Title

Interactive Effect of Traumatic Brain Injury and Psychiatric Symptoms on Cognition among Late Middle-Aged Men: Findings from the Vietnam Era Twin Study of Aging

Journal

Journal of Neurotrauma, 36(2)

ISSN

0897-7151

Authors

Kaup, Allison R
Toomey, Rosemary
Bangen, Katherine J
et al.

Publication Date

2019-01-15

DOI

10.1089/neu.2018.5695

Peer reviewed

JOURNAL OF NEUROTRAUMA 36:338–347 (January 15, 2019)

DOI: 10.1089/neu.2018.5695

Interactive Effect of Traumatic Brain Injury and Psychiatric Symptoms on Cognition among Late Middle-Aged Men: Findings from the Vietnam Era Twin Study of Aging

Allison R. Kaup,[1,*] Rosemary Toomey,[2,*] Katherine J. Bangen,[3,4] Lisa Delano-Wood,[3–5] Kristine Yaffe,[6] Matthew S. Panizzon,[3,4,7] Michael J. Lyons,[2] Carol E. Franz,[4,7] and William S. Kremen[4,7]

Abstract

Traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), and depressive symptoms each increase the risk for cognitive impairment in older adults. We investigated whether TBI has long-term associations with cognition in late middle-aged men, and examined the role of current PTSD/depressive symptoms. Participants were 953 men (ages 56–66) from the Vietnam Era Twin Study of Aging (VETSA), who were classified by presence or absence of (1) history of TBI and (2) current elevated psychiatric symptoms (defined as PTSD or depressive symptoms above cutoffs). TBIs had occurred an average of 35 years prior to assessment. Participants completed cognitive testing examining nine domains. In mixed-effects models, we tested the effect of TBI on cognition including for interactions between TBI and elevated psychiatric symptoms. Models adjusted for age, pre-morbid cognitive ability assessed at average age 20 years, apolipoprotein E genotype, and substance abuse; 33% ($n=310$) of participants had TBI, mostly mild and remote; and 23% ($n=72$) of those with TBI and 18% ($n=117$) without TBI had current elevated psychiatric symptoms. TBI and psychiatric symptoms had interactive effects on cognition, particularly executive functioning. Group comparison analyses showed that men with both TBI and psychiatric symptoms demonstrated deficits primarily in executive functioning. Cognition was largely unaffected in men with either risk factor in isolation. Among late middle-aged men, the combination of even mild and very remote TBI with current elevated psychiatric symptoms is associated with deficits in executive function and related abilities. Future longitudinal studies should investigate how TBI and psychiatric factors interact to impact brain aging.

Keywords: aging; cognition; psychiatric symptoms; TBI

Introduction

The Centers for Disease Control and Prevention (CDC) estimated there were 2,500,000 traumatic brain injury (TBI)-related emergency department visits, hospitalizations, or deaths in the United States in 2010.[1] Many more TBIs, particularly milder injuries referred to as mild TBI (mTBI) or concussion, are likely not captured in such estimates.[2] TBI can cause cognitive deficits and other symptoms post-injury,[3] followed by variable recovery over time.[4] Growing evidence suggests that TBI may have long-term negative effects on aging. TBI-associated cognitive deficits can persist for years to decades,[5,6] and older adults with a lifetime history of TBI may be at increased risk of developing mild cognitive impairment (MCI) and dementia.[7–9] However, whether remote TBI leads to cognitive problems in aging remains controversial,[10,11] particularly for mTBI. Although associations between moderate and severe TBI and risk of dementia are fairly well supported,[12] few studies have specifically evaluated the long-term effects of mTBI[13] with little focus on single mTBI.

Other factors may influence whether individuals with a history of TBI develop cognitive impairment as they age. Psychiatric conditions, especially depression and post-traumatic stress disorder (PTSD), are relatively common among individuals with TBI,[14–18] and TBI and psychiatric factors may be related to each other.[14–18] These psychiatric conditions are themselves associated with cognitive performance deficits[19–21] and increased risk for dementia.[22,23]

[1]Research Service, San Francisco VA Health Care System and Department of Psychiatry, Weill Institute for Neurosciences, University of California San Francisco, San Francisco, California.
[2]Department of Psychological and Brain Sciences, Boston University, Boston, Massachusetts.
[3]Veterans Affairs San Diego Healthcare System, San Diego, California.
[4]Department of Psychiatry and [7]Center for Behavior Genetics of Aging, University of California, San Diego, La Jolla, California.
[5]Veterans Affairs San Diego Healthcare System, Center of Excellence for Stress and Mental Health, La Jolla, California.
[6]Departments of Psychiatry, Neurology, and Epidemiology and Biostatistics, University of California San Francisco and San Francisco VA Health Care System, San Francisco, California.
*The first two authors contributed equally.

Particularly in younger populations with mTBI, it has even been argued that persistent cognitive difficulties post-injury may be driven by psychiatric symptoms rather than by the TBI itself.[24–26] However, in contrast, another study of younger individuals found that TBI and PTSD have compounding deleterious effects on cognition.[27] The impact of TBI and psychiatric symptoms in combination has been less well studied in aging, and findings have been mixed. One study suggested that psychiatric factors were driving associations between TBI and cognitive impairment in older adulthood because the association between TBI and MCI was eliminated after adjusting for depression.[28] In contrast, another study found additive effects of TBI and psychiatric factors on the risk of dementia in older veterans.[29]

We aimed to investigate whether prior TBI has long-term associations with cognition in late midlife and determine whether and how midlife psychiatric factors (specifically, PTSD and depressive symptoms) influence associations between TBI and cognition. Alternatively, the same research approach can be viewed as determining whether the association between midlife psychiatric factors and cognition differs as a function of having prior TBI. We investigated these questions among late middle-aged men from the Vietnam Era Twin Study of Aging (VETSA), a sample that is largely representative of the general population of similarly-aged men in the United States with respect to health and lifestyle factors based on CDC data.[30] We hypothesized that TBI would be associated with worse cognitive functioning, above and beyond the effect of current psychiatric factors, and that cognitive dysfunction would be greatest among men with both TBI and current psychiatric conditions.

Methods

Population

Participants were from the VETSA project, a longitudinal study of cognitive and brain aging among middle-aged male twins who served in the United States military sometime between 1965 and 1975. VETSA methodology has been detailed elsewhere.[30,31] VETSA participants were recruited from the Vietnam Era Twin Registry, a national database of male-male twin pairs who both served in the military during the Vietnam Era, although most VETSA participants ($\sim$80%) did not experience combat.[32,33] Data collection took place at the University of California, San Diego and Boston University. A total of 1237 men (ages 51–60) participated in VETSA Wave 1. An average of 5.6 years later, 1018 of these men (ages 56–66) returned to participate in Wave 2. The study was approved by institutional review boards at both sites, and all participants provided written informed consent.

Here, we focused on Wave 2 data, as the most comprehensive assessment of lifetime TBI was conducted at that time. Of the 1018 Wave 2 participants, 37 had missing TBI data, 17 could not be clearly classified for TBI status, and 11 had missing psychiatric symptom data. The present analyses focused on the remaining 953 participants. The 65 participants who had missing TBI or psychiatric data or were unclassifiable for TBI status were similar to the 953 remaining participants in terms of age, education, pre-morbid cognitive ability, and apolipoprotein E (*APOE*)-ε4 status (all $p > 0.05$). Although they had lower levels of current alcohol use ($p = 0.04$) than the 953 remaining participants, there were no differences in the other health variables listed in the subsequent sections (all $p > 0.05$).

Measures

TBI. Participants were interviewed to ascertain lifetime exposure to TBI. First, participants were asked: (1) ''Have you ever had a severe head injury that was associated with loss of consciousness or confusion?'' (2) ''Have you ever been told by a doctor that you had a concussion? (If yes, how many times?),'' and (3) ''Altogether, how many different head injuries or concussions (all total) have you had?'' Participants who denied head injury on all questions were considered to have no history of TBI. Participants who responded in the affirmative to any of these questions were interviewed regarding the details of each head injury, including age and cause of injury, presence/duration of loss of consciousness (LOC), confusion or memory loss, seizures related to the injury, and whether they received medical attention or were hospitalized overnight. LOC was coded as follows: No LOC, LOC ≤5 min, LOC >5 min to ≤20 min, LOC >20 min to several hours, LOC for several hours to 1 day, and LOC >1 day. Duration of post-traumatic amnesia (PTA) was coded as follows: No PTA, PTA <1 h, PTA ≥1 h to <24 h, PTA ≥24 h to 7 days, and PTA >7 days.

We utilized details about each head injury to distinguish likely TBIs from asymptomatic head injuries. A head injury was considered to meet criteria for TBI if descriptions were positive for: (1) LOC for any length of time, (2) confusion or memory loss, (3) seizures related to the injury, (4) receipt of medical attention, or (5) overnight hospitalization. We considered 17 individuals who had experienced only asymptomatic head injury to be unclassifiable, and we excluded them from our analysis. For participants with a history of TBI, each TBI was further classified by injury severity based on LOC and PTA duration, approximating standard Veterans Administration (VA)/Department of Defense (DOD) recommendations for defining mild, moderate, and severe TBI,[34] although these guidelines were not used in the original design of the TBI assessment. mTBI was defined as LOC ≤20 min and/or PTA <24 h. Moderate TBI was defined as LOC >20 min to 1 day and/or PTA ≥24 h to 7 days. Severe TBI was defined as LOC >1 day and/or PTA >7 days.

Current psychiatric symptoms. PTSD and depressive symptoms. To assess current PTSD symptoms, participants completed the PTSD Checklist (PCL) – Civilian version,[35,36] a 17-item checklist that assesses PTSD symptoms as outlined in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Revision* (DSM-IV). Total possible score ranges from 17 to 85, with higher scores indicating greater symptoms. (The Civilian, rather than the Military, version of the PCL was used so that assessment was not limited to symptoms from military-related traumatic events, particularly because most VETSA participants did not see combat [as noted] and had had military service that had ended decades prior to this assessment). To assess current depressive symptoms, participants completed the Center for Epidemiologic Studies – Depression Scale (CES-D),[37] a 20-item symptom checklist. Total score ranges from 0 to 60, with higher scores indicating greater symptoms.

PTSD is often comorbid with depression,[38,39] and the two symptom scales were strongly correlated ($r = 0.77$, $p < 0.001$) in our cohort, making it difficult to disentangle the effects of these different conditions. Therefore, we classified individuals based on whether or not they had current clinically significant symptoms for *either* condition, reflecting overall presence/absence of elevated symptoms. For depressive symptoms, we applied the recommended cutoff score of ≥16 for the CES-D.[40] For PTSD symptoms, we applied a cutoff score of ≥36 for the PCL.[41] This cut-point is recommended for detection of elevated PTSD symptoms among veterans in general settings (e.g., VA Primary Care) and strikes a balance between lower cut-points recommended for use in general civilian settings and higher cut-points recommended for use among veterans and civilians in mental health clinics.[41] Participants who met or exceeded either symptom cut-off are henceforth referred to as having current elevated psychiatric symptoms (abbreviated as ''Psych'').

Cognition. Participants were administered a comprehensive neurocognitive battery of standard measures, from which domain scores representing nine cognitive functions were derived.[42,43] Raw scores for individual tests were converted to z-scores using means and standard deviations calculated from all Wave 2 VETSA participants, such that higher z-scores indicate better performance. For cognitive functions measured with multiple tests, a domain score was calculated by averaging z-scores across tests. Several executive function tasks were included in the test battery, but these were examined individually, because these are differentiated in the executive function literature.[44] Visual spatial function was assessed with the Mental Rotation Test[45] and the Hidden Figures Test.[46] Working memory was assessed with Digit Span – Forward and Backward, Letter-Number Sequencing, and Spatial Span – Forward and Backward tests from the Wechsler Memory Scale – III (WMS-III)[47] and a modified Reading Span test.[48] Episodic memory was assessed with the California Verbal Learning Test – Second Edition (CVLT-II)[49] – Total Learning, Short Delay Free Recall, and Long Delay Free Recall; WMS-III Logical Memory[47] – Immediate Recall and Delayed Recall; and WMS-III Visual Reproduction[47] – Immediate Recall and Delayed Recall. Processing speed was assessed with the Stroop Word Reading and Color Reading Subtests[50] and the Delis-Kaplan Executive Function System (D-KEFS) Trails Number Sequencing and Letter Sequencing tests.[51] Verbal fluency was assessed with the D-KEFS Letter Fluency and Category Fluency tests.[51] Abstract reasoning was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) Matrix Reasoning.[52] Trails switching was assessed with the D-KEFS Trails Letter-Number Switching test[51] (score adjusted for D-KEFS Trails Number Sequencing and Letter Sequencing performance). Category switching was assessed with the D-KEFS Verbal Fluency Category Switching test[51] (score adjusted for D-KEFS Category Fluency performance). Inhibition was assessed with the Stroop Color-Word interference score,[50] which is adjusted for word reading and color reading performance.

Other variables. Participants self-reported their age and education. As a measure of pre-morbid cognitive ability, we used Armed Forces Qualification Test (AFQT)[53] scores, completed just prior to military induction (at mean age of 20 years old; score range 10–100). *APOE*-ε4 is the major risk allele for Alzheimer's disease.[54] Carrier status was determined from blood samples and was based on presence/absence of at least one ε4 allele.[55,56] Hypertension, high cholesterol, diabetes, and history of substance abuse (alcohol or drugs) were determined via self-report (''have you ever been told by a physician that you had…''). Participants self-reported current alcohol use (within the past 14 days), and this was coded as none, ≤1 drink per day, >1 and ≤2 drinks per day, or >2 drinks per day. Body mass index (BMI) was calculated from height and weight.

Statistical analysis

Using mixed-effects models, we examined whether men with and without a history of TBI (TBI+ or TBI-) differed by demographics (age, education), pre-morbid cognitive functioning (age 20 AFQT score), *APOE*-ε4 status (ε4+ vs. ε4-), cardiovascular health factors, substance abuse, current alcohol use, current PTSD and depressive symptoms, and presence/absence of current elevated psychiatric symptoms (Psych). These models account for correlated observations (persons nested within twin pairs) as a random effect. We used SAS PROC MIXED for continuous variables and SAS PROC GLIMMIX for binary and count variables.

In mixed-effects models, we first tested the main effect of TBI on the cognitive outcomes, adjusting for presence of current elevated psychiatric symptoms (Psych). The models also adjusted for age, pre-morbid cognitive ability, *APOE*-ε4 status, and other health factors that differed between those with and without TBI ($p < 0.05$) as detailed. Next, we tested for TBI × Psych interactions by adding an interaction term. These analyses were conducted using SAS PROC MIXED. We used the false discovery rate (FDR)[57] to correct for multiple testing.

Results

Of the 953 participants, 33% ($n = 310$) met criteria for history of TBI, and 67% ($n = 643$) had no TBI. Participant characteristics are shown in Table 1. The TBI+ group was similar to the TBI- group in terms of age, education, pre-morbid cognitive ability, *APOE*-ε4 status, and cardiovascular health factors (all $p > 0.05$). However, those with TBI were more likely to have a history of substance abuse ($p = 0.046$) as well as more symptoms on the PCL ($p = 0.007$). Most of the TBI group reported only one TBI over their lifetimes, and the vast majority were classified as mild at worst (see Table 2).

Main effect and interaction results

Table 3 shows results of mixed model analyses testing for a main effect of TBI on the cognitive outcomes, and for the main effect of Psych. All models accounted for correlated observations (persons nested within twin pairs) as a random effect and adjusted for age, age 20 AFQT, APOE-ε4, and history of substance abuse. The only significant main effect of TBI was on abstract reasoning ($p < 0.05$), such that TBI was associated with lower performance. However, this did not survive FDR control. In these same models, there was a significant main effect of Psych on multiple cognitive domains, such that presence of current elevated psychiatric symptoms was associated with lower performance on the episodic memory, verbal fluency, visual spatial, working memory, abstract reasoning, and processing speed domains, with effects for the latter four domains surviving FDR control. As shown in Table 3, adding the TBI × Psych interaction term to these models revealed significant interactions for multiple domains, specifically abstract reasoning, verbal fluency, trails switching, category switching, and inhibition. The interaction effect on inhibition, which survived FDR control, is shown in Figure 1A and B. The other interaction effects were in a similar pattern, although they did not survive FDR control.

Group comparisons

Given findings of TBI × Psych interactions on several cognitive domains, we further explored these relationships by characterizing cognitive profiles of clinically relevant groups. We classified individuals into the following four groups: (1) those who had ''TBI only'' (TBI+ and Psych-; $n = 238$), (2) those who had only current elevated psychiatric symptoms; that is, ''Psych only'' (TBI- and Psych+; $n = 117$), (3) those who had ''both TBI and Psych'' (TBI+ and Psych+; $n = 72$), and (4) those who had ''neither'' TBI nor current elevated psychiatric symptoms (TBI- and Psych-; $n = 526$). Using this four-level categorical variable, we tested for group differences on cognition relative to the ''neither'' group as the reference category, thus testing for cognitive deficits compared with those with neither risk factor. These models accounted for the same factors as mentioned (i.e., correlated observations as random effect and adjusted for age, age 20 AFQT, APOE-ε4, and history of substance abuse). As shown in Figure 2, the ''TBI only'' and ''Psych only'' groups did not differ from the ''neither'' group on any cognitive domain. In contrast, the ''both TBI and Psych'' group showed significant cognitive deficits on working memory (Estimate = -0.21, $p = 0.009$), abstract reasoning (Estimate = -0.56,

Table 1. Participant Characteristics by TBI Status

Mean (SD) or %(n)	*TBI+ (n = 310)*	*TBI-(n = 643)*	F	p
Age				
56 to <61 years	52.2%	46.0%	3.2	0.07
≥61 to 66 years	47.7%	54.0%		
Education, years	14.0 (2.1)	13.8 (2.1)	1.1	0.30
AFQT at age 20, score out of 100[a]	62.1 (21.6)	61.3 (22.6)	0.4	0.55
APOE-ε4+	28.9% (89)	30.9% (196)	0.4	0.53
Hypertension	55.7% (172)	53.7% (345)	0.3	0.56
High cholesterol	57.1% (177)	55.3% (354)	0.3	0.60
Diabetes	17.4% (54)	17.4% (112)	<0.01	0.99
BMI, kg/m^2	29.8 (5.3)	29.6 (5.2)	0.6	0.45
Substance abuse	7.1% (22)	4.1% (26)	4.0	0.046*
Current alcohol use (past 14 days)				
None	37.7% (117)	36.0% (230)	0.03	0.87
≤ 1 drink per day	37.7% (117)	40.0% (257)		
> 1 or ≤2 drinks per day	8.4% (26)	11.0% (71)		
> 2 drinks per day	16.1% (50)	13.2% (85)		
PCL, total score out of 85[a]	27.6 (11.6)	25.7 (10.1)	7.3	0.007*
CES-D, total score out of 60[a]	8.3 (8.9)	6.9 (7.6)	2.5	0.11
Elevated psychiatric symptoms (PCL ≥36 and/or CES-D ≥ 16)	23.2% (72)	18.2% (117)	3.3	0.07

Results are from mixed model analyses that accounted for twin status (persons nested within twin pairs) as a random effect.
[a]Transformed variable used in mixed model analysis.
*$p < 0.05$.
TBI, traumatic brain injury; AFQT, Armed Forces Qualification Test; *APOE*, apolipoprotein E; BMI, body mass index; PCL, PTSD Checklist; CES-D, Center for Epidemiologic Studies – Depression Scale.

$p < 0.001$), verbal fluency (Estimate = -0.24, $p = 0.03$), inhibition (Estimate = -0.37, $p = 0.004$), and processing speed (Estimate = -0.23, $p = 0.01$).

We conducted sensitivity analyses to explore the influence of number of TBIs, time since TBI, and TBI severity on group comparison results. First, we excluded 95 men who had two or more TBIs, and results remained similar. Similarly, our results remained unchanged when we focused on remote TBI (through exclusion of 21 men who had had TBI within the past 5 years). Finally, to examine whether results might be driven by individuals with moderate or severe TBI, we divided participants into the following groups: (1) ''mTBI only'' (mTBI+ and Psych- ; $n = 167$), 2) ''moderate-to-severe TBI only'' (moderate-to-severe TBI+ and Psych- ; $n = 69$), (3) ''Psych only'' (TBI- and Psych+; $n = 117$), (4) ''mTBI and Psych'' (mTBI+ and Psych+; $n = 56$), and (5) ''moderate-to-severe TBI and Psych'' (moderate-to-severe TBI+ and Psych+; $n = 14$), versus those who had ''neither'' (TBI- and Psych- ; $n = 526$). As shown in Figure 3, the overall pattern of results remained similar to results when not distinguishing by TBI severity, in that deficits were primarily seen in individuals who had both TBI and Psych. The ''mTBI and Psych'' group showed cognitive deficits compared with the ''neither'' group on multiple domains: working memory (Estimate = -0.22, SE = 0.09, $p = 0.01$), abstract reasoning (Estimate = -0.48, SE = 0.13, $p < 0.001$), inhibition (Estimate = -0.36, SE = 0.15, $p = 0.01$), and processing speed (Estimate = -0.22, SE = 0.10, $p = 0.03$). The ''mTBI Only'' group showed a deficit on abstract reasoning (Estimate = -0.16, SE = 0.08, $p = 0.04$), but did not demonstrate difficulties in other cognitive domains. Statistical tests for the ''moderate-to-severe TBI + Psych'' group had limited power because of the small sample size ($n = 14$). Nevertheless, this group showed a significant deficit on abstract reasoning (Estimate = -0.79, SE = 0.24, $p = 0.001$), whereas the ''moderate-to-severe TBI only'' group did not show deficits in any cognitive domain and performed relatively better than the ''neither'' group on episodic memory (Estimate = 0.17, SE = 0.09, $p = 0.04$).

Table 2. TBI History Details

Mean (SD) or %(n)	*TBI+ (n = 310)*
TBI severity, % of participants	
mTBI	71.9% (223)
Any moderate-to-severe TBI	26.8% (83)
Unknown	1.3% (4)
Number of TBI(s), % of participants	
1	69.4% (215)
2	18.7% (58)
3+	11.9% (37)
TBI cause, % of participants	
Motor vehicle accident	33.9% (105)
Fall	31.9% (99)
Sports	30.3% (94)
Assault or fight	10.6% (33)
Combat	3.9% (12)
Other	17.4% (54)
Age at first TBI, years	20.7 (13.8)
Time since most recent TBI, years	35.3 (16.3)

Descriptive features of TBI history among 310 individuals with history of TBI. TBI, traumatic brain injury; mTBI, mild TBI.

Table 3. Main and Interaction Effects: Effect of TBI, Psych, and TBI×Psych on Cognition

	Main effect of TBI[a]		*Main effect of Psych*[b]		*TBI×Psych interaction*[c]	
Cognitive domain	*Estimate (SE)*	p	*Estimate (SE)*	p	F	p
Visual spatial	0.08 (.06)	0.18	-0.19 (0.07)	0.01*[d]	2.0	0.17
Working memory	0.02 (0.04)	0.71	-0.17 (0.05)	0.001*[d]	1.6	0.20
Episodic memory	0.06 (0.05)	0.22	-0.12 (0.06)	0.04*	2.0	0.16
Abstract reasoning	-0.17 (0.06)	0.007*	-0.24 (0.07)	0.001*[d]	5.8	0.02*
Verbal fluency	0.05 (0.06)	0.41	-0.16 (0.07)	0.03*	4.0	0.046*
Trails switching	0.03 (0.07)	0.61	-0.11 (0.08)	0.21	4.7	0.03*
Category switching	0.03 (0.07)	0.71	-0.05 (0.09)	0.53	5.2	0.02*
Inhibition	0.01 (0.07)	0.88	-0.12 (0.09)	0.16	12.4	<0.001*[d]
Processing speed	0.04 (0.05)	0.41	-0.18 (0.06)	0.004*[d]	3.4	0.06

Results from mixed model analyses. All models accounted for twin status (persons nested within twin pairs) as a random effect and adjusted for age, Armed Forces Qualification Test (AFQT) score at age 20, apolipoprotein E (*APOE*)-ε4status, and history of substance abuse. [a,b]Main effect of TBI and main effect of Psych are results from same model, such that TBI effect is adjusted for Psych and Psych effect is adjusted for TBI.

[c]TBI×Psych interaction term when added to main effect model.

[d]Survives false discovery rate (FDR) control (9 tests).

*$p < 0.05$.

TBI, traumatic brain injury; Psych, elevated psychiatric symptoms.

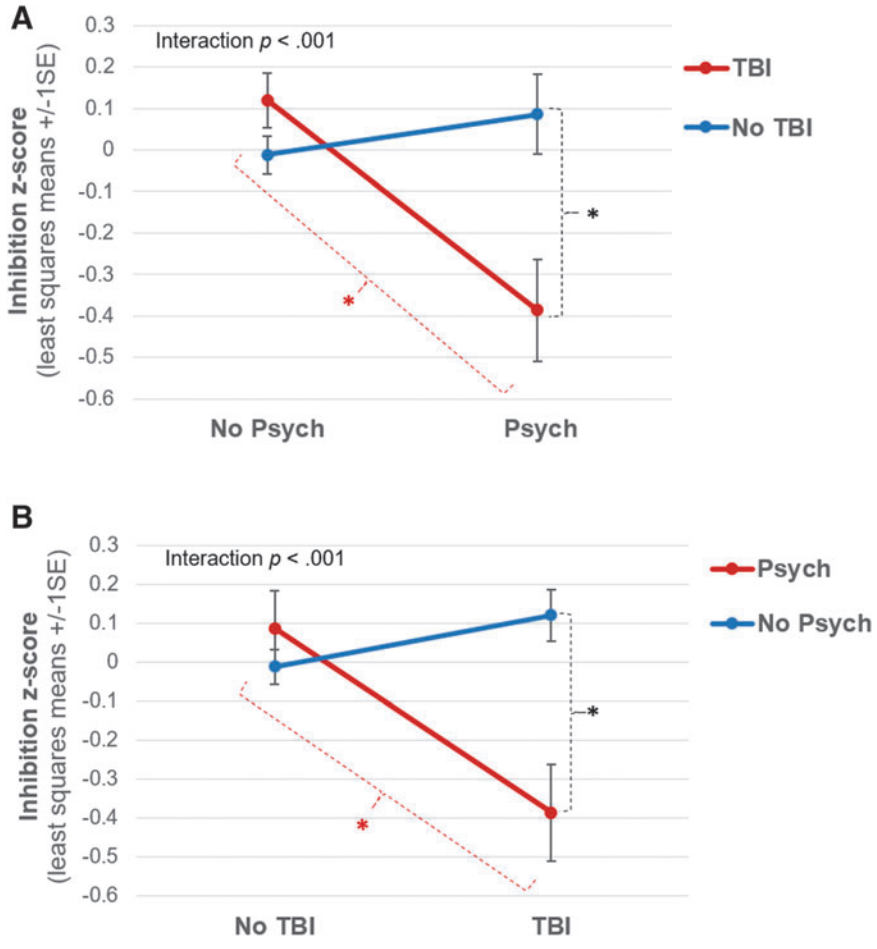

FIG. 1. TBI×Psych interaction on inhibition. **A** and **B** depict the same data, but differ in which factor is shown on the x-axis. In simple effect comparisons, there is a significant effect of Psych among those with TBI ($p < 0.001$). Likewise, there is a significant effect of TBI among those with Psych ($p = 0.002$). Model accounted for correlated observations (persons nested within twin pairs) as a random effect and adjusted for age, Armed Forces Qualification Test (AFQT) at age 20, apolipoprotein E (*APOE*)-ε4, and history of substance abuse. TBI, traumatic brain injury; Psych, elevated psychiatric symptoms. Color image is available online at www.liebertpub.com/neu

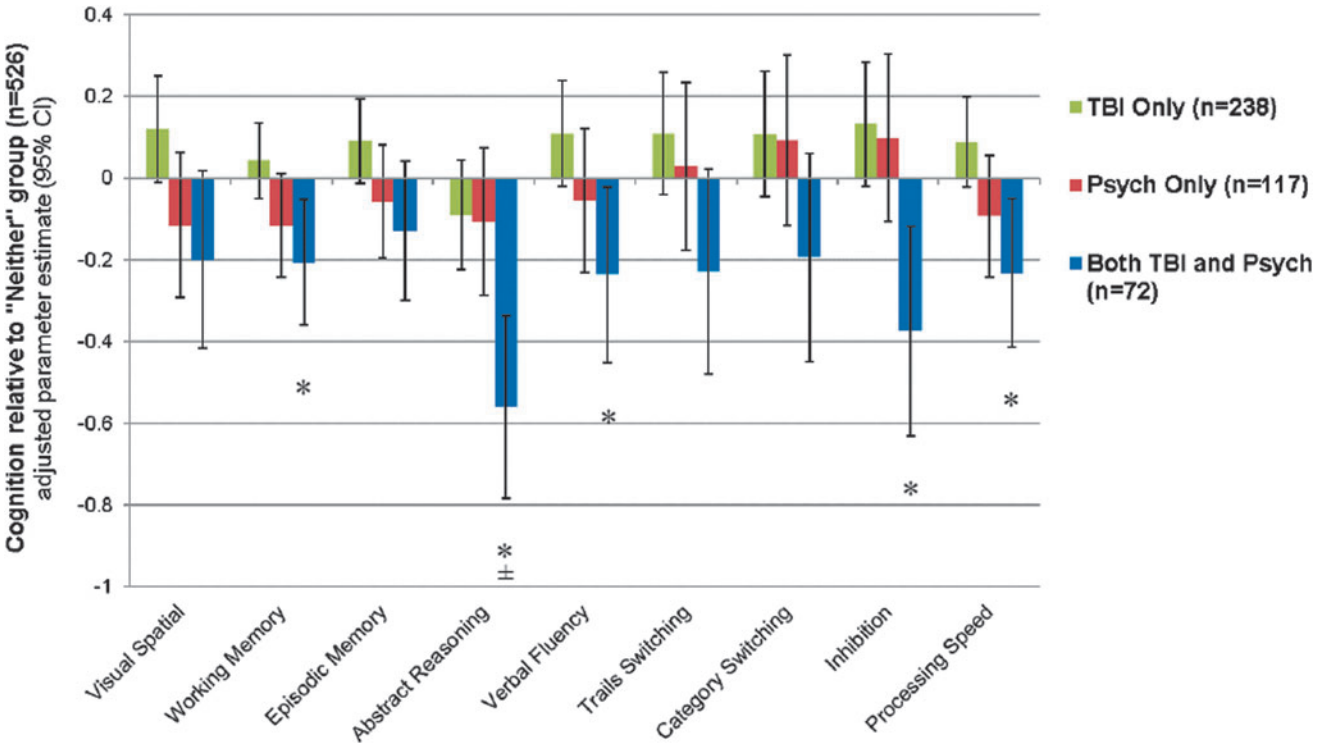

FIG. 2. Group differences, compared to the ''neither'' reference group (men with neither TBI nor elevated psychiatric symptoms; n = 526). Results from mixed-effects models adjusted for age, Armed Forces Qualification Test (AFQT) score at age 20, apolipoprotein E (*APOE*)-ε4status, and history of substance abuse. *significant deficit ($p < 0.05$) compared with the ''neither'' group; ± survives false discovery rate (FDR) control (27 tests); TBI, traumatic brain injury; Psych, elevated psychiatric symptoms. Color image is available online at www.liebertpub.com/neu

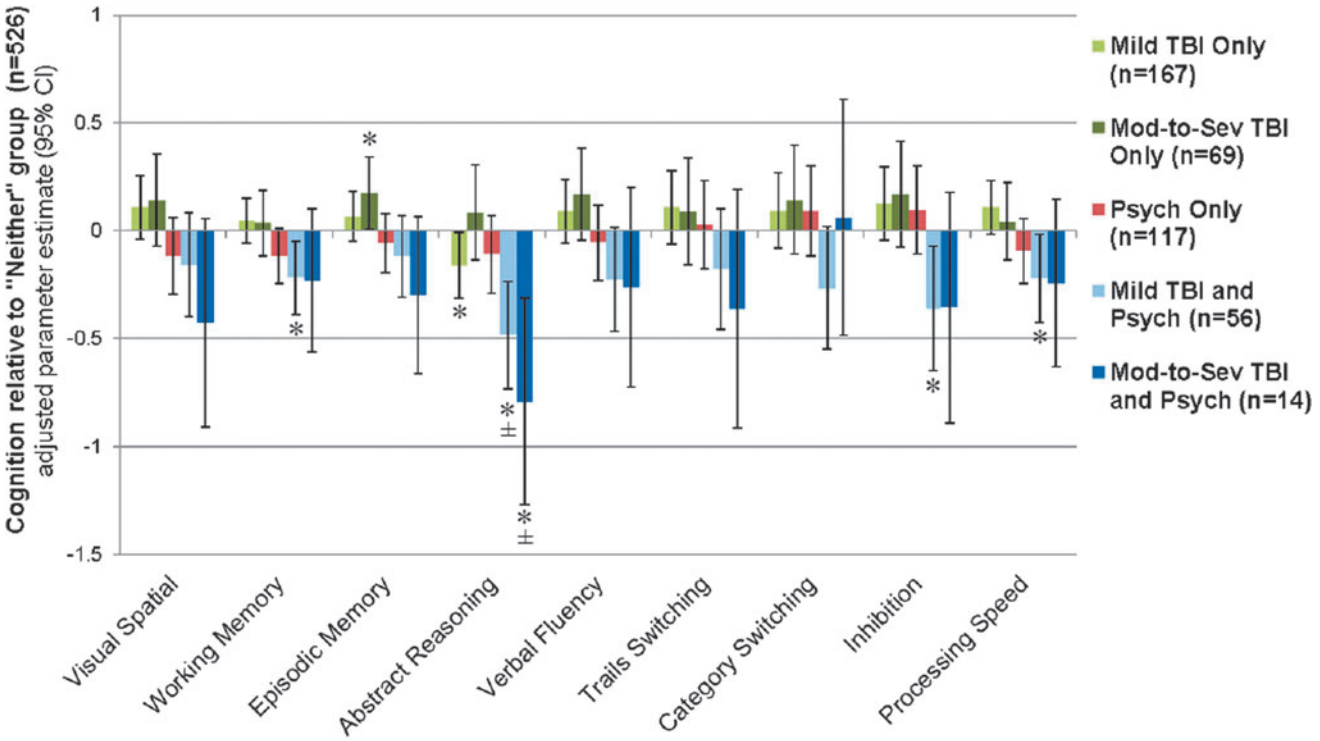

FIG. 3. Group differences, compared with the ''neither'' reference group (men with neither TBI nor elevated psychiatric symptoms). Results from mixed effects models adjusted for age, Armed Forces Qualification Test (AFQT) score at age 20, apolipoprotein E (*APOE*)-ε4status, and history of substance abuse. *significant deficit ($p < 0.05$) compared with the ''neither'' group; ± survives false discovery rate (FDR) control (45 tests); Mod-to-Sev TBI, moderate-to-severe traumatic brain injury; Psych, elevated psychiatric symptoms. Color image is available online at www.liebertpub.com/neu

Discussion

Among community-dwelling middle-aged men, we examined the relationship between history of TBI and midlife cognitive functioning, and whether current elevated psychiatric symptoms (PTSD or depressive symptoms) influenced associations. Main effect analyses revealed minimal association between prior TBI and midlife cognition (the only significant effect was for abstract reasoning). Current psychiatric symptoms were associated with lower cognitive performance on several domains, but only with two out of five executive function measures (including abstract reasoning). However, interaction analyses suggested that the combination of prior TBI and current psychiatric symptoms has a negative synergistic association with lower midlife cognition, which is not apparent when examining each factor in isolation. Put another way, this interaction also indicates that the association between current psychiatric symptoms and cognition differs as a function of having had a prior TBI. This negative synergistic effect was especially strong on the cognitive domain of inhibition (significant after FDR correction), and was also seen on all other executive function domains (abstract reasoning, verbal fluency, trails switching, category switching).

When comparing cognitive profiles among groups of individuals who had the combination of both prior TBI and current psychiatric symptoms, either risk factor in isolation, versus neither, only those who had *both* demonstrated cognitive deficits. Cognition was largely unaffected among those with either risk factor alone. In contrast, individuals with both risk factors demonstrated deficits in five outcomes. Three overlapped with domains identified by the interaction analyses (abstract reasoning, verbal fluency, inhibition) and two (working memory, processing speed) overlapped with domains for which current psychiatric symptoms had a main effect. Overall, our results suggest that the combination of prior TBI and current elevated psychiatric symptoms is associated with deficits in executive functioning, and perhaps working memory and processing speed, above and beyond the influence of either risk factor in isolation.

Our finding that the presence of current psychiatric symptoms changes the association between TBI history and cognition in late midlife dovetails with suggestions that a variety of factors may influence whether TBI has long-term effects in older adulthood.[58,59] Genetics[60,61] and cognitive reserve[62] appear to influence long-term cognitive outcomes following TBI. Here we showed that, even after controlling for (1) a significant genetic factor (*APOE*-ε4)[63] and (2) cognitive reserve as indexed by general cognitive ability at age 20, TBI status and psychiatric symptoms interact in relating to worse late-midlife cognition. Our results are similar to those from a study of older veterans, which found risk of dementia to be higher among individuals with both TBI and PTSD or both TBI and depression, relative to those with either factor alone.[29] Our findings extend those results to a sample of well-characterized non-demented, middle-aged adults, underscoring how prior mTBI in the presence of current psychiatric distress is associated with lower cognition as early as midlife.

An unanswered question in TBI research is whether a mTBI, even if sustained earlier in life, increases the risk for cognitive dysfunction later in life.[59,64] It is notable that we found a deleterious interactive effect of prior TBI and current psychiatric symptoms on cognition among middle-aged men whose TBI histories primarily consisted of remote exposure to only mTBI, ~35 years earlier on average. Sensitivity analyses suggest that our results were not driven by the minority of participants who had moderate-to-severe TBI, repetitive TBI, or recent TBI. Instead, our findings support other suggestions in the literature that even individuals with a past history of mTBI may be at increased risk for cognitive problems in aging.[5,65–68] Our results indicate that this is primarily the case when compounded with current psychiatric distress, but that it is the case even when TBI exposure is limited to a single mTBI. The finding that without FDR correction, the TBI × Psych interaction effect was significant for five out of five executive function measures suggests a broad effect on executive functions. The effect was not strong enough to survive FDR correction for four out of the five measures, but it seems notable that these associations were seen for mTBIs occurring ~35 years earlier on average. These long-term associations raise the possibility that the combination of prior TBI and current psychiatric symptoms might have an even stronger negative association with cognition with advancing age.

Relationships among TBI, psychiatric symptoms, and cognition in aging are complex and difficult to disentangle without repeated measurement of these factors across the lifespan. Therefore, a limitation of this study is that we did not have sufficient information to attempt to disentangle the timing of participants' TBI exposure relative to the onset and course of psychiatric symptoms across their lives. Exposure to TBI among our participants largely occurred decades prior to our study's psychiatric symptom and cognitive assessments. It could be, for example, that a history of TBI makes people with certain psychiatric symptoms more vulnerable to cognitive deficits, or that TBI might make people with cognitive deficits more susceptible to psychiatric symptoms. Our study does not directly test the temporal direction of these associations, limiting conclusions on causality. Nevertheless, our findings do suggest that individuals who have both a history of TBI and current elevated psychiatric symptoms are more likely to demonstrate cognitive deficits in midlife. Unlike in most studies, we were able to account for early general cognitive ability, suggesting that results were not caused by pre-morbid cognitive differences. However, that our study tested associations with cognitive function at one midlife time point remains a limitation, and future longitudinal studies are needed to test for associations with cognitive decline over time in aging.

With the abovementioned caveat in mind, our results raise considerations toward understanding how TBI and psychiatric symptoms may influence cognitive aging. One possibility is that these two risk factors may have compounding negative effects on brain health, as both TBI[69,70] and psychiatric conditions[71,72] are associated with alterations in brain structure and function. Longitudinal studies are needed to understand if and how TBI and psychiatric symptoms might biologically interact to influence brain aging. Rather than simply being separate co-occurring conditions, it may be that TBI and psychiatric symptoms are intrinsically biologically linked, at least among some individuals. It has been suggested that TBI can damage brain regions involved in processing and regulating emotion, as well as triggering inflammation and other biological stress response processes associated with psychiatric symptoms.[73] Our study provides further support for a link between TBI and psychiatric symptoms, given our findings of a synergistic association between these factors and lower cognition.

Finally, our results may provide clarification regarding the role of TBI as a risk factor for dementia. Although some evidence has linked TBI to risk for Alzheimer's disease in particular,[74] we did not find any TBI-related episodic memory deficits, which are often an early symptom of an Alzheimer's process. Our finding of a pattern reflecting executive dysfunction in men with both prior TBI and current psychiatric symptoms suggests that executive deficits

may be an early symptom of a TBI-related neurodegenerative process, particularly among individuals with current psychiatric symptoms. Our results resemble those from a study that found that older veterans with TBI demonstrated executive dysfunction and slowed processing speed but not memory impairment; however, that study adjusted for psychiatric symptoms and did not examine the interaction of TBI and psychiatric symptoms.[5] Another study comparing older Vietnam veterans with TBI only, PTSD only, and TBI and PTSD versus those with neither of these conditions showed no memory differences or evidence of Alzheimer's neuropathology in the TBI groups, but they did not report on executive function.[75]

An intriguing aspect of our findings was that a subset of TBI-exposed men did not have either current elevated psychiatric symptoms or clear evidence of cognitive dysfunction. Although speculative, this raises the possibility that important individual differences may influence whether someone who sustains a TBI earlier in life will also have psychiatric symptoms and cognitive dysfunction in aging. Perhaps a subset of individuals who experience TBI are resilient against its negative effects on both psychological health and cognition, or psychological health itself may help to buffer against the negative effects of TBI on cognition in aging. Alternatively, there may be qualitative differences, such as location of brain damage and mechanism of brain injury, that contribute to the comorbid presence of psychiatric symptoms in a more complicated mTBI group, who in turn may also be more likely to have long-term cognitive deficits.

Strengths of the study include examination of a large, well-characterized cohort of middle-aged men. Although men in the present study did serve in the military, the cohort is largely representative of the general population of similarly-aged men in the United States,[30] and the vast majority of TBI exposure among this cohort was not combat related. Therefore, the results are likely to be generalizable to community-dwelling men of the same age range and ethnicity. Additional strengths include a detailed TBI assessment, comprehensive neurocognitive testing, and adjustment for intellectual functioning at age 20. However, it is important to note that the sample focused predominately on white non-Hispanic men. Lack of medical records may be a limitation in studies investigating lifetime history of neurotrauma. However, even when there are physician or hospital records, duration of unconsciousness is virtually always based on self-report. With the vast majority of cases in this study being mTBI, very few even involved medical assessment or treatment. That strongly favors the argument that these were indeed only mTBIs because more severe TBIs would be far more likely to have come to medical attention. Finally, it should be emphasized that although our findings include statistically significant differences in cognitive functioning, these effects were modest and potential impact on everyday functioning is unclear (e.g., none of the group means in Figs. 2 or 3 were ≥1 SD below the reference group mean, and therefore did not cross the threshold suggestive of clinically significant impairment). Nevertheless, it is possible that these subtle group differences could reflect important population shifts that may have further bearing as these middle-aged men advance into older age.

Our findings suggest that the combination of a history of TBI and current elevated psychiatric symptoms is associated with deficits in executive functioning and related abilities among late middle-aged men. Participants with this combination of risk factors evidenced these deficits even though their TBI histories consisted primarily of only a single mTBI. Moreover, the association is observed despite a very extended time period between TBI occurrence and cognitive testing (average of 35 years). Future longitudinal studies are needed in order to advance understanding of how TBI and psychiatric symptoms may interact to negatively impact cognitive and brain aging.

Acknowledgments

The content of this manuscript is the responsibility of the authors and does not represent official views of the National Institutes of Health (NIH), the VA, the United States Department of Veterans Affairs, or the United States government. The United States Department of Veterans Affairs, DOD; National Personnel Records Center, National Archives and Records Administration; Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University provided invaluable assistance in the conducting of the VET Registry. The authors gratefully acknowledge the continued cooperation of the twins and the efforts of many staff members. VETSA has been supported by the National Institute of Aging: R01s AG018384, AG018386, and AG050595 (PIs: Drs. Kremen and Lyons), R01 AG022381 (PI: Dr. Kremen), and R01 AG022982 (PI: Dr. Kremen). Dr. Kaup is supported by Career Development Award (1IK2RX001629) from the United States Department of Veterans Affairs, Rehabilitation Research and Development Service. Dr. Bangen is supported by Career Development Award (1IK2CX000938) from the United States Department of Veterans Affairs, Clinical Science Research and Development Service.

Author Disclosure Statement

For all authors, no competing financial interests exist. Dr. Kaup has been given access to cognitive assessment/cognitive intervention software and tablet devices by Akili Interactive Labs for utilization in a separate research study related to TBI in aging; Dr. Kaup has no financial relationship with Akili Interactive Labs.

References

1. Centers for Disease Control and Prevention (2016). TBI: Get the Facts. https://www.cdc.gov/traumaticbraininjury/get_the_facts.html (last accessed April 12, 2017).
2. Voss, J.D., Connolly, J., Schwab, K.A., and Scher, A.I. (2015). Update on the epidemiology of concussion/mild traumatic brain injury. Curr. Pain Headache Rep. 19, 1–8.
3. Ashman, T.A., Gordon, W.A., Cantor, J.B., and Hibbard, M.R. (2006). Neurobehavioral consequences of traumatic brain injury. Mt. Sinai J. Med. 73, 999.
4. Millis, S.R., Rosenthal, M., Novack, T.A., Sherer, M., Nick, T.G., Kreutzer, J.S., High Jr, W.M., and Ricker, J.H. (2001). Long-term neuropsychological outcome after traumatic brain injury. J. Head Trauma Rehabil. 16, 343–355.
5. Kaup, A.R., Peltz, C., Kenney, K., Kramer, J.H., Diaz-Arrastia, R., and Yaffe, K. (2017). Neuropsychological profile of lifetime traumatic brain injury in older veterans. J. Int. Neuropsychol. Soc. 23, 56–64.
6. Draper, K., and Ponsford, J. (2008). Cognitive functioning ten years following traumatic brain injury and rehabilitation. Neuropsychology 22, 618.
7. Guskiewicz, K.M., Marshall, S.W., Bailes, J., McCrea, M., Cantu, R.C., Randolph, C., and Jordan, B.D. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. Neurosurgery 57, 719–726.
8. Plassman, B.L., and Grafman, J. (2015). Traumatic brain injury and late-life dementia. Handb. Clin. Neurol. 128, 711–722.
9. Perry, D.C., Sturm, V.E., Peterson, M.J., Pieper, C.F., Bullock, T., Boeve, B.F., Miller, B.L., Guskiewicz, K.M., Berger, M.S., and Kramer, J.H. (2015). Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. J Neurosurg 124, 511–526.

10. Albrecht, M.A., Masters, C.L., Ames, D., Foster, J.K., et al. (2016). Impact of mild head injury on neuropsychological performance in healthy older adults: longitudinal assessment in the AIBL Cohort. Front. Aging Neurosci. 8, 105.
11. Dams-O'Connor, K., Gibbons, L.E., Bowen, J.D., McCurry, S.M., Larson, E.B,. and Crane, P.K. (2013). Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. J. Neurol. Neurosurg. Psychiatry 84, 177–182.
12. Institute of Medicine (IoM) (2008). *Gulf War and Health:Volume 7: Long-Term Consequences of Traumatic Brain Injury.* The National Academies Press, Washington, DC.
13. Gardner, R.C., and Yaffe, K. (2015). Epidemiology of mild traumatic brain injury and neurodegenerative disease. Mol. Cell Neurosci. 66, 75–80.
14. Rogers, J.M., and Read, C.A. (2007). Psychiatric comorbidity following traumatic brain injury. Brain Inj. 21, 1321–1333.
15. Tanev, K.S., Pentel, K.Z., Kredlow, M.A., and Charney, M.E. (2014). PTSD and TBI co-morbidity: scope, clinical presentation and treatment options. Brain Inj. 28, 261–270.
16. Miller, S.C., Whitehead, C.R., Otte, C.N., Wells, T.S., Webb, T.S., Gore, R.K., and Maynard, C. (2015). Risk for broad-spectrum neuropsychiatric disorders after mild traumatic brain injury in a cohort of US Air Force personnel. Occup. Environ. Med. 72, 560–566.
17. Rapoport, M.J. (2012). Depression following traumatic brain injury. CNS Drugs 26, 111–121.
18. Vassallo, J.L., Proctor-Weber, Z., Lebowitz, B.K., Curtiss, G., and Vanderploeg, R.D. (2007). Psychiatric risk factors for traumatic brain injury. Brain Inj. 21, 567–573.
19. Johnsen, G.E., and Asbjørnsen, A.E. (2008). Consistent impaired verbal memory in PTSD: a meta-analysis. J. Affect. Disord. 111, 74–82.
20. Polak, A.R., Witteveen, A.B., Reitsma, J.B., and Olff, M. (2012). The role of executive function in posttraumatic stress disorder: a systematic review. J. Affect. Disord. 141, 11–21.
21. Castaneda, A.E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., and Lönnqvist, J. (2008). A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J. Affect. Disord. 106, 1–27.
22. Byers, A.L., and Yaffe, K. (2011). Depression and risk of developing dementia. Nat. Rev. Neurol. 7, 323–331.
23. Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K.E., Neylan, T., Kluse, M., and Marmar, C. (2010). Posttraumatic stress disorder and risk of dementia among US veterans. Arch. Gen. Psychiatry 67, 608–613.
24. Soble, J.R., Spanierman, L.B., and Fitzgerald Smith, J. (2013). Neuropsychological functioning of combat veterans with posttraumatic stress disorder and mild traumatic brain injury. J. Clin. Exp. Neuropsychol. 35, 551–561.
25. Verfaellie, M., Lafleche, G., Spiro III, A., and Bousquet, K. (2014). Neuropsychological outcomes in OEF/OIF veterans with self–report of blast exposure: associations with mental health, but not MTBI. Neuropsychology 28, 337.
26. Vasterling, J.J., Brailey, K., Proctor, S.P., Kane, R., Heeren, T., and Franz, M. (2012). Neuropsychological outcomes of mild traumatic brain injury, post-traumatic stress disorder and depression in Iraq-deployed US Army soldiers. Br. J. Psychiatry 201, 186–192.
27. Combs, H.L., Berry, D.T., Pape, T., Babcock-Parziale, J., Smith, B., Schleenbaker, R., Shandera-Ochsner, A., Harp, J.P., and High Jr, W.M. (2015). The effects of mild traumatic brain injury, post-traumatic stress disorder, and combined mild traumatic brain injury/post-traumatic stress disorder on returning veterans. J. Neurotrauma 32, 956–966.
28. LoBue, C., Denney, D., Hynan, L.S., Rossetti, H.C., Lacritz, L.H., Hart Jr, J., Womack, K.B., Woon, F.L., and Cullum, C.M. (2016). Self-reported traumatic brain injury and mild cognitive impairment: increased risk and earlier age of diagnosis. J. Alzheimers Dis. 51, 727–736.
29. Barnes, D.E., Kaup, A.R., Kirby, K., Byers, A.L., Diaz-Arrastia, R., and Yaffe, K. (2014). Traumatic brain injury and risk for dementia in older veterans. Neurology 83, 312–319.
30. Kremen, W.S., Franz, C.E., and Lyons, M.J. (2013). VETSA: the Vietnam era twin study of aging. Twin Res. Hum. Genet. 16, 399–402.
31. Kremen, W.S., Thompson-Brenner, H., Leung, Y.-M.J., Grant, M.D., Franz, C.E., Eisen, S.A., Jacobson, K.C., Boake, C., and Lyons, M.J. (2006). Genes, environment, and time: the Vietnam era twin study of aging (VETSA). Twin Res. Hum. Genet. 9, 1009–1022.
32. Eisen, S., True, W., Goldberg, J., Henderson, W., and Robinette, C. (1987). The Vietnam Era Twin (VET) registry: method of construction. Acta Genet. Med. Gemellol. 36, 61–66.
33. Henderson, W.G., Eisen, S., Goldberg, J., True, W.R., Barnes, J.E., and Vitek, M.E. (1990). The Vietnam Era Twin Registry: a resource for medical research. Public Health Rep. 105, 368.
34. Department of Veterans Affairs and Department of Defense (2009). *Clinical Practice Guidelines: Management of Concussion /Mild Traumatic Brain Injury.* Department of Veterans Affairs and Department of Defense: Washington, DC.
35. Blanchard, E.B., Jones-Alexander, J., Buckley, T.C., and Forneris, C.A. (1996). Psychometric properties of the PTSD Checklist (PCL). Behav. Res. Ther. 34, 669–673.
36. Ruggiero, K.J., Del Ben, K., Scotti, J.R., and Rabalais, A.E. (2003). Psychometric properties of the PTSD Checklist—Civilian version. J. Trauma Stress 16, 495–502.
37. Radloff, L.S. (1977). The CES-D scale a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1, 385–401.
38. Campbell, D.G., Felker, B.L., Liu, C.-F., Yano, E.M., Kirchner, J.E., Chan, D., Rubenstein, L.V., and Chaney, E.F. (2007). Prevalence of depression–PTSD comorbidity: implications for clinical practice guidelines and primary care-based interventions. J. Gen. Intern. Med. 22, 711–718.
39. Ikin, J.F., Creamer, M.C., Sim, M.R., and McKenzie, D.P. (2010). Comorbidity of PTSD and depression in Korean War veterans: prevalence, predictors, and impairment. J. Affect. Disord. 125, 279–286.
40. Lewinsohn, P.M., Seeley, J.R., Roberts, R.E., and Allen, N.B. (1997). Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychol. Aging 12, 277.
41. U.S. Department of Veterans Affairs and National Center for PTSD (2014). *Using the PTSD Checklist for DSM-IV(PCL).* U.S. Department of Veterans Affairs and National Center for PTSD: Washington, DC.
42. Franz, C.E., Lyons, M.J., O'brien, R., Panizzon, M.S., Kim, K., Bhat, R., Grant, M.D., Toomey, R., Eisen, S., and Xian, H. (2011). A 35-year longitudinal assessment of cognition and midlife depression symptoms: the Vietnam Era Twin Study of Aging. Am. J. Geriatr. Psychiatry 19, 559–570.
43. Moore, C.S., Grant, M.D., Zink, T.A., Panizzon, M.S., Franz, C.E., Logue, M.W., Hauger, R.L., Kremen, W.S., and Lyons, M.J. (2014). Erectile dysfunction, vascular risk, and cognitive performance in late middle age. Psychol. Aging 29, 163.
44. Friedman, N.P., and Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. Cortex 86, 186–204.
45. Ekstrom, R.B., French, J.W., Harmon, H.H., and Dermen, D. (1976). *Manual for Kit of Factor-Referenced Cognitive Tests.* Educational Testing Service: Princeton, NJ.
46. Thurstone, L. (1944). *A Factorial Study of Perception.* University of Chicago Press: Chicago.
47. Wechsler, D. (1997). *Manual for the Wechsler Memory Scale*, 3rd ed. Psychological Corporation: San Antonio.
48. Daneman, M., and Carpenter, P.A. (1980). Individual differences in working memory and reading. J. Verbal Learning Verbal Behav. 19, 450–466.
49. Delis, D.K., Kramer, J.H., Kaplan, E., and Ober, B.A. (2000). *California Verbal Learning Test–Second Edition.* The Psychological Corporation: San Antonio.
50. Golden, C.J. (1978). *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses.* Skoelting: Chicago.
51. Delis, D.C., Kaplan, E., and Kramer, J.H. (2001). *Delis–Kaplan Executive Function System Technical Manual.* The Psychological Corporation: San Antonio.
52. Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence Manual*. Psychological Corporation: San Antonio.
53. Uhlaner, J., and Bolanovich, D.J. (1952). *Development of Armed Forces Qualification Test and Predecessor Army Screening Tests, 1946–1950. DTIC Document*. Adjutant General's Office (ARMY), Washington, DC.
54. Bookheimer, S., and Burggren, A. (2009). APOE-4 genotype and neurophysiological vulnerability to Alzheimer's and cognitive aging. Annu. Rev. Clin. Psychol. 5, 343–362.
55. Emi, M., Wu, L.L., Robertson, M.A., Myers, R.L., Hegele, R.A., Williams, R.R., White, R., and Lalouel, J.-M. (1988). Genotyping and

sequence analysis of apolipoprotein E isoforms. Genomics 3, 373–379.
56. Hixson, J.E., and Vernier, D.T. (1990). Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J. Lipid Res. 31, 545–548.
57. Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Series B Stat. Methodol. 57, 289–300.
58. Moretti, L., Cristofori, I., Weaver, S.M., Chau, A., Portelli, J.N., and Grafman, J. (2012). Cognitive decline in older adults with a history of traumatic brain injury. Lancet Neurol. 11, 1103–1112.
59. Young, J.S., Hobbs, J.G., and Bailes, J.E. (2016). The impact of traumatic brain injury on the aging brain. Curr. Psychiatry Rep. 18, 1–10.
60. Sundström, A., Nilsson, L.-G., Cruts, M., Adolfsson, R., Van Broeckhoven, C., and Nyberg, L. (2007). Increased risk of dementia following mild head injury for carriers but not for non-carriers of the APOE $\varepsilon 4$ allele. Int. Psychogeriatr. 19, 159–165.
61. Isoniemi, H., Tenovuo, O., Portin, R., Himanen, L., and Kairisto, V. (2006). Outcome of traumatic brain injury after three decades—relationship to ApoE genotype. J. Neurotrauma 23, 1600–1608.
62. Rassovsky, Y., Levi, Y., Agranov, E., Sela-Kaufman, M., Sverdlik, A., and Vakil, E. (2015). Predicting long-term outcome following traumatic brain injury (TBI). J. Clin. Exp. Neuropsychol. 37, 354–366.
63. Ashford, J.W. (2004). APOE genotype effects on Alzheimer's disease onset and epidemiology. J. Mol. Neurosci. 23, 157–165.
64. Vincent, A.S., Roebuck–Spencer, T.M., and Cernich, A. (2014). Cognitive changes and dementia risk after traumatic brain injury: implications for aging military personnel. Alzheimers Dement. 10, S174–S187.
65. Gardner, R.C., Burke, J.F., Nettiksimmons, J., Kaup, A., Barnes, D.E., and Yaffe, K. (2014). Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. JAMA Neurol. 71, 1490–1497.
66. Monti, J.M., Voss, M.W., Pence, A., McAuley, E., Kramer, A.F., and Cohen, N.J. (2013). History of mild traumatic brain injury is associated with deficits in relational memory, reduced hippocampal volume, and less neural activity later in life. Front. Aging Neurosci. 5, 41.
67. Li, W., Risacher, S.L., McAllister, T.W., and Saykin, A.J. (2016). Traumatic brain injury and age at onset of cognitive impairment in older adults. J. Neurol. 263, 1280–1285.
68. Barnes, D.E., Byers, A.L., Gardner, R.C., Seal, K.H., Boscardin, W.J., and Yaffe, K. (2018). Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. JAMA Neurol. [Epub ahead of print].
69. Bigler, E.D. (2013). Traumatic brain injury, neuroimaging, and neurodegeneration. Front. Hum. Neurosci. 7, 395.
70. Bryer, E., Medaglia, J., Rostami, S., and Hillary, F.G. (2013). Neural recruitment after mild traumatic brain injury is task dependent: a meta-analysis. J. Int. Neuropsychol. Soc. 19, 751–762.
71. Liberzon, I., and Sripada, C.S. (2007). The functional neuroanatomy of PTSD: a critical review. Prog. Brain Res. 167, 151–169.
72. Gong, Q., and He, Y. (2015). Depression, neuroimaging and connectomics: a selective overview. Biol. Psychiatry 77, 223–235.
73. Hoffman, S.W., and Harrison, C. (2009). The interaction between psychological health and traumatic brain injury: a neuroscience perspective. Clin. Neuropsychol. 23, 1400–1415.
74. Johnson, V.E., Stewart, W., and Smith, D.H. (2010). Traumatic brain injury and amyloid-β pathology: a link to Alzheimer's disease? Nat. Rev. Neurosci. 11, 361–370.
75. Weiner, M.W., Harvey, D., Hayes, J., Landau, S.M., Aisen, P.S., Petersen, R.C., Tosun, D., Veitch, D.P., Jack, C.R., and Decarli, C. (2017). Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: preliminary report. Alzheimers Dement. (N. Y.) 3, 177–188.

Address correspondence to:
Allison R. Kaup, PhD
Research Service
San Francisco VA Health Care System
and Department of Psychiatry
Weill Institute for Neurosciences
University of California
San Francisco
4150 Clement Street (116B)
San Francisco, CA, 94121

E-mail: allison.kaup@ucsf.edu