics unique to a military population that may mediate the current results may not have been fully addressed by the scope of this study, further limiting the generalisability of these implications. Secondly, the present sample size, while comparable with those in previously published reports,[25 41] is relatively small. Thirdly, given the exploratory nature of our study, the present analyses may be somewhat limited by our necessary balance between statistical conservativism and sensitivity to detect group differences. Fourthly, because referral to the DVBIC is contingent on being observed and appropriately referred by a health care provider, the possibility of a significant selection bias cannot be ruled out. This selection bias might have selected out cases of TBI that did not cause a sufficient enough disruption in duties or quality of life to warrant medical attention, or more severe cases of TBI that did not appropriately get referred to the DVBIC because of either physician or patient preference. Finally, inclusion of a non-TBI comparison group would have clarified whether young ϵ4 participants show a general trait of better performances than non-ϵ4 participants, apart from TBI, or whether TBI ''activates'' these better performances, which in turn lead to the greater likelihood of AD pathology in later life.

In summary, the present findings revealed comparable performances demonstrated on most neuropsychological measures, although better performances by ϵ4 carriers were found on select measures of attention, executive functioning and episodic memory encoding, approximately 1 month following TBI. Using participant groups that were carefully matched according to demographic and psychosocial measures, the current study does not support the notion of relatively poorer neuropsychological functioning associated with the APOE-ϵ4 genotype shortly following mild or moderate brain injury. Results further suggest compensatory mechanisms modified by APOE genotype wherein dynamic changes may occur in the brain according to one's age and possibly in response to CNS insult. Future functional brain imaging studies investigating the possibility of this compensatory model by age and recovery period will help to further contextualise the present results.

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Competing interests: Dr Delis is a co-author of the D-KEFS (Delis–Kaplan Executive Functions System) and receives royalties from the test. There were no other actual or potential conflicts of interest for the authors that could have inappropriately influenced the present work. Subjects were recruited in accordance with Internal Review Board (IRB) approved policies and procedures. Standard professional and ethical guidelines were upheld during the research study and manuscript preparation. The views expressed in this article do not necessarily reflect those of the funding agency, the United States Navy, the United States Marine Corps, the Department of Defense or the United States Government.

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