

Neuropsychological Profile of Lifetime Traumatic Brain Injury in Older Veterans

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Abstract

Objectives: The aim of this study was to characterize the neuropsychological profile of lifetime traumatic brain injury (TBI) in older Veterans. **Methods:** Participants were 169 older Veterans [mean age = 79.1 years (range, 51–97 years), 89% male, 92% Caucasian], 88 with lifetime TBI and 81 without TBI, living in Veterans' retirement homes in independent residence. TBI history was ascertained with the Ohio State TBI Identification Method structured interview. Cognition was assessed with neuropsychological tests: Raw scores were converted to Z-scores compared to age-corrected normative data and combined into five domain composite Z-scores (attention/working memory, learning/memory, language, processing speed, executive functioning). We investigated the association between TBI and performance in each cognitive domain in linear mixed effects models, with and without adjustment for demographics, medical comorbidities, and psychiatric variables. **Results:** Compared to those without TBI, older Veterans with TBI had greater deficits in processing speed (*estimate* = $-.52$; $p = .01$; $f^2 = .08$ in fully adjusted model) and executive functioning (*estimate* = $-.41$; $p = .02$; $f^2 = .06$ in fully adjusted model) but performed similarly in the attention/working memory, learning/memory, and language domains (all $p > .05$). TBI-associated deficits were most prominent among individuals with multiple mild TBIs and those with any moderate-to-severe TBI, but were not clearly present among those with single mild TBI. **Conclusions:** The neuropsychological profile of lifetime TBI in older Veterans is characterized by slowed processing speed and executive dysfunction, especially among those with greater injury burden. This pattern may reflect long-standing deficits or a TBI-associated cognitive decline process distinct from Alzheimer's disease. (*JINS*, 2017, 23, 56–64)

Keywords: Traumatic brain injury, Head injury, Aging, Veterans, Cognition, Cognitive deficits

INTRODUCTION

Epidemiological studies have identified traumatic brain injury (TBI) as a risk factor for dementia (Perry et al., 2015; Plassman & Grafman, 2015). Not only are individuals who sustain TBI in older adulthood at high risk for dementia (Gardner et al., 2014), but there is evidence of long-term associations such that individuals who experienced TBI earlier in life are at increased risk of developing mild cognitive impairment (MCI) (Guskiewicz et al., 2005) and dementia (Barnes et al., 2014; Plassman et al., 2000) in late life. Despite this evidence, the profile of cognitive deficits

that may be present among older adults with a lifetime history of TBI remains unclear. Investigation of whether lifetime TBI is associated with deficits in specific cognitive abilities in aging may clarify what type of dementia process is most likely to occur among older adults with TBI, and perhaps elucidate potential targets for intervention or prevention efforts.

Most research examining the effect of TBI on specific cognitive abilities has been conducted among younger to middle-aged adults. From such studies, it is clear that individuals with recent TBI may exhibit deficits in a variety of cognitive domains, including problems with executive functioning (McDonald, Flashman, & Saykin, 2002; Rochat, Ammann, Mayer, Annoni, & Linden, 2009), attention (Chan, 2005), working memory (McAllister, Flashman, McDonald, & Saykin, 2006), processing speed (Mathias, Beall, & Bigler, 2004),

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and memory (Curtiss, Vanderploeg, Spencer, & Salazar, 2001). In the months to initial years following a TBI, individuals tend to experience at least some cognitive improvement over time (Finnanger et al., 2013; Schretlen & Shapiro, 2003), and some, particularly those with mild TBI, may experience complete cognitive recovery (Karr, Areshenkoff, & Garcia-Barrera, 2014; Schretlen & Shapiro, 2003). These patterns of cognitive stability or improvement following recent TBI contrast with findings of long-term associations between lifetime TBI and the development of dementia in late life.

The few studies (Ashman et al., 2008; Dams-O'Connor et al., 2013; Himanen et al., 2006) that have addressed the effect of lifetime and/or remote TBI on specific cognitive abilities in older adulthood have produced mixed findings and have had important methodological limitations. For example, a study by Dams-O'Connor et al. (2013) compared dementia patients with and without a history of TBI to evaluate differences in the clinical features of dementia between these groups; although this study compared cognitive performance between groups, cognitive results are difficult to interpret as specific to TBI when both groups, by definition, already had cognitive impairment rising to the level of dementia. Other studies have not accounted for medical or psychiatric comorbidities when examining the association between TBI and late-life cognition. This is an important limitation because comorbidities are relatively common in individuals with TBI (Scholten et al., 2016) and are known to have important effects on cognition in aging (Byers & Yaffe, 2011; Qiu & Fratiglioni, 2015; Yaffe et al., 2010).

Our group is conducting the Brain Aging in Veterans (BRAVE) study to investigate the long-term effects of TBI in aging, by comparing groups of older Veterans with and without a lifetime history of TBI (Peltz et al., 2016). TBI is a particularly common injury among military personnel (Okie, 2005; Ommaya, Ommaya, Dannenberg, & Salazar, 1996; Raymont, Salazar, Krueger, & Grafman, 2011; Sayer, 2012); thus older Veterans are an important population among which to investigate this question. For the present study, we aimed to characterize the neuropsychological profile of lifetime TBI in aging, by comparing neuropsychological functioning between older Veterans with and without TBI in the BRAVE study. Because they share many similarities with older Veterans with TBI, older Veterans without TBI serve as an important comparison group for the BRAVE study.

However, it should be noted that this comparison group is not representative of a typical “healthy control” group. Other risk factors for cognitive impairment, such as cardiovascular risk factors and prior psychiatric and substance abuse conditions, are relatively common among older Veterans without TBI (Peltz et al., 2016). Therefore, in the present study, we aimed to first evaluate the extent to which each participant group in the BRAVE study exhibited neuropsychological deficits compared to healthy older adult norms. Then, we examined whether and how neuropsychological profiles differed between groups. Given that cognitive risk factors were present in both groups, we hypothesized that older Veterans with and without TBI would show cognitive deficits compared to normative data, but that older Veterans with TBI would show

a different profile of deficits. We also hypothesized that cognitive deficits would be more extensive among older Veterans with greater TBI history burden (i.e., among those with multiple mild TBIs or any moderate or severe TBI).

METHODS

Population

Participants were older Veterans (≥ 50 years old) with and without a lifetime history of TBI from the Brain Aging in Veterans (BRAVE) study. For the BRAVE study, Veterans were recruited from one of two Veteran’s retirement homes: the Armed Forces Retirement Home in Washington, DC and the Veterans Home of California-Yountville in Yountville, California. Recruitment and eligibility criteria for the BRAVE study have been described previously (Peltz et al., 2016). In brief, to be included in the BRAVE study, individuals were required to score ≥ 20 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) to help ensure they were cognitively capable of providing informed consent. Individuals were also required to be residents of the independent-living sections of their retirement home; to reside in independent-living, the facilities required individuals to be functionally independent and free of active substance abuse.

To be included in the TBI group, participants were required to self-report ≥ 1 head injury over their lifetime that required medical care, and TBI history was further assessed as detailed below. To be included in the non-TBI group, participants were required to self-report no significant head injury history. Individuals with penetrating TBI, disabling medical or psychiatric conditions, or significant sensory limitations were excluded from the study. The BRAVE study was approved by institutional review boards at each site, all participants provided written informed consent, and all data were obtained in compliance with institutional regulations. All participants were informed during the informed consent process that there would be no direct benefit to them from study participation, other than their contribution to the gain of research knowledge.

Measures

TBI History

Detailed TBI history was ascertained using the Ohio State University TBI Identification Method (OSU TBI-ID) (Bogner & Corrigan, 2009; Corrigan & Bogner, 2007), a structured interview recommended by the National Institute of Neurological Disorders and Stroke (NINDS) as a Common Data Element (CDE) for the retrospective assessment of lifetime TBI in clinical research [National Institute of Neurological Disorders and Stroke (NINDS), 2012]. During the OSU TBI-ID, participants were asked to self-report the TBI(s) they had experienced over their lifetime, including age of injury, injury cause, presence and length of loss of consciousness (LOC), and yes/no response to “were you dazed or did you have a gap in your

memory from the injury?" indicating alteration in consciousness or post-traumatic amnesia (PTA).

Each injury was classified as a (1) Mild TBI if an individual experienced an alteration in consciousness or PTA without LOC or LOC < 30 min, (2) Moderate TBI if LOC \geq 30 min but < 24 hr, or (3) Severe TBI if LOC \geq 24 hr (Department of Veterans Affairs & Department of Defense, 2009). Medical charts available at participants' retirement home were reviewed to corroborate history of TBI to the extent possible. Of individuals in the present study, 41% in the TBI group had TBI documented in their retirement home charts, while none of the individuals in the non-TBI group had TBI in their charts.

Cognitive functioning

Participants completed a comprehensive neuropsychology battery, an expanded version of the Alzheimer's Disease Centers' Uniform Data Set battery (Weintraub et al., 2009). This battery was comprised of measures assessing cognitive functioning in five domains: (1) attention/working memory, (2) learning/memory, (3) language, (4) processing speed, and (5) executive functioning. Specifically, measures of attention/working memory included the Wechsler Memory Scale-Revised (WMS-R) Digit Span Forward and Backwards (Wechsler, 1987) and the Working Memory Factor score from the National Institutes of Health - Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (NIH-EXAMINER) battery (Kramer et al., 2014b). The Auditory Verbal Learning Task (AVLT) (Rey, 1941; Taylor, 1959) was used to assess learning/memory, including AVLT Learning Trials (total trials 1–5), AVLT Delayed Recall, and AVLT Recognition total. Language was assessed using the Boston Naming Test—30 item version (Kaplan, Goodglass, & Weintraub, 1983) and Animal Fluency (Morris et al., 1989). Measures of processing speed included Trail Making Test Part A (Reitan & Wolfson, 1985) and Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol (Wechsler, 1981). Executive functioning was assessed with the Trail Making Test Part B (Reitan & Wolfson, 1985), and the NIH-EXAMINER battery Fluency Factor and Cognitive Control Factor scores (Kramer et al., 2014b).

Other variables

Participants self-reported their age, race, sex, education, military service history, and cigarette smoking status. Comorbidities, including hypertension, myocardial infarction, stroke, diabetes, and history of mental health conditions and substance abuse were determined *via* a combination of participant self-report and chart review. Current psychiatric symptoms were assessed *via* self-report inventories. Namely, depressive symptoms were assessed with the Geriatric Depression Scale—Short Form (GDS) (Yesavage et al., 1983), a 15-item inventory of yes/no questions with a score > 5 being suggestive of clinical depression. Current symptoms of post-traumatic stress disorder (PTSD) were assessed with the

PTSD Checklist—Civilian version (PCL-C) (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996), for which a score \geq 36 may be suggestive of significant PTSD among Veterans in general settings (U.S. Department of Veterans Affairs & National Center for PTSD, 2014).

Statistical Analysis

We compared participant characteristics between individuals in the TBI group *versus* the non-TBI group using *t* tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables, as well as Cohen's *d* and Phi coefficients as effect size measures in correspondence with these tests. To evaluate whether the TBI and non-TBI groups differed in terms of their neuropsychological profile, we first compared each participant's raw cognitive test scores to age-corrected normative data for each measure [Mayo's Older Americans Normative Studies (MOANS) age-corrected norms for AVLT Learning Trials (Ivnik et al., 1990) and Delayed Recall and Recognition (Ivnik et al., 1992); age-corrected norms for the NIH EXAMINER battery (Kramer et al., 2014a); and Alzheimer's Disease Centers' Uniform Data Set age-corrected norms (Shirk et al., 2011) for the remaining measures], similar to standard practice in clinical neuropsychological evaluations.

Using these normative data, we converted each individual's raw test scores into age-corrected Z-scores, reflecting the extent to which an individual's test performance diverges from that of healthy, age-matched peers. To minimize multiple comparisons, individuals' Z-scores for individual tests within a cognitive domain were averaged to create five cognitive domain composite scores: attention/working memory, learning/memory, language, processing speed, and executive functioning composites. Thus, these composites reflect the extent to which an individual's overall performance within a cognitive domain diverges from that of healthy, age-matched peers.

We conducted linear mixed effects model analyses, using SAS PROC MIXED, to investigate the association between TBI and performance on the cognitive domain composite scores. These models accounted for study site (participants nested within site) as a random effect. We conducted these models with and without addition of covariates. We first adjusted for demographics (age, gender, race, education) and a binary variable indicating whether or not participants had any of the following medical comorbidities/health factors (hypertension, myocardial infarction, stroke, diabetes, or current smoking). Then, we additionally adjusted for a binary variable indicating whether or not participants had a history of any of the following psychiatric or substance use conditions (depression, anxiety, PTSD, bipolar disorder, or substance abuse), as well as their current level of psychiatric symptoms (i.e., GDS and PCL-C scores for depressive and PTSD symptoms, respectively). For each of these models, we calculated Cohen's f^2 values from SAS PROC MIXED using procedures outlined in Selya, Rose, Dierker, Hedeker, and

Mermelstein (2012), reflecting the effect size for the association between TBI and each cognitive domain composite score, unadjusted or adjusted for covariates.

To explore whether the association between TBI and neuropsychological functioning differs depending on details of an individual's injury history, we created a four-level categorical variable to classify participants based on whether they had a single mild TBI, multiple mild TBIs (i.e., individuals who self-reported multiple head injuries that each met criteria for mild TBI as detailed in the "TBI History" section above), or at least one TBI that was moderate-to-severe in severity, compared to individuals without TBI. Using linear trend tests, we investigated the effect of TBI history category (no TBI, single mild TBI, multiple mild TBI, or any moderate-to-severe TBI) on the cognitive domain composite scores. These analyses were conducted by using the ESTIMATE statement in PROC MIXED to specify a test of linear trend across the four-level

TBI variable (coefficients: $-3 \ -1 \ 1 \ 3$). All analyses were conducted in SAS version 9.4, and p -values $< .05$ were considered statistically significant.

RESULTS

As previously reported in the BRAVE study (Peltz et al., 2016), Veteran participants with and without lifetime TBI were generally similar in terms of demographics and most medical comorbidities, although Veterans with TBI were more likely to be Caucasian and to have diabetes (see Table 1). Veterans with TBI were also more likely to have a history of depression and substance abuse and endorsed greater current depressive symptoms and current PTSD symptoms compared to those without TBI (see Table 1). Nevertheless, few individuals in either group endorsed

Table 1. Demographics and other participant characteristics

Mean (SD) or %	Non-TBI (<i>n</i> = 81)	TBI (<i>n</i> = 88)	Test statistic	<i>p</i> -Value	Effect size
Demographics					
Age, years	80.3 (8.6)	77.9 (10.3)	$t(167) = 1.63$.11	$d = .25$
Gender, % males	85.2%	92.1%	$X^2(1) = 1.99$.16	$\phi = .11$
Race, % minority	13.6%	2.3%	Fisher's exact test	.008*	$\phi = -.21$
Education, years	14.6 (2.6)	14.4 (2.7)	$t(167) = .63$.53	$d = .08$
Military Service, years	10.7 (8.8)	10.7 (9.1)	$t(162) = -.02$.98	$d = .00$
TBI history					
Injury number/severity:					
Single mild TBI	—	22.7%	—	—	—
Multiple mild TBIs	—	46.6%	—	—	—
Any moderate-to-severe TBI	—	30.7%	—	—	—
Age at first TBI, years	—	26.2 (21.9)	—	—	—
Time since most recent TBI, years	—	33.0 (24.7)	—	—	—
Medical History					
Hypertension	79.0%	75.6%	$X^2(1) = .28$.60	$\phi = -.04$
Myocardial infarction	10.4%	11.8%	$X^2(1) = .08$.78	$\phi = .02$
Stroke	11.1%	14.0%	$X^2(1) = .31$.58	$\phi = .04$
Diabetes	22.2%	36.8%	$X^2(1) = 4.25$.04*	$\phi = .16$
Current smoking	18.5%	12.6%	$X^2(1) = 1.11$.29	$\phi = -.08$
Psychiatric history/ substance abuse history					
Depression	20.0%	43.5%	$X^2(1) = 10.46$.001*	$\phi = .25$
Anxiety	15.0%	23.0%	$X^2(1) = 1.72$.19	$\phi = .10$
PTSD	8.9%	15.3%	$X^2(1) = 1.58$.21	$\phi = .09$
Bipolar disorder	3.7%	7.0%	Fisher's exact test	.50	$\phi = .07$
Substance abuse	18.5%	43.7%	$X^2(1) = 12.30$	<.001*	$\phi = .27$
Current psychiatric symptoms					
Depressive symptoms (GDS)	1.0 (1.5)	1.9 (2.7)	$t(140.7) = -2.66$.009*	$d = -.41$
PTSD symptoms (PCL-C)	19.5 (6.3)	22.8 (8.3)	$t(161.5) = -2.92$.004*	$d = -.45$
Global cognition					
MMSE	28.3 (1.5)	27.6 (2.6)	$t(143.76) = 2.01$.046*	$d = .33$

Note. Effect sizes reported are Cohen's d and phi coefficient (ϕ) values.

* $p < .05$.

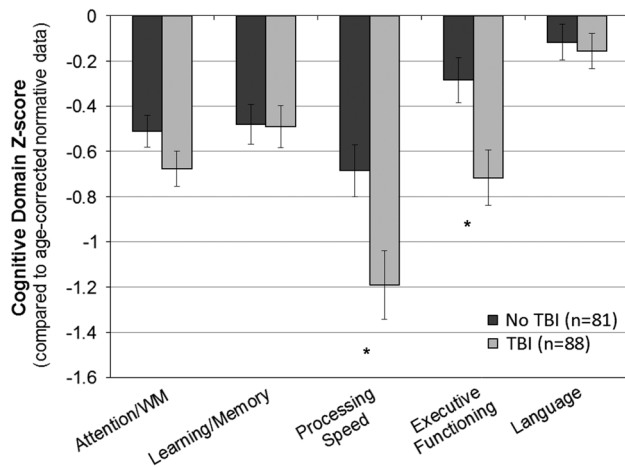


Fig. 1. Neuropsychological profile among older veterans with and without TBI. Graph shows mean cognitive domain composite scores with standard error bars by group. * $p < .05$ in unadjusted and adjusted models (see Table 2).

current psychiatric symptoms that exceeded clinical cut-offs on the symptom inventory measures [% individuals with GDS > 5: TBI = 9.1% ($n = 8$), non-TBI = 2.5% ($n = 2$); % individuals with PCL-C ≥ 36 : TBI = 6.8% ($n = 6$), non-TBI = 1.2% ($n = 1$)]. Regarding details of Veterans' lifetime exposure to TBI, individuals' TBI histories were quite heterogeneous.

As shown in Table 1, experience of multiple mild TBIs was the most common lifetime injury pattern. The vast majority of Veterans had experienced their TBI(s) many years ago, although some had experienced TBI in more recent years. Namely, 18 TBI participants had sustained TBI within the past 5 years, although 14 of these individuals had had multiple lifetime TBIs with at least one of their injuries occurring >5 years ago. No participant had experienced TBI < 1 year ago.

Figure 1 depicts the neuropsychological profile exhibited by older Veterans with and without lifetime TBI compared to

age-corrected normative data. On average, older Veterans without TBI performed nearly .7 *SD* below the mean compared to normative data in the processing speed domain, and approximately .5 *SD* below the normative mean in the domains of attention/working memory and learning/memory, but performed more similarly to normative data in the executive functioning and language domains. On average, older Veterans with TBI performed nearly 1.2 *SD* below the normative mean in the processing speed domain, approximately .7 *SD* below the normative mean in the attention/working memory and executive functioning domains, and nearly .5 *SD* below the normative mean in the learning/memory domain, but performed more similarly to normative data in the language domain.

Results of linear mixed effects models examining the association between TBI and cognitive domain composite scores, with and without adjustment for covariates (demographics, presence of any medical history factor, any psychiatric or substance abuse condition, and current depressive and PTSD symptoms), are detailed in Table 2. There were no significant associations between TBI and performance on the attention/working memory, learning/memory, or language domain scores in any model. Individuals with TBI evidenced greater deficits in processing speed and executive functioning compared to those without TBI, associations which remained statistically significant in the fully adjusted model. Per standard guidelines for interpretation of Cohen's f^2 values ("small": $f^2 \geq .02$, "medium": $f^2 \geq .15$, "large": $f^2 \geq .35$) (Cohen, 1988), these associations (both unadjusted and adjusted for covariates) were in the range of "small" effect sizes.

As shown in Figure 2, tests of trend for the four-level TBI variable (no TBI, single mild TBI, multiple mild TBIs, or any moderate-to-severe TBI) indicated that deficits in processing speed and executive functioning were most prominent among individuals with multiple mild TBIs or any moderate-to-severe TBI, while such deficits were not clearly present among those with single mild TBI. Specifically, in the fully adjusted model for processing speed, there was a significant

Table 2. Association between TBI and cognitive domain composite scores in older veterans

Cognitive domain	Effect of TBI on cognitive domain composite score								
	Unadjusted model			Model adjusted for demographics and presence of any medical history factor			Fully adjusted model (+ any history of psychiatric or substance abuse conditions, current depressive and PTSD symptoms)		
	Parameter estimate [95% CI]	p	f^2	Parameter estimate [95% CI]	p	f^2	Parameter estimate [95% CI]	p	f^2
Attention/working memory	-.17 [-.38, .04]	.12	.01	-.13 [-.34, .07]	.20	.01	-.10 [-.31, .12]	.37	.00
Learning/memory	-.01 [-.27, .24]	.93	-.01	.03 [-.23, .28]	.83	-.01	.04 [-.22, .31]	.74	-.01
Processing speed	-.50 [-.89, -.12]	.01*	.09	-.54 [-.94, -.14]	.008*	.10	-.52 [-.94, -.11]	.01*	.08
Executive functioning	-.43 [-.75, -.12]	.007*	.08	-.46 [-.79, -.14]	.006*	.09	-.41 [-.75, -.07]	.02*	.06
Language	-.04 [-.26, .18]	.72	-.01	-.07 [-.29, .16]	.55	-.01	-.02 [-.25, .21]	.86	-.01

Effect sizes reported are Cohen's f^2 values.

* $p < .05$.

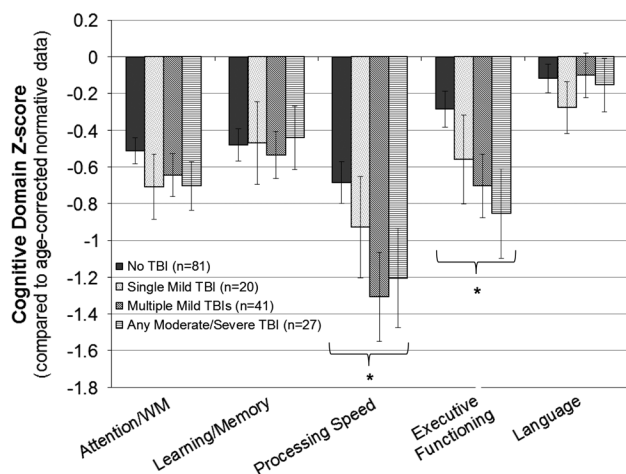


Fig. 2. Neuropsychological profile by TBI history category. Graph shows mean cognitive domain composite scores with standard error bars by group. * p -trend < .05 in unadjusted and adjusted models.

linear trend effect across levels of the four-level TBI variable {parameter estimate for linear trend = -2.21 , $SE = .99$, $p = .03$; parameter estimate [95% confidence interval (CI)]: no TBI = ref, single mild TBI = $-.20$ ($-.83, .44$), multiple mild TBI = $-.70$ ($-1.22, -.18$), any moderate-to-severe TBI = $-.57$ ($-1.16, .02$)}. Likewise, in the fully adjusted model for executive functioning, there was a significant linear trend effect across levels of the four-level TBI variable [parameter estimate for linear trend = -1.80 , $SE = .81$, $p = .03$; parameter estimate (95% CI): no TBI = ref, single mild TBI = $-.23$ ($-.75, .29$), multiple mild TBI = $-.44$ ($-.87, -.02$), any moderate-to-severe TBI = $-.53$ [$-1.02, -.04$]}. There were no significant linear trend effects for the remaining cognitive domain composite scores (all $p > .05$).

In sensitivity analyses, we re-ran the above models excluding the 18 individuals who had had a TBI within the past 5 years to explore whether findings differed among those whose injuries were exclusively remote TBI(s) rather than most recent injuries. Results remained similar to the above findings.

DISCUSSION

By evaluating the neuropsychological profiles of older Veterans with and without lifetime TBI, we found that both groups evidenced diminished cognitive performance compared to normative data from healthy older adults, but that the two groups had different neuropsychological profiles. On average, older Veterans with TBI (whose injuries were largely remote TBIs) had even greater deficits in processing speed than those without TBI. Older Veterans with TBI also showed evidence of executive dysfunction, whereas executive difficulties were not clearly present among those without TBI. The groups did not differ on measures of attention/working memory, learning and memory, and language.

When examining neuropsychological profiles of Veterans who differed in the number or severity of TBI(s) they had

experienced, we found that deficits in speed and executive functioning were most prominent among individuals with more significant TBI injury histories (i.e., those with multiple mild TBIs, or any moderate-to-severe TBI), whereas history of single mild TBI was not clearly associated with greater deficits in these domains. Importantly, the neuropsychological profile differences we observed between groups did not appear to be explained by other factors present in individuals' medical or psychiatric history, and results were unchanged when excluding the few individuals who sustained a TBI in more recent years. Overall, these results suggest that a lifetime history of multiple mild TBIs or any moderate-to-severe TBI, even when remote, is associated with a unique profile of cognitive deficits in older adulthood, characterized by slowed processing speed and executive dysfunction.

Despite epidemiological evidence that TBI is a risk factor for dementia (Plassman & Grafman, 2015), much remains to be understood regarding how a lifetime history of TBI might influence cognitive aging to ultimately lead to cognitive decline and increase risk for dementia. Our study results provide some clarity among several possibilities that have been raised in the literature. First, it has been suggested that the association between TBI and risk of dementia may simply be contributed to by normal aging processes, such that older adults with a lifetime history of TBI may have long-standing neural and cognitive vulnerabilities that further worsen in aging, eventually resulting in cognitive decline significant enough to meet the clinical threshold for a dementia diagnosis (Moretti et al., 2012).

Our results would be compatible with this hypothesis. Indeed, a common neural sequelae of TBI is diffuse axonal injury (Hayes, Bigler, & Verfaellie, 2016), which is known to be associated with deficits in processing speed and executive functioning (Spitz, Maller, O'Sullivan, & Ponsford, 2013) similar to the neuropsychological profile observed in the present study. It is possible that the processing speed and executive deficits we found among older Veterans with lifetime TBI, particularly among those with greater injury burden, may reflect long-standing deficits these individuals have had since their TBI(s) or deficits in these domains that have been further exacerbated by aging. The latter possibility is supported by a longitudinal study that found that older adults with TBI evidenced significant decline in processing speed over an 8-year follow-up period (executive functioning was not assessed) (Eramudugolla et al., 2014).

Alternatively, it is possible TBI may give rise to neuro-pathologic changes that initiate a neurodegenerative disease process (Johnson, Stewart, & Smith, 2010; Shively, Scher, Perl, & Diaz-Arrastia, 2012; Smith, Johnson, & Stewart, 2013), leading to a particular type of dementia. For example, some studies have identified TBI as a risk factor for Alzheimer's dementia (AD), particularly among those with moderate or severe TBI (Plassman et al., 2000). Other research suggests repetitive mild TBI in particular may lead to a distinct neuropathology referred to as chronic traumatic encephalopathy (CTE) (Smith et al., 2013; Stern et al., 2013). Our results argue against a specific association between TBI

and AD since we did not find prominent memory or language deficits in older Veterans with TBI, as is typical in prodromal AD and mild AD (Bondi et al., 2008; Verma & Howard, 2012). It is possible that our findings are capturing cognitive manifestations of another neurodegenerative process, such as CTE, although much remains to be investigated regarding the prevalence and cognitive profile of CTE. Moreover, it is unclear how likely it is for CTE neuropathology to be present among older Veterans whose TBI exposure may be qualitatively and quantitatively different from populations among whom CTE has been identified to date, namely football players and other athletes with extensive histories of repeated concussive and subconcussive head injuries (Bieniek et al., 2015; Gavett, Stern, & McKee, 2011).

That we found an association between the number/severity of TBIs and the extent to which individuals had cognitive deficits may also inform potential mechanism(s) linking lifetime TBI to cognitive impairment in aging. Namely, it is interesting that older Veterans who differed in the number and/or severity of TBI(s) they had experienced did not differ from each other in *which* cognitive domains they had deficits. Instead, they differed in the *degree* to which they had deficits within the same domains of processing speed and executive functioning. This pattern of findings suggests the same mechanism may underlie the association between lifetime TBI and cognition in aging among individuals with diverse TBI histories, but that the effects are more deleterious among those exposed to greater injury burden over their lifetime. Perhaps individuals with a history of multiple mild TBIs or any moderate-to-severe TBI have accumulated more extensive diffuse axonal injury or other neural damage than those with single mild TBI, increasing their vulnerability to cognitive impairment in aging. It is also possible that differences in TBI number and severity may influence whether or what type of neuropathologic cascade may develop to lead to cognitive decline and dementia in aging (Smith et al., 2013).

Strengths of the present study include our ability to investigate functioning in specific cognitive domains among older Veterans with diverse TBI histories, as well as our characterization of neuropsychological profiles among these individuals compared to normative data. Our study also benefits from assessment of participants' medical comorbidities, psychiatric and substance abuse history, and current psychiatric symptoms, enabling our results to reveal that cognitive profile differences between Veterans with and without TBI remain above and beyond the influence of these other factors. While accounting for these factors as covariates strengthens our conclusions regarding the independent impact of TBI on neuropsychological performance, it is also possible that factors such as psychiatric symptoms may themselves be features of a TBI-related decline process, a possibility that is further discussed in Peltz et al. (2016).

A key limitation of our study is its cross-sectional design, such that we cannot determine whether the deficits we observed may be longstanding or incident in aging. We plan to investigate this in future work as we continue to follow these Veterans over time. We also cannot rule out the potential for

reverse causality in this cross-sectional study, for example, perhaps individuals with lower pre-morbid cognitive functioning may be at greater risk for TBI in general, or at greater risk for sustaining repetitive or more severe TBIs. As accuracy of participants' self-report of their TBI history could not be verified for many individuals, it is unclear how this may have influenced our results, or whether participants' self-report may have tended to under- *versus* over-estimate the number or severity of TBI(s) they had experienced.

In defining our TBI group, we required individuals to self-report ≥ 1 head injury that *required medical care*, which may have influenced our TBI group to have more significant injury histories than the general population of older Veterans, particularly as a substantial proportion of individuals with TBI do not seek medical attention (Setnik & Bazarian, 2007). Additionally, normative corrections for our neuropsychological test battery necessitated comparisons to different sources of normative data (no one source was available that encompassed all of the tests), which may have introduced an unclear pattern of bias to our results. As this study focused on older, primarily male and caucasian Veterans, a unique population among whom medical and psychiatric comorbidities are common (Kramarow & Pastor, 2012), we cannot be certain how well our results may generalize to non-Veteran populations or to Veterans living in different settings who may differ from our participants in important ways.

Moreover, we cannot be certain of how findings from this research study may diverge from what is seen among patients presenting for neuropsychological evaluations as part of their clinical care, particularly in clinical situations where secondary gain factors may be present. As the associations we observed between TBI and cognitive functioning were in the range suggestive of "small" effect sizes, the extent to which such associations have clear clinical impacts remains unclear, including whether and how these TBI-associated cognitive deficits impact individuals' daily functioning.

In summary, our findings suggest that the neuropsychological profile of older Veterans with lifetime TBI, even when remote, is characterized by slowed processing speed and executive dysfunction. This pattern of deficits was most prominent among individuals with a history of multiple mild TBIs or any moderate-to-severe TBI, but were not clearly present among those with single mild TBI. Older Veterans with lifetime TBI appear to be a cognitively vulnerable population, for whom clinical care should include close monitoring and routine assessment to evaluate whether patients need additional resources and care. Future research is needed to understand whether it might be possible to intervene to improve cognitive functioning among older adults with TBI, and whether such interventions might also help to prevent, or at least delay, the development of dementia in this high-risk population. Our results suggest that intervention and prevention research efforts should focus on older Veterans who have had multiple mild TBI or any moderate-to-severe TBI in particular, and that research investigating potential cognitive interventions should emphasize processing speed and executive functioning skills as intervention targets.

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