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Apolipoprotein E (*APOE*) ε4 Status Moderates the Relationship Between Close-Range Blast Exposure and Cognitive Functioning

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Abstract

Objectives: Recent studies suggest that close-range blast exposure (CBE), regardless of acute concussive symptoms, may have negative long-term effects on brain health and cognition; however, these effects are highly variable across individuals. One potential genetic risk factor that may impact recovery and explain the heterogeneity of blast injury's long-term cognitive outcomes is the inheritance of an apolipoprotein *(APOE)* ε4 allele, a well-known genetic risk factor for Alzheimer's disease. We hypothesized that *APOE* ε4 carrier status would moderate the impact of CBE on long-term cognitive outcomes. **Methods:** To test this hypothesis, we examined 488 post-9/11 veterans who completed assessments of neuropsychological functioning, psychiatric diagnoses, history of blast exposure, military and non-military mild traumatic brain injuries (mTBIs), and available *APOE* genotypes. We separately examined the effects of CBE on attention, memory, and executive functioning in individuals with and without the *APOE* ε4 allele. **Results:** As predicted, we observed a differential impact of CBE status on cognition as a function of *APOE* ε4 status, in which CBE ε4 carriers displayed significantly worse neuropsychological performance, specifically in the domain of memory. These results persisted after adjusting for clinical, demographic, and genetic factors and were not observed when examining other neurotrauma variables (i.e., lifetime or military mTBI, distant blast exposure), though these variables displayed similar trends. **Conclusions:** These results suggest *APOE* ε4 carriers are more vulnerable to the impact of CBE on cognition and highlight the importance of considering genetic risk when studying cognitive effects of neurotrauma.

Keywords: *APOE*, Blast, Memory, Concussive, Genetic, Veterans, Mild traumatic brain injury

INTRODUCTION

Close-range blast exposure (CBE) is defined as exposure to detonated blast munitions within 10 meters (Fortier et al., 2014). An estimated 78% of combat injuries from Operations Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND) are associated with blasts, as the use of weapons that emit high amounts of kinetic energy resulting in an over-pressurized shock wave such as improvised explosive devices, landmines, and rocket-propelled grenades have become a hallmark of modern warfare (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009). CBE is commonly associated with a number of physical injuries such as vestibular dysfunction, hearing impairment, musculoskeletal injury as well as acute mild traumatic brain injury (mTBI), but recent evidence suggests potential detriments can occur without acute symptoms of TBI (Grande et al., 2018; Sullivan et al., 2019; Vanderploeg et al., 2012). This is critical to evaluate further, as nearly half of the soldiers who have not experienced an acute brain injury during deployment have reported being near two or more explosions (Hoge et al.,

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2008). Despite the prevalence of CBE in modern war, research on long-term neurological and cognitive consequences is limited (Elder, Stone, & Ahlers, 2014).

Emerging evidence suggests CBE may negatively affect cognition and brain health. Pagulayan and colleagues found blast-related military mTBI was associated with poorer prospective memory performance on the Memory for Intentions Test compared to combat exposed controls (Pagulayan et al., 2018). Veterans exposed to CBE, independent of acute mTBI symptoms, also have displayed poorer verbal episodic memory performance and a higher rate of clinically significant memory impairment post-deployment (Grande et al., 2018). A recent US Army survey found veterans placed in roles exposed to high levels of low-grade close-blast experienced more concussive and post-concussive symptoms post-deployment, often interfering with activities of daily living (Carr et al., 2016). CBE may play a central role in military mTBI memory impairments through neurochemical alterations in the medial temporal lobe (MTL). Recent work utilizing high resolution (7 T) MR spectroscopy imaging of the MTL found those with blast-related mTBI and memory impairment had signs of neuronal injury, specifically deficits in *N*-acetyl aspartate/choline and *N*-acetyl aspartate/creatine, compared to controls (Hetherington et al., 2014). CBE may even be more sensitive to structural and functional brain alterations than traditional mTBI assessment based on acute symptoms (Robinson et al., 2015; Sullivan et al., 2019; Trotter, Robinson, Milberg, McGlinchey, & Salat, 2015). For example, CBE has been found to reduce microstructural white matter integrity in the absence of diagnosed mTBI compared to unexposed controls (Taber et al., 2015). Furthermore, CBE has been associated with more rapid cross-sectional brain-aging trajectories at a microstructural tissue level, a relationship not found with mTBI (Trotter et al., 2015). Utilizing functioning magnetic resonance imaging, researchers found CBE in the absence of mTBI was associated with decreased connectivity between the default mode network and somatomotor regions, with similar effects in participants with blast-related mTBI (Robinson et al., 2015). These alternations in brain functioning were notably absent in non-blast concussions and more distant blast exposures.

Recent work suggests the apolipoprotein (*APOE*) ε4 locus, the largest genetic risk factor for late-onset Alzheimer's disease (AD), may exacerbate neurocognitive deficits following neurotrauma (Corder et al., 1993; Crawford et al., 2002; Eramudugolla et al., 2014; Jiang et al., 2006; Merritt, Clark, et al., 2018; Raber, Huang, & Ashford, 2004; Sullivan et al., 2019). The effect of *APOE* ε4 on neurocognitive function has been consistently observed across populations that carry the variant, although the particular odds ratio conferred by *APOE* ε4 varies by ancestry (Farrer, 1997; Graff-Radford et al., 2002; Kuwano et al., 2013). *APOE's* primary role in the brain is cholesterol and lipid transport, playing a vital role in many of the basic processes that promote healthy neurocognitive functioning; such as neural recovery, repair, and maintaining synaptic integrity (Mahley & Huang, 1999). *APOE* ε4 is associated with several disruptions in homeostatic processes that may impede recovery from neurotrauma; such as increased beta-amyloid accumulation, inhibition of neurite outgrowth, diminished neuroplasticity, and less efficient lipid transport (Haan, 1999; Jiang et al., 2006; Johnson, Stewart, & Smith, 2010; Mahley & Huang, 1999). In severe head injuries, researchers have found ε4 carriers suffer less favorable outcomes (death, coma, and severe disability) than ε4 non-carriers (Teasdale, Nicoll, Murray, & Fiddes, 1997). *APOE* ε4 carriers have displayed worse verbal recall performance and less favorable functional outcomes six months following TBI compared to ε4 non-carriers, despite no differences in demographics or injury severity (Crawford et al., 2002; Zhou et al., 2008). The largest study to explore this relationship ($N = 6{,}333$), also found worse long-term outcomes in verbal episodic memory performance among young adult ε4 carriers compared to non-carriers following mild-to-severe TBI (Eramudugolla et al., 2014). This has also been demonstrated when restricted to mTBI, as researchers found ε4 carriers have diminished verbal episodic memory performance six months following injury (Yue et al., 2017). Additional studies suggest that individuals with mTBI and the *APOE* ε4 allele experience worse post-concussive symptoms, memory performance, and processing speed (Merritt, Lapira, et al., 2018; Merritt, Clark, et al., 2018). However, these effects are not universally replicated. Other studies have failed to find differential cognitive outcomes in ε4 carriers *versus* non-carriers following TBI, especially when limiting analyses to mTBI (Chamelian, 2004; Han et al., 2007; Lawrence, Comper, Hutchison, & Sharma, 2015; Padgett, Summers, & Skilbeck, 2016; Shadli, Pieter, Yaacob, & Rashid, 2011). Three of these studies specifically assessed verbal episodic memory performance, and failed to find impairments in ε4 carriers exposed to mTBI (Chamelian, 2004; Han et al., 2007; Shadli et al., 2011). In addition to cognitive impairments, *APOE* ε4 may also increase the likelihood of microstructural white matter alterations following CBE (Sullivan et al., 2019). The neural vulnerability associated with *APOE* ε4 may be strongest in the MTL, as studies have shown that healthy asymptomatic adult ε4 carriers exhibit reduced cortical thickness, and aberrant functional connectivity in the MTL (Borghesani et al., 2008; Burggren et al., 2008; Kukolja, Thiel, Eggermann, Zerres, & Fink, 2010; Wishart et al., 2006).

While multiple studies have explored how *APOE* ε4 modifies the relationship between neurotrauma and cognition, these studies have failed to consider the role of CBE, with and without acute concussive symptoms (Ariza, 2006; Chamelian, 2004; Clark et al., 2018; Han et al., 2007; Merritt, Clark, et al., 2018; Noé, Ferri, Colomer, Moliner, & Chirivella, 2010; Shadli et al., 2011; Yue et al., 2017). The present study employed a large sample size ($n = 302$–343 depending on the cognitive domain), which enabled the examination of the potentially differential impact of neurotrauma on multiple domains of cognition as a function of ε4 status. As more reports of memory impairments in veterans exposed to blast emerge, it is critically important to characterize the degree to which genetic and environmental risk factors

alter long-term cognitive functioning (Baalman, Cotton, Rasband, & Rasband, 2013; Carr et al., 2016; Chao, 2017). Blast-related mTBI and ε4 carrier status are known risk factors for the development of AD and Chronic Traumatic Encephalopathy (CTE), yet CBE has not been examined with cognition as a function of ε4 status, as has been previously done with military and lifetime mTBI (Eramudugolla et al., 2014; Goldstein et al., 2012; Rohling et al., 2011; Smith, Johnson, & Stewart, 2013). Pathophysiological mechanisms implicated in brain injuries have been found to differ between the blast and non-blast neurotrauma, suggesting previous work in non-blast-related mTBI may not generalize to CBE (De Gasperi et al., 2012; Elder et al., 2014; Johnson et al., 2010; Stone et al., 2002). Further identifying novel gene–environment interactions that underlie subclinical memory impairments in young (mean age = 32 years old) veterans may offer significant clinical utility by identifying an important early window for clinical interventions aimed at ameliorating further decline.

In this study, we examined the impact of military CBE on long-term cognitive functioning ($M = 3.33$ years post-deployment) in a well-characterized cohort of post-9/11 veterans. Based on the previous literature, we hypothesized that CBE would differentially affect cognition, particularly memory, as a function of *APOE* ε4 status, such that CBE ε4 carriers would exhibit worse memory performance compared to those without CBE and/or ε4 non-carriers (Eramudugolla et al., 2014; Grande et al., 2018; Merritt, Clark, et al., 2018; Yue et al., 2017). To test this hypothesis, we explored whether *APOE* ε4 status impacted the relationship between CBE and performance on standardized neuropsychological measures, after adjusting for lifetime mTBI, clinical (post-traumatic stress disorder severity and anxiety), demographic (estimated pre-morbid intellectual functioning, sex, and educational attainment), and genetic covariates (principle components representing population substructure). Secondarily, we assessed additional predictors (lifetime mTBI, military mTBI, and distant blast exposures, DBE, within 11–100 m) to explore more commonly researched neurotrauma variables with *APOE* ε4 and cognition, and to probe if CBE was uniquely sensitive to these genetic/cognitive outcome interactions. To assess three broad domains of cognition, previously validated standardized composite measures of cognitive functioning in the domains of attention, executive functioning, and memory were used as dependent variables (Riley et al., 2019).

METHODS

Participants

Our sample included 488 post-9/11 veterans deployed to OEF/OIF/OND. These participants were consecutively enrolled in the Translational Research Center for TBI and Stress Disorders (TRACTS), VA RR&D TBI National Network Research Center at VA Boston Healthcare System. TRACTS recruitment, exclusionary criteria, and study procedures are described in full in a previous publication (McGlinchey, Milberg, Fonda, & Fortier, 2017). Participants were excluded if they displayed inadequate task effort as determined by a score of ≤85 on any measure of the Medical Symptom Validity Test, with the exception of free recall ($n = 26$) (Green, 2004), and/or those who obtained a score of ≤14 on the Forced Choice trial of California Verbal Learning Test – 2nd Edition ($n = 15$) (Delis, Kramer, Kaplan, & Ober, 1999). Performance on PVTs and subsequent exclusions across groups based on PVTs are reported in supplementary materials (Table S1). Additional supplemental analyses further excluded those who failed the Reliable Digit Span [>7 on the WAIS-IV (Weschler, 2008), ($n = 8$, Tables S2–S3)]. We further excluded participants who had not yet been deployed ($n = 13$); reported a history of moderate or severe TBI ($n = 13$); self-identified as having psychiatric diagnoses with known cognitive symptoms (e.g., attention deficit hyperactivity disorder) ($n = 5$), or suffer from a severe neurological illness ($n = 1$). Participants were further excluded from primary analyses if they were missing any covariate used in the model. This includes those without principle components representing global population substructure, to account for ancestry ($n = 49$), those missing the measure for anxiety ($n = 15$), and those missing the measure of estimated pre-morbid IQ ($n = 7$). Final samples used in moderation analyses were ($n = 343$) for memory, ($n = 302$) for attention, and ($n = 326$) for executive functioning. Most veterans had served in the Army (63.0%), but the Marines (24.4%), Air Force (7.1%), Navy (4.0%), and Coast Guard (.3%) were also represented. A small number of veterans (2.0%) served in multiple branches. Participant demographic and clinical characteristics are presented in Table 1.

All study procedures are in accordance with the Declaration of Helsinki and were reviewed and approved by the VA Boston Healthcare System's Institutional Review Board. All participants provided written informed consent.

Clinical Measures

A doctoral-level psychologist conducted a clinical interview to assess participants' history of blast exposure, military mTBI, and lifetime mTBI using the Boston Assessment of TBI-Lifetime (BAT-L) (Fortier et al., 2014). The BAT-L is a semi-structured interview designed to assess military blast exposure, military blast-related TBI, pre-military head injury and TBI, and post-military head injury and TBI. TBI was diagnosed based on the joint Department of Defense and the Department of Veterans Affairs TBI diagnostic criteria (Management of Concussion/mTBI Working Group, 2009). The BAT-L has been demonstrated to have strong inter-rater reliability and validity when compared to the Ohio State University TBI Identification Method and clinically administered Veterans Affairs TBI screening (Fortier et al., 2014). The BAT-L classifies blast exposure

Table 1. Demographic and clinical characteristics across close-range blast exposure and *APOE* ε4 groups

Variable	CBE− *APOE* ε4−	CBE− *APOE* ε4+	CBE+ *APOE* ε4−	CBE+ *APOE* ε4+	Group comparison
Sample size ($n = 352$)	$n = 156$	$n = 47$	$n = 111$	$n = 38$	
APOE genotype, *n* (%)	ε23: 25 (16.0) ε33: 131 (84.0)	ε24: 7 (14.9) ε34: 38 (80.8) ε44: 2 (4.3)	ε23: 18 (16.2) ε33: 93 (83.8)	ε24: 4 (10.5) ε34: 30 (79.0) ε44: 4 (10.5)	
Male, *n* (%)	137 (87.8)	39 (83.0)	104 (93.7)	38 (100)	$\chi^2(3) = 9.55$, $p = .02$*
Age in years, *M* (*SD*)	32.9 (9.1)	32.8 (7.0)	30.9 (7.9)	30.8 (7.5)	$F(3,348) = 1.76$, $p = .19$, $\eta p^2 = .013$
Education, *M* (*SD*)	14 (1.9)	14.3 (2.0)	13.8 (2.1)	13.5 (1.7)	$F(3,348) = 1.31$, $p = .27$, $\eta p^2 = .011$
Lifetime mTBI, *n* (%)	93 (59.6)	26 (55.3)	87 (78.4)	34 (89.5)	$\chi^2(3) = 22.1$, $p < .001$**
Military mTBI, *n* (%)	51 (32.1)	11 (23.4)	68 (61.3)	28 (73.7)	$\chi^2(3) = 44.0$, $p < .001$**
Total duration of deployment, months (*SD*)	14.1 (9.0)	12.4 (7.1)	17.2 (9.9)	18.1 (10.6)	$F(3,348) = 5.06$, $p = .002$**, $\eta p^2 = .042$
Time since last deployment, months (*SD*)[a]	34.1 (33.9)	40.1 (33.6)	46.9 (32.8)	44.3 (33.0)	$F(3,347) = 3.39$, $p = .02$*, $\eta p^2 = .028$
CAPS, *M* (*SD*)	41.3 (28.3)	42.4 (27.1)	60.2 (27.6)	61.5 (30.4)	$F(3,348) = 13.0$, $p < .001$**, $\eta p^2 = .101$
PSQI-G, *M* (*SD*)[a]	8.9 (4.8)	8.6 (4.0)	11.1 (4.7)	11.2 (4.1)	$F(3,340) = 7.22$, $p < .001$**, $\eta p^2 = .060$
DASS-D, *M* (*SD*)	7.29 (9.4)	7.74 (8.1)	10.9 (10.9)	10.5 (9.4)	$F(3,348) = 3.53$, $p = .02$*, $\eta p^2 = .030$
DASS-A, *M* (*SD*)	5.68 (6.8)	5.11 (6.2)	8.59 (8.8)	10.2 (7.9)	$F(3,348) = 6.56$, $p < .001$**, $\eta p^2 = .054$
SF-MPQ, *M* (*SD*)[a]	24.1 (23.8)	27.7 (22.5)	35.6 (26.4)	34.4 (27.9)	$F(3,329) = 4.90$, $p = .002$**, $\eta p^2 = .043$
LDH AVG, *M* (*SD*)[a]	6.0 (3.8)	5.46 (2.8)	6.87 (4.1)	6.84 (4.6)	$F(3,343) = 2.04$, $p = .11$, $\eta p^2 = .018$
DRRI, *M* (*SD*)[a]	11.4 (9.0)	10.8 (9.1)	23.9 (10.4)	29.2 (12.1)	$F(3,344) = 59.8$, $p < .001$**, $\eta p^2 = 343$
Ethnicity					
White, *n* (%)	120 (77.0)	27 (57.4)	90 (81.1)	29 (76.3)	$\chi^2(3) = 10.4$, $p = .02$*
Black, *n* (%)	11 (7.1)	10 (21.3)	4 (3.6)	3 (7.9)	$\chi^2(3) = 14.4$, $p < .01$**
Hispanic, *n* (%)	24 (15.4)	9 (19.1)	15 (13.5)	5 (13.2)	$\chi^2(3) = .9$, $p = .82$
Asian, *n* (%)	0 (0)	0 (0)	4 (3.6)	0 (0)	$\chi^2(3) = 8.78$, $p = .03$*
American Indian, *n* (%)	0 (0)	1 (2.1)	0 (0)	0 (0)	$\chi^2(3) = 6.51$, $p = .09$
Pacific Islander, *n* (%)	0 (0)	0 (0)	0 (0)	1 (2.6)	$\chi^2(3) = 8.29$, $p = .04$*
Unknown, *n* (%)	1 (.6)	0 (0)	0 (0)	1 (2.6)	$\chi^2(3) = 3.78$, $p = .29$

Note: Group comparisons were done using analysis of variance (ANOVA) tests for continuous variables and χ^2 test of association for categorical variables. *$p < .05$ and **$p < .01$.
CBE = close-range blast exposure, *APOE* = apolipoprotein E, mTBI = mild traumatic brain injury, CAPS = clinician-administered post-traumatic stress disorder scale – severity, PSQI-G = Pittsburgh Sleep Quality Index Global score, DASS-D = Depression Anxiety Stress scales – depression subscale DASS-A = Depression Anxiety Stress scales – anxiety subscale, LDH = lifetime drinking history average drinks on a drinking day, SF-MPQ = short-form McGill pain questionnaire average pain – average pain, DRRI = Deployment Risk and Resiliency Inventory Average Combat Exposure. Participants included in sample size were not missing any covariates used in main analyses.
[a]Variables with incomplete sample: Time since last deployment ($n = 1$), PSQI-G score ($n = 8$), SF-MPQ ($n = 19$), LDH ($n = 5$), DRRI ($n = 4$).

(with or without acute symptoms of TBI) based on proximity to the event (0–10 m, 11–25 m, 26–100 m). Our primary analysis used CBE as the main predictor variable. Secondary analyses utilized additional neurotrauma measures (head injury including DBE, lifetime mTBI, and military mTBI) to replicate previous findings and examine the specificity of CBE relative to other neurotrauma variables. Participants who reported being within a 0–10 m proximity to a blast were defined as CBE positive (CBE+). Participants who did not experience a blast within 0–10 m were defined as CBE negative (CBE−). Lifetime and military mTBI were defined as loss of consciousness less than 30 min and/or post-traumatic amnesia less than 24 hr and/or the presence of altered mental status less than 24 hr. Lifetime mTBI (s) could have occurred prior to, during, or post-military experience. Military mTBI(s) could have occurred only during military experience related to blast or other blunt mechanisms. DBE was defined as positive if the individual experienced at least one blast in an 11–100 m range (DBE+) or negative if the individual experienced no blasts in that range (DBE−). Individuals who were CBE+ were excluded from DBE analyses. The number of total blast exposures includes all blasts within a 0–100 m range.

Post-traumatic stress disorder (PTSD) presence and severity were assessed with the CAPS for DSM-IV by doctoral-level psychologists (Blake et al., 1995). All diagnoses were completed in accordance with DSM-IV criteria. PTSD severity was captured by a continuous CAPS total score (the sum of the frequency and intensity ratings for symptom clusters B–D; ranges from 0 to 150). A diagnostic team consensus was conducted with at least three doctoral-level psychologists and psychiatrists for confirmation of TBI and PTSD diagnoses. The Wechsler Test of Adult Reading (Weschler, 2008) was used to estimate pre-morbid intellectual functioning (scaled score). Self-report questionnaires were used to assess chronic pain, sleep dysfunction, drinking history, depression, and anxiety symptoms. All variables were continuous measures. Specifically, self-reported pain symptoms were evaluated with the Short Form of the McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987). Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). PSQI global score was used as the measure of current sleep quality. The Depression Anxiety Stress Scales (DASS) (Brown, Chorpita, Korotitsch, & Barlow, 1997) was used to assess depression and anxiety severity with the total of each subscale. The Lifetime Drinking History (LDH) interview was used to assess alcohol use/abuse, specifically average drinks on a drinking day (Skinner & Sheu, 1982). The Deployment Risk and Resiliency Inventory (DRRI) combat exposure subscale was used to assess combat exposure in our cohort (King, King, Vogt, Knight, & Samper, 2006). Only 17 of 488 participants (3.5%) reported current substance abuse other than alcohol; therefore, abuse of other substances was not included in our analysis.

Neuropsychological Assessment

To assess neuropsychological function, participants were administered a battery of validated neuropsychological tests in the domains of memory, attention, and executive function (Table 2). Performance across measures was converted to scaled, age-corrected *z*-scores, and then averaged to form composite measures of each domain. This method was recently validated in a subset of our current sample (Riley et al., 2019). The memory composite was comprised of three California Verbal Learning Test-II (CVLT-II) assessments (short-delay free recall, long-delay free recall, long-delay recognition) (Delis, Kramer, Kaplan, & Ober, 1999). The attention composite was comprised of four measures; Test of Variables of Attention (TOVA) mean reaction time and d' (Henry, 2005), Digit Span (forward) (Weschler, 2008), and the Number Sequencing Subtest of the Trail Making Task (Trails-A) (Delis, Kaplan, & Kramer, 2001). The executive functioning composite was comprised of six measures; the Number/Letter Switching Subtest of the Trail Making Test (Trails-B), Stroop Test (Inhibition total time) (Delis et al., 2001), CANTAB Intra-Extra Dimensional Set Shift (IED) (http://www.cantab.com), Verbal Fluency (FAS) assessments (letter fluency and category fluency) (Delis et al., 2001), and Auditory Consonant Trigrams (averaged across delays) (Stuss et al., 1985). Composite scores were excluded for the following; (memory: ≥1/3 assessments missing; attention: >1/4 assessments missing; executive functioning: >1/6 assessments missing). Unadjusted means for standardized neuropsychological assessments are reported in Table 2.

Generation of Genotype Data

DNA extraction and generation of whole-genome genotype data for the TRACTS cohort has been described in detail elsewhere (Logue et al., 2013; Miller et al., 2015). Briefly, DNA was extracted from whole blood, and genotypes were assessed using the Illumina HumanOmni2.5-8 microarray (Illumina, San Diego, CA, USA) BeadChip according to the manufacturer's protocols. Genotype data were screened for relatedness and sex mismatches. Cleaning genotype data, ancestry determination, and imputation of un-genotyped variants was done using the Psychiatric Genomics Consortium (PGC)-PTSD pipeline, which consists of the standard PGC core pipeline for data cleaning and imputation (https://sites.google.com/a/broadinstitute.org/ricopili/ and https://github.com/orgs/Nealelab/teams/ricopili), augmented to account for greater diversity in terms of ancestry for PTSD cohorts compared to cohorts previously studied by many of the other PGC phenotype focus groups (Logue et al., 2015; Nievergelt et al., 2019). We will describe the process briefly here. Ancestry was assessed using an analysis based on single nucleotide polymorphism (SNP)weights (Chen et al., 2013) and a principal component (PC) analysis of TRACTS subjects merged together with Thousand Genomes Phase 3

Table 2. Cognitive performance across close-range blast exposure and *APOE* ε4 groups

Variables	CBE− *APOE* ε4−	CBE− *APOE* ε4+	CBE+ *APOE* ε4−	CBE+ *APOE* ε4+	Group comparison
Sample size ($n = 352$)	$n = 156$	$n = 47$	$n = 111$	$n = 38$	
Memory composite, *M* (*SD*)	–.251 (.919)	–.166 (1.01)	–.286 (.927)	–.718 (1.05)	$F(3,339) = 2.79$, $p = .041$*, $\eta p^2 = .024$
CVLT-II SD, *M* (*SD*)	–.098 (1.03)	.064 (1.11)	–.123 (1.06)	–.653 (1.19)	$F(3,340) = 3.43$, $p = .017$*, $\eta p^2 = .029$
CVLT-II LD, *M* (*SD*)	–.237 (1.11)	–.106 (1.08)	–.307 (1.06)	–.764 (1.15)	$F(3,340) = 2.87$, $p = .036$*, $\eta p^2 = .025$
CVLT-II REC, *M* (*SD*)	–.447 (1.12)	–.457 (1.23)	–.427 (1.18)	–.736 (1.22)	$F(3,339) = .697$, $p = .56$, $\eta p^2 = .006$
Attention composite, *M* (*SD*)	.068 (.549)	–.007 (.634)	–.081 (.627)	–.079 (.615)	$F(3,298) = .779$, $p = .51$, $\eta p^2 = .008$
TOVA RT, *M* (*SD*)	–.211 (1.18)	–.475 (.939)	–.225 (1.45)	–.566 (1.11)	$F(3,298) = 1.13$, $p = .34$, $\eta p^2 = .011$
TOVA *d′*, *M* (*SD*)	.092 (.973)	.129 (.874)	.211 (1.02)	.080 (.979)	$F(3,296) = .308$, $p = .82$, $\eta p^2 = .003$
DS F, *M* (*SD*)	–.088 (.977)	–.036 (1.09)	–.117 (1.02)	–.063 (.978)	$F(3,346) = .08$, $p = .97$, $\eta p^2 = .001$
TMT NS, *M* (*SD*)	.409 (.699)	.217 (1.09)	.444 (.679)	.196 (.592)	$F(3,331) = 1.73$, $p = .16$, $\eta p^2 = .015$
EF composite, *M* (*SD*)	.118 (.537)	.162 (.620)	.152 (.520)	.057 (.561)	$F(3,322) = .325$, $p = .81$, $\eta p^2 = .003$
TMT NLS, *M* (*SD*)	.149 (.770)	.116 (1.02)	.013 (.977)	–.167 (.792)	$F(3,331) = 1.42$, $p = .24$, $\eta p^2 = .013$
STRP IS TT, *M* (*SD*)	.187 (.750)	.130 (1.06)	.220 (.977)	–.038 (.791)	$F(3,326) = .849$, $p = .47$, $\eta p^2 = .008$
IED, *M* (*SD*)	.144 (.972)	.055 (1.13)	.106 (1.10)	.266 (.962)	$F(3,267) = .234$, $p = .872$, $\eta p^2 = .003$
FAS-LF, *M* (*SD*)	.279 (1.08)	.370 (1.12)	.346 (1.04)	.463 (1.32)	$F(3,336) = .313$, $p = .82$, $\eta p^2 = .003$
FAS-CF, *M* (*SD*)	.362 (1.09)	.609 (1.23)	.487 (.966)	.371 (1.11)	$F(3,335) = .761$, $p = .52$, $\eta p^2 = .007$
ACT, *M* (*SD*)	–.458 (1.01)	–.434 (.971)	–.315 (.956)	–.522 (1.09)	$F(3,303) = .543$, $p = .65$, $\eta p^2 = .005$
WTAR, *M* (*SD*)	105 (10.8)	103 (13.4)	103 (11.9)	102 (11.9)	$F(3,348) = .754$, $p = .52$, $\eta p^2 = .006$

Note: Group comparisons were done using analysis of variance (ANOVA) tests.
CBE = close-range blast exposure, *APOE* = apolipoprotein, WTAR = Wechsler Test of Adult Reading scaled score, CVLT-II = California Verbal Learning Test – 2nd edition, SD = short delay, LD = long delay, REC = recognition score, DS F = Digit Span Forward, TOVA = Test of Variables of Attention, RT = Reaction Time, *d′* = discrimination ability, TMT NL = Number Sequencing Subtest of the Trail Making Task (Trails-A), EF = Executive Functioning, TMT NLS = Number/Letter Switching Subtest of the Trail Making Test (Trails-B), STRP IS TT = Stroop Test (Inhibition total time), IED = CANTAB Intra-Extra Dimensional Set Shift, FAS-LF = Verbal Fluency (Letter), FAS-CF = Verbal Fluency (Category), ACT = Auditory Consonant Trigrams (averaged across delays).

(1KG) data (The 1000 Genomes Project Consortium, 2015). Phasing and imputation were performed using SHAPEIT2 v2.r837 (Delaneau, Zagury, & Marchini, 2013) and IMPUTE2 v2.2.2 (Howie, Donnelly, & Marchini, 2009) with a 1KG Phase 3 reference panel. For the purposes of adjusting for population-level effects, PCs were computed based on 10,000 randomly chosen common (>5% frequency) variants. This was done once in the entire TRACTS cohort to generate PCs to account for global-ancestry differences when analyzing the cohort as a whole.

APOE genotypes were calculated from the imputed genotypes for rs429358 and rs7412. Both of these SNPs had high imputation quality (info score >.9) and low missing rates (<1%). Based on these imputed data, *APOE* genotypes were available for 488 participants. We validated these imputations based on our previously generated ABI TaqMan®-based genotypes for 306 participants (Sullivan et al., 2019). For 306 participants, we observed 100% concordance between the imputed SNP- and TaqMan-based genotypes. The *APOE* genotype was coded as *APOE* ε4 carriers *versus* non-carriers (i.e., participants with at least one ε4 allele *vs.* participants with ε2/ε2, ε2/ε3, or ε3/ε3 genotypes) due to the low number of participants with ε4/ε4 homozygotes in our sample ($n = 6$). The main analyses were repeated and constrained to participants with ε33 and ε34 genotypes in supplementary analyses (Tables S4–S5).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). To examine the potential moderating effects of *APOE* ε4 status on the relationship between CBE and cognition, we used non-parametric regression analyses (Hayes, 2018) using the PROCESS macro for bootstrapping moderating effects (Hayes, 2018) as implemented in the SPSS macro of Hayes (2012). Bootstrapping is a non-parametric approach to estimating effect sizes and testing hypotheses while making no inherent assumptions on the distribution of the data (Preacher, Rucker, & Hayes, 2007). In these models, CBE was entered as the independent predictor and cognitive composite scores (memory, executive functioning, and attention) as the dependent measure, with *APOE* ε4 status as the moderator (Table 3). Bootstrapping was carried out using a bias-corrected approach with 5000 samples. A statistical significance was set at $p < .05$. To further validate and characterize significant effects, hierarchical linear regression analyses were conducted for any moderation analysis that reached significance, in which cognitive composite scores were the dependent variable (Table 4). PTSD severity, anxiety severity, gender, education, lifetime mTBI, estimated pre-morbid intellectual functioning, and the first three principle components representing population substructure were added as covariates in the first step of the model, main effects of the CBE and *APOE* group were added in the second step, and the interaction between CBE and *APOE* groups were added in the final step of the model. Secondary analyses replaced CBE with additional neurotrauma variables (lifetime mTBI, military mTBI, and DBE) as the independent predictor (Tables 3 and 5). Several supplementary analyses were conducted to further characterize the specificity of main effects. Moderation analyses and hierarchical linear regressions assessing the relationship between memory outcomes after CBE as a function of *APOE* group were repeated when excluding ε2 carriers and those with the ε44 genotype to isolate differences between the largest genotype groups (ε33 and ε34; Tables S4–S5). Additionally, analyses were conducted replacing memory performance with the WTAR scaled score in the model to further characterize any potential influence of estimated pre-morbid IQ (Tables S6–S7). To further dissect significant moderation effects between CBE and memory performance as a function of an *APOE* group, we repeated moderation analyses on the three components of the memory composite (short-delay free recall, long-delay free recall, and recognition memory; Table S8).

Table 3. Differential effects of the relationship between neurotrauma (close blast exposure, lifetime mTBI, military mTBI, and distant blast exposure) and cognition as a function of *APOE* ε4 carrier status

Cognitive composite measures	Moderation analyses
	Close blast exposure × *APOE* ε4 carrier status
Memory	$\Delta R^2 = .0162$, $F(1, 330) = 6.03$, $p = .015$*
	APOE ε4+: $t = -2.78$, $B = -.589$, $p = .006$**
	APOE ε4−: $t = -.08$, $B = -.010$, $p = .94$
Attention	$\Delta R^2 = .0005$, $F(1, 289) = .168$, $p = .68$
Executive functioning	$\Delta R^2 = .0054$, $F(1, 313) = 2.22$, $p = .14$
	Lifetime mTBI × *APOE* ε4 carrier status
Memory	$\Delta R^2 = .0135$, $F(1, 331) = 4.88$, $p = .047$*
	APOE ε4+: $t = -1.87$, $B = -.44$, $p = .062$
	APOE ε4−: $t = .607$, $B = .08$, $p = .55$
Attention	$\Delta R^2 = .0007$, $F(1, 290) = .219$, $p = .64$
Executive functioning	$\Delta R^2 = .0007$, $F(1, 314) = .302$, $p = .58$
	Military mTBI × *APOE* ε4 carrier status
Memory	$\Delta R^2 = .0020$ $F(1, 331) = .730$, $p = .39$
Attention	$\Delta R^2 = .0043$, $F(1, 290) = 1.46$, $p = .23$
Executive functioning	$\Delta R^2 = .0006$, $F(1, 314) = .23$, $p = .63$
	Distant blast exposure × *APOE* ε4 carrier status
Memory	$\Delta R^2 = .0107$, $F(1, 186) = 2.28$, $p = .13$
Attention	$\Delta R^2 = .0006$, $F(1, 162) = .119$, $p = .73$
Executive functioning	$\Delta R^2 = .0014$, $F(1, 179) = .342$, $p = .56$

Note. *$p < .05$ and **$p < .01$.
mTBI = mild traumatic brain injury, *APOE* = apolipoprotein E, bootstrapped regression analyses were used to assess moderation effects of *APOE* ε4 status on close-range blast exposure (CBE) and cognition. Significant differential effects were further probed based on *APOE* ε4 carrier status.

Table 4. Hierarchical regression summary table for the association of close-range blast exposure by *APOE* ε4 status on memory

	Model 1			Model 2			Model 3		
Variables	*B*	*SE(B)*	*β*	*B*	*SE(B)*	*β*	*B*	*SE(B)*	*β*
CAPS (PTSD)	–.003	.002	–.086	–.002	.002	–.062	–.002	.002	–.072
DASS anxiety	–.002	.009	–.019	–.003	.009	–.021	–.001	.009	–.006
PC1	3.441	1.312	.143*	3.446	1.339	.143*	3.689	1.332	.154*
PC2	–1.455	1.700	–.050	–1.695	1.715	–.058	–1.571	1.703	–.054
PC3	.138	1.616	.005	.312	1.626	.011	.070	1.617	.003
Gender	–.170	.179	–.053	–.211	.181	–.065	–.237	.180	–.073
Education	.047	.027	.097	.047	.027	.098	.045	.026	.094
Lifetime mTBI	–.031	.113	–.015	–.010	.114	–.005	.005	.114	.003
WTAR	.013	.005	.154*	.012	.005	.150*	.012	.005	.148*
APOE ε4 status				–.052	.119	–.023	.779	.358	.350**
CBE				–.144	.111	–.075	.570	.311	.295
CBE × *APOE* ε4 status							–.579	.236	–.546**
R^2		.095			.100			.117	
F for change in R^2					.954			6.033**	

Note. *$p < .01$ and **$p < .05$.
B = effect size, *SE(B)* = standard deviation for effect size, *β* = standardized effect size, CAPS = clinician-administered PTSD scale, PTSD = post-traumatic stress disorder, DASS = depression anxiety stress scales, PC = principle component representing population substructure, mTBI = mild traumatic brain injury, WTAR = Wechsler Test of Adult Reading scaled score, *APOE* = apolipoprotein E, CBE = close-range blast exposure.

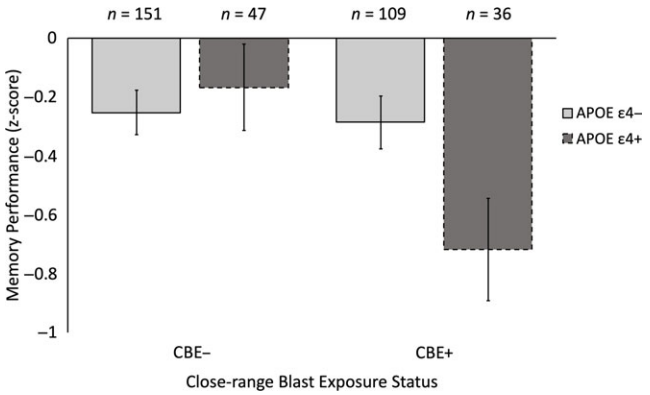

Fig. 1. Memory composite scores (unadjusted for covariates) across close-range blast exposed (CBE) and apolipoprotein (*APOE*) ε4 carrier status groups. Group sizes are reported at the base of each group. *Note.* Plus sign (+) denotes group membership and minus sign (−) denotes non-group membership. Bars included represent standard error across groups.

Subsequent hierarchical linear regressions were conducted for significant moderation effects to verify a significant CBE/*APOE* interaction predicting performance on memory subcomponents (Tables S9–S10). The number of total blast exposures replaced CBE in a hierarchical linear regression to assess the role of cumulative blast load across close and distant exposures (Table S11).

Covariates. Selected *a priori* confounders (age, sex, years of education, sleep quality, average pain, LDH, PTSD severity, depression severity, anxiety severity, estimated pre-morbid IQ, and the use of psychotropic medication) were first assessed individually for relationships with each dependent variable (individual cognitive composite scores) *via* on Pearson correlations ($p < .05$). Of these *a priori* confounders, those that met significance with at least two of the three composite scores were included as covariates in all analyses (covariates included: sex, years of education, PTSD severity, anxiety severity, and estimated pre-morbid IQ). Analyses involving CBE included lifetime mTBI as an additional covariate. Linear regressions were conducted for each dependent variable (individual cognitive composite scores) with selected covariates in each model.

Accounting for ancestry. Analyses additionally included the first three principle components (PC1, PC2, and PC3), representing the global population substructure, to account for ancestry (Price et al., 2006).

RESULTS

Close-Range Blast Exposure

Participant demographics were significantly different based on CBE, with those exposed to close blast reporting greater lifetime and military mTBI burden, greater deployment duration and time since deployment, worse sleep and psychiatric distress (PTSD, depression, and anxiety), more pain, and included a greater percentage of males than those not exposed to close blast (Table 1). The overall regression models with CBE predicting cognitive performance were significant for memory, $F_{12, 330} = 3.63$, $p < .0001$, attention, $F_{12, 289} = 3.95$, $p < .0001$, and executive functioning, $F_{12, 313} = 8.22$, $p < .0001$. The moderation analysis revealed a significant differential effect on the relationship between CBE and memory as a function of *APOE* ε4 status, $\Delta R^2 = .0163$, $F_{1, 330} = 6.033$, $p = .015$ (Figure 1; Tables 3 and 4). The conditional effects of CBE on memory showed a negative association between the CBE group and memory among *APOE* ε4 carriers; $t = –2.78$, $B = –.59$, $p = .006$.

However, there was not a significant association between the CBE group and memory among *APOE* ε4 non-carriers; $t = -.08$, $B = -.01$, $p = .94$. Further analyses replacing the memory composite with its three subcomponents (short delay, long delay, and recognition) revealed there was a significant differential effect on the relationship between CBE and memory performance on the short-delay free recall ($\Delta R^2 = .0218$, $F_{1,\ 331} = 8.45$, $p = .004$), and long-delay free recall ($\Delta R^2 = .0144$, $F_{1,\ 331} = 5.35$, $p = .02$) as a function of *APOE* ε4 status (Tables S8–S10). There was no significant differential effect on the relationship between CBE and recognition memory ($\Delta R^2 = .0044$, $F_{1,\ 330} = 1.51$, $p = .22$) as a function of *APOE* ε4 status. There was no significant differential effect on the relationship between CBE and attention ($\Delta R^2 = .0005$, $F_{1,\ 289} = .168$, $p = .68$), executive functioning ($\Delta R^2 = .0054$, $F_{1,\ 313} = 2.41$, $p = .14$), or estimated pre-morbid intellectual functioning ($\Delta R^2 = .0001$, $F_{1,\ 340} = .026$, $p = .87$; Tables S6–S7) as a function of *APOE* ε4 status. Further analyses revealed these results remained consistent when constrained to only participants with the ε33 and ε34 genotype (Tables S4–S5), and after further excluding participants who failed the Reliable Digit Span as a PVT (Tables S2–S3). There was no significant differential effect on the relationship between number of total blast exposures and memory performance as a function of *APOE* ε4 status ($\Delta R^2 = .0036$, $F_{1,\ 330} = 1.322$, $p = .25$; Table S11).

Lifetime mTBI

The overall regression models with lifetime mTBI predicting cognitive performance were significant for memory, $F_{11,\ 331} = 3.58$, $p = .0001$, attention, $F_{11,\ 290} = 4.25$, $p < .0001$, and executive functioning, $F_{11,\ 314} = 8.75$, $p < .0001$. There was a significant differential effect on the relationship between lifetime mTBI and memory as a function of *APOE* ε4 status, $\Delta R^2 = .0116$, $F_{1,\ 331} = 3.97$, $p = .047$ (Tables 3 and 5). However, the conditional effects of lifetime mTBI on memory did not show an association between lifetime mTBI group and memory among *APOE* ε4 carriers; $t = -1.87$, $B = -.44$, $p = .06$, nor *APOE* ε4 non-carriers; $t = .607$, $B = .08$, $p = .55$. There was no significant differential effect on the relationships between lifetime mTBI and attention ($\Delta R^2 = .0007$, $F_{1,\ 290} = .22$, $p = .64$) or executive functioning ($\Delta R^2 = .0007$, $F_{1,\ 314} = .30$, $p = .58$) as a function of *APOE* ε4 status.

Military mTBI

The overall regression models with military mTBI predicting cognitive performance were significant for memory, $F_{11,\ 331} = 3.25$, $p = .0003$, attention, $F_{11,\ 290} = 3.34$, $p = .0004$, and executive functioning, $F_{11,\ 314} = 8.67$, $p < .0001$. However, there were no significant differential effects on the relationships between military mTBI and memory ($\Delta R^2 = .0020$, $F_{1,\ 331} = .73$, $p = .39$), attention ($\Delta R^2 = .0043$, $F_{1,\ 290} = 1.46$, $p = .23$), or executive functioning ($\Delta R^2 = .0006$, $F_{1,\ 314} = .23$, $p = .63$) as a function of *APOE* ε4 status.

Distant Blast Exposure

The overall regression models with distant blast exposure predicting cognitive performance were significant for memory, $F_{11,\ 186} = 2.52$, $p = .0055$, attention, $F_{11,\ 162} = 2.85$, $p = .0019$, and executive functioning, $F_{11,\ 179} = 5.69$, $p < .0001$. However, there were no significant differential effects on the relationships between DBE and memory ($\Delta R^2 = .0107$, $F_{1,\ 186} = 2.28$, $p = .13$), attention ($\Delta R^2 = .0006$, $F_{1,\ 162} = .12$, $p = .73$), or executive functioning ($\Delta R^2 = .0014$, $F_{1,\ 179} = .342$, $p = .56$) as a function of *APOE* ε4 status.

DISCUSSION

These results demonstrate that in a cohort of young veterans (mean age = 32 years old), ε4 carriers exposed to CBE displayed poorer memory performance than those without CBE or ε4 carrier status (Figure 1; Tables 2–4). Specifically, there was a moderation effect such that CBE was associated with poorer verbal episodic memory performance only among ε4 carriers (Table 3). This was further corroborated by the significant interaction term of CBE and ε4 carrier status in the final model of the hierarchical linear regression adjusted for covariates (Table 4). This result was also robust to controlling for lifetime mTBI status, estimated pre-morbid intellectual functioning, neuropsychiatric distress, gender, and educational attainment across all analyses (Tables 3 and 4). Further, this effect was specific to memory, and not observed for executive functioning, attention, or estimated pre-morbid intellectual functioning. Exploring the three subcomponents of the memory composite measure, CBE ε4 carriers displayed worse performance on measures of short- and long-delayed free recall, but not long-delay recognition (Tables 2, S8–S10).

In our alternative analyses using other neurotrauma indicators, there was a significant interaction between lifetime mTBI and *APOE* ε4 status, but this interaction was not significant when constrained to participants with ε33 and ε34 genotypes (Tables 5, S4–S5). Additionally, this memory effect was only a trend or absent for other neurotrauma variables (military mTBI, DBE) (Table 3). We did not find differential relationships between neurotrauma and attention or executive functioning based on ε4 status. These significant moderating effects of *APOE* ε4 on verbal episodic memory performance were only observed in response to CBE across analyses, and were not sensitive to more distant blast exposures, or other mTBI-related variables, despite a similar trend across neurotrauma variables.

This work does not directly support previous findings that *APOE* plays a central role in distinguishing verbal episodic memory performance following non-blast-related neurotrauma. Several previous studies have found ε4 carriers exposed to mTBI exhibit worse verbal episodic memory performance on the CVLT-II in non-blast-exposed civilian samples (Eramudugolla et al., 2014; Yue et al., 2017), and blast-exposed veteran samples (Crawford et al., 2002;

Table 5. Hierarchical regression summary table for the association of lifetime mTBI by *APOE* ε4 status on memory

	Model 1			Model 2			Model 3		
Variables	*B*	*SE(B)*	*β*	*B*	*SE(B)*	*β*	*B*	*SE(B)*	*β*
CAPS (PTSD)	–.003	.002	–.091	–.003	.002	–.085	–.002	.002	–.074
DASS anxiety	–.002	.009	–.019	–.002	.009	–.019	–.003	.009	–.020
PC1	3.425	1.309	.143*	3.326	1.337	.139*	3.584	1.337	.149*
PC2	–1.430	1.696	–.049	–1.422	1.704	–.049	–1.372	1.697	–.047
PC3	.133	1.614	.005	.102	1.620	.004	.085	1.612	.003
Gender	–.163	.177	–.050	–.173	.179	–.054	–.239	.181	–.074
Education	.047	.026	.097	.047	.027	.097	.041	.027	.085
WTAR	.013	.005	.153*	.013	.005	.154*	.013	.005	.157*
APOE ε4 status				–.055	.119	–.025	.829	.459	.372
Lifetime mTBI				–.029	.114	–.014	.595	.333	.292
Lifetime mTBI × *APOE* ε4 status							–.520	.261	–.523**
R^2		.095			.096			.106	
F for change in R^2					.145			3.297**	

Note. *$p < .01$ and **$p < .05$.
B = effect size, *SE(B)* = standard deviation for effect size, *β* = standardized effect size, CAPS = clinician-administered PTSD scale, PTSD = post-traumatic stress disorder, DASS = depression anxiety stress scales, PC = principle component representing population substructure, WTAR = Wechsler Test of Adult Reading scaled score, mTBI = mild traumatic brain injury; *APOE* = apolipoprotein E.

Merritt, Clark, et al., 2018). On the other hand, several publications report null effects of mTBI on verbal episodic memory performance among ε4 carriers in non-blast-exposed civilian samples (Chamelian, 2004; Han et al., 2007; Shadli et al., 2011). The current work suggests that CBE may be a more sensitive predictor of verbal episodic memory performance in ε4 carriers compared to traditional neurotrauma measures such as military or lifetime mTBI. CBE may be uniquely sensitive because this measure accounts for sub-concussive injuries that may have adverse consequences on long-term cognitive outcomes (Carr et al., 2016; Grande et al., 2018; Talavage et al., 2014). In contrast, the neurobehavioral symptoms often reported after mTBI may be more associated with pre-morbid intellectual, emotional, and physical traits than actual injury severity or post-injury outcome (Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007). It is also possible that mechanistic properties of blast exposure play a role in discrepancies in the literature. Previous work suggests that blast-related TBI may have stronger associations with accelerated cortical thinning, aberrant regional brain metabolism, worse neurobehavioral symptoms, and greater deficits in executive functioning and attentional control compared to non-blast TBI (Clark et al., 2018; Mendez et al., 2013; Reid & Velez, 2015).

CBE may have played a major role in previous work that found associations between mTBI, ε4 carrier status, and long-term memory outcomes in veteran samples, as many presumably experienced CBE. It should be noted that our interaction term, though significant, only explained 2% more of the variance beyond the demographic, psychiatric, and genetic covariates included ($\Delta R^2 = .0163$, $F_{1,\ 330} = 6.033$, $p = .015$). Though this effect size is modest, it is similar to previous work on long-term neurocognitive outcomes following neurotrauma in ε4 carriers (Sullivan et al., 2019; Crawford et al., 2002). Given the young age of the sample, the effect may be exacerbated with aging, as has been demonstrated with aging trajectories of white matter integrity and CBE (Trotter et al., 2015). Taking into account blast exposure, with or without acute concussive symptoms, is vital to better characterize long-term memory outcomes in veterans. While *APOE* ε4 and mTBI are established risk factors for neurodegenerative disorders such as CTE and AD, the relationship between CBE and neurodegeneration has not been characterized to the same extent. This is despite emerging evidence suggesting CBE is associated with similar neurodegenerative process implicated in mTBI (Carr et al., 2016; De Gasperi et al., 2012; Goldstein et al., 2012; Mendez et al., 2013). Longitudinal studies in soldiers are needed better understand the role CBE plays in long-term trajectories of memory impairments, especially in ε4 carriers.

There are several limitations to this study. First, the cross-sectional nature of this study does not allow for causal inferences. Future longitudinal studies are needed to confirm the moderating effect of *APOE* ε4 in blast-related memory dysfunction. Second, the use of weapons such as the shoulder-launched multipurpose assault weapon was not included in our CBE measure. Recent evidence shows that these types of weapons may expose users to repeated low-grade blast exposure, and reports of adverse effects among users are starting to emerge (Carr et al., 2016). Third, our sample was predominately male (90%), limiting our ability to generalize results to service women. Our sex disparity also limited our ability to explore the role of sex in the complex interactions of cognition, neurotrauma, and *APOE* ε4 status, which has been found to be substantial in past work (Eramudugolla et al., 2014). Finally, CBE and TBI accounts were obtained from a retrospective self-report for events that may have occurred months to years prior. The accuracy of reported events and symptoms at the time of the event cannot be confirmed, and there is some evidence of inconsistency of

TBI recollection in service members with PTSD (Friedland & Swash, 2016). Due to these inherent limitations, we are unable to characterize blast exposure in a precise manner beyond rough proximity estimates. However, the BAT-L has high internal validity and uses a forensic approach taking into account the limitations associated with retrospective interviews (Fortier et al., 2014).

CONCLUSIONS

In summary, our findings provide novel evidence of genetic vulnerability in young veterans to disruptions in memory associated with CBE years after trauma exposure, even after accounting for symptomatic lifetime mTBI history and neuropsychiatric distress such as PTSD. Given the prevalence of blast exposure in returning service members, these findings stress the importance of future longitudinal research exploring the underlying mechanisms in blast exposure, its interaction with *APOE*, and additional clinical, demographic, and neuropsychiatric variables that may impact long-term cognitive outcomes. Future studies are also needed to further characterize the role of proximity to blast during combat in a precise manner, beyond the current categorical retrospective estimates used. This work also points to potentially distinct aspects of neural recovery in CBE that may be practical for clinical considerations. Specifically, these findings present a window for critical early intervention for young ε4 carriers with CBE to prevent subclinical memory deficits from progressing to clinically meaningful cognitive dysfunction. Due to the young age of our sample and the subclinical nature of the memory deficits reported in CBE ε4 carriers, non-invasive interventions should be strongly considered. For example, programs aimed to improve memory with psychoeducation and cognitive enhancement strategies have shown efficacy in decreasing subjective memory complaints and improving functional outcomes in young veterans (Roberts et al., 2020; Twamley, Jak, Delis, Bondi, & Lohr, 2014).

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617720001034.

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