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Cognitive deficits four decades after traumatic brain injury in Australian Vietnam war veterans

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DOI: 10.52095/gp.2021.8111
Received: 2020-11-16; Accepted: 2021-01-20

Abstract

Objective: Since 2000, over 350,000 US military personnel have been diagnosed with a traumatic brain injury (TBI) (VA, 2010). Whilst epidemiological studies report up to a fourfold increased risk for dementia associated with brain injury amongst veterans there is limited controlled research into the long-term neuropsychological burden of injury.

Main aim: The study aimed to determine whether Australian Vietnam war veterans with service-related TBI were more likely to exhibit cognitive deficits, 30-50 years after injury when compared to healthy veteran controls.

Materials and methods: 69 male veterans 60-85 years old, underwent psychiatric and neuropsychological assessment; 40 with a TBI (mean age = 68.0 ± 2.5) and 29 without (mean age = 70.1 ± 5.3). The TBI cohort included 15 mild, 16 moderate and nine severe TBI.

Results: After adjustment for identified covariates, veterans with moderate-to-severe TBI performed significantly worse than controls on composite measures of memory and learning (M = -0.55 ± 0.69, t(67) = 2.86, p=0.006, d=0.70) and attention and processing speed (M = -0.71 ± 1.08, t(52) = 2.53, p=0.014, d=0.69). There were no differences in cognitive performance between veterans with mild TBI (mTBI) and controls.

Conclusion: Results from this study suggest that amongst ageing veterans, a moderate-to-severe TBI sustained during early adulthood is associated with later-life cognitive deficits in memory and learning, attention and processing speed.

Keywords

TBI; Cognition; Neuropsychology; Traumatic Brain Injury; Military Injury

INTRODUCTION

Traumatic brain injury is associated with a number of long-term sequelae, including an increased risk of dementia (Barnes et al., 2014; Plassman et al., 2000), however, there is limited longitudinal research regarding the neuropsychological impact of an injury. Whilst injuries are heterogeneous, cognitive domains particularly vulnerable to TBI include memory and learning, attention, processing speed, and executive function (Belanger & Vanderploeg, 2005; Carroll et al., 2004; Frencham et al., 2005; Schretlen & Shapiro, 2003). Moderate-to-severe TBI may additionally cause deficits in fine motor speed and complex language and discourse (Levin, 1993; Millis et al., 2001). The extent of cognitive disruption following TBI is dependent upon the severity of the injury, with mTBI typically resulting in transient cognitive, emotional or physical symptoms which in most cases remit over a period of days or weeks (Belanger & Vanderploeg, 2005). Repetitive or more complicated and severe injuries may result in variable recovery (Carroll et al., 2004; Frencham et al., 2005; Schretlen & Shapiro, 2003; Dagher et al., 2013; Guskiewicz et al., 2003; McCrea et al., 2013). Up to 60% of survivors of moderate-to-

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severe TBI, and 75% of survivors of very severe TBI, report persisting cognitive deficits 10-15 years following injury. These complaints include memory problems, difficulty concentrating, slowed thinking, cognitive fatigue and word-finding difficulties (Ponsford et al., 2014; Thomsen, 1984). Studies that include objective neuropsychological testing a decade or more following TBI have also confirmed the presence of persistent injury related cognitive impairments (McCrea et al., 2013; Millis et al., 2001). When compared with demographically matched controls, both veterans and civilians with TBI perform more poorly on measures of processing speed, memory and executive function many years after an injury, with injury severity relating to the degree of cognitive impairment (Draper & Ponsford, 2008; Kaup et al., 2017). In addition, when compared with their non-injured counterparts, veterans with varying severities of penetrating TBI have shown accelerated cognitive decline 30 years post-injury (Corkin et al., 1989). Whilst it has been suggested that more severe injuries may represent a risk factor for accelerated cognitive ageing (Hoofien et al., 2001; Wood & Rutterford, 2006), other studies suggest that this observed cognitive decline many years following injury, may be mediated by other factors such as gender and age, and is qualitatively different from the early signs of an Alzheimer's type dementia (Himanen et al., 2006; Senathi-Raja et al., 2010). The presence of long-term cognitive deficits following mTBI is debated and studies have yielded ambiguous results. Retired athletes with a history of three or more mTBIs have significant memory deficits (Guskiewicz et al., 2005), and in other studies, cognitive deficits have been reported eight years following a singular mTBI (Dagher et al., 2013; Guskiewicz et al., 2003). However, more recent work in veterans has failed to show an association between a single mTBI and later-life cognitive impairment (Kaup et al., 2017).

MAIN AIM AND HYPOTHESIS

The main objective of the current study was to determine whether veterans with TBI exhibited greater cognitive deficits than veterans without TBI, as evidenced by poorer performance on neuropsychological measures of memory and learning, executive functioning, language, attention and processing speed, and visuospatial functioning. In line with the current literature, the main hypothesis was that veterans with a history of mild, moderate or severe TBI would perform worse on measures of cognitive function when compared with veterans without TBI. The secondary hypothesis was that severity of injury would show a linear relationship with cognitive performance, with more severe injuries resulting in greater cognitive deficits.

METHODS

Participants

Ex-military service personnel 60-85 years old, with and without TBI, were recruited through retired veteran organisations such as the Returned Services League, the Australian Federation of Totally and Permanently Incapacitated Ex-Service Men and Women, the Vietnam Veterans' Association of Australia, as well as the Older Veterans' Psychiatry Program located at a local hospital. To be included in the study, participants had to be free of any prior diagnosis of bipolar affective disorder, schizophrenia, dementia, mild cognitive impairment (MCI), substance abuse/dependence within the last five years, any immediate MRI contraindication and any major, unstable medical condition. The decision to exclude persons with an existing diagnosis of dementia or MCI was to reduce potential recruitment and injury recall bias.

To be included in the TBI cohort, participants had to have sustained at least one TBI between the ages of 16-40 years old. Those with childhood TBI were not accepted into the study due to the well-documented neuropathophysiological differences between paediatric and adult TBI (Araki et al., 2017; Ommaya et al., 2002). To ensure the study was investigating the long-term effects of TBI there was an age cut-off of 40 years. TBI severity was assessed based on criteria set down by the US Department of Defense (DoD) and Department of Veterans' Affairs (VA) ("VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury," 2009 – see table 1). Medical records from the time of injury were not available. Given the reliance on self-reporting, and to ensure injuries were given accurate severity ratings (mild/moderate/severe) only participants who were confident in the details of their injury were included. Due to recruiting challenges, it was not possible to exclude participants with post-traumatic stress disorder (PTSD) in the TBI cohort, however, the authors' prior work has demonstrated the neuropsychological performance of Vietnam veterans with PTSD, and without TBI, to be within the normal range of published norms (Elias et al., 2019). To be included in the control group, participants were required to report no prior history of TBI or PTSD.

To assess whether the veteran healthy control cohort (HC) was representative of the general population, data from healthy participants who took part in the Australian Imaging, Biomarker & Lifestyle (AIBL) study of ageing were accessed. Description of the cohort and procedure of the AIBL study are described elsewhere (Ellis et al., 2009). Age-matched AIBL participants who met the same criteria as the veteran controls and had sufficient

neuropsychological data for comparison were randomly selected from a database.

Ethical approval was granted by the Austin Health Human Ethics Research Committee (Ref: H2013/04947). All participants provided informed consent before participating and there were no direct incentives offered for participation. The consent process included a 45-minute face-to-face discussion with a member of the research team to ensure participants understood the nature of the study as well as any risks or benefits.

PROCEDURE & MATERIALS

All participants were screened over the phone to ensure they met study criteria. Those deemed suitable for initial assessment were invited to the research centre for psychiatric evaluation, 90-minute neuropsychological assessment and an interview to obtain TBI history. During the TBI interview, participants were asked to give a detailed account of events surrounding their most severe head injury including: age at injury, injury cause, presence and length of unconsciousness, alteration of consciousness and post-traumatic amnesia, as well as information on medical attention sought, and disruption of usual activities due to injury. Based on this information, each injury was classified as either mild, moderate or severe (see table 1).

Cognitive functioning

The psychometric measures chosen for this study represent cognitive domains of interest within TBI and Alzheimer's disease (AD) and assessed the following five domains: memory and learning, executive functioning, language, attention and processing speed, and visuospatial functioning. Tests included: Logical Memory Test I and II (story A only) (Wechsler, 1987), Rey Auditory Verbal Learning Test (RAVLT), (Rey, 1964) the Rey Complex Figure Test (RCFT) (Meyers & Meyers, 1995), the Trail Making Test (Reitan, 1958), the 30-item version of the Boston Naming Test (Kaplan et al., 1983), the Category Fluency Test (Butters et al., 1987), the Wechsler Adult Intelligence Scale III (WAIS-III), the Digit Span Task (Kaufman & Lichtenberger, 1999), the Clock Drawing Task (Kaplan, 1983), the Mini-Mental State Exam (MMSE) (Folstein et al., 1975), the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2003), and the Wechsler Test of Adult Reading (WTAR) (Venegas & Clark, 2011).

Psychiatric wellbeing

The psychiatric evaluation included measures of PTSD severity, drug and alcohol use, sleep quality, overall psychological wellbeing and medical history. The Clinician Administered PTSD Scale for DSM-IV (CAPS-IV) (Aker et al., 1999) was used to rate lifetime and current PTSD severity. A lifetime CAPS score of over 40 was indicative of lifetime PTSD, whilst a current CAPS score of over 40 indicated current PTSD.–The Addiction Severity Index-Lite (McLellan et al., 1980) was used to assess alcohol and substance use, and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) measured sleep quality and sleep disturbance. Clinical judgement by a review panel consisting of two psychiatrists and one neurologist was employed to decide whether responses to the Addiction Severity Index-lite was sufficient to indicate a current or recent substance abuse/dependence. A score of above five on the PSQI was indicative of poor-quality sleep. The Geriatric Depression Scale (GDS) (Shiekh, 1986) and the Symptom Checklist 90-Revised (Derogatis & Unger, 2010) were used to measure current depressive and psychopathological symptoms and overall psychological distress. Participants also completed the Combat Exposure Scale (Lund et al., 1984) to classify the level of wartime stressors experienced.

Other measures

Participants also self-reported their age, years of education, military-service history, cigarette smoking status and medical history. Medical comorbidities such as hypertension, ischemic heart disease, stroke, diabetes, migraine, and sleep apnoea were determined via self-

Table 1. Criteria used by DoD/VA to categorise head injury severity.

	Mild	Moderate	Severe
Loss of consciousness	0 - 0.5 hrs	0.5 - 24 hrs	>24 hrs
Alteration of consciousness	A moment - 24 hrs	>24 hrs; severity based on other criteria	>24 hrs; severity based on other criteria
Post-traumatic amnesia	0 - 1 day	1 - 7 days	>7 days
Glasgow Coma Scale	13 - 15	9 - 12	3 - 8
Structural imaging	Normal	Normal/abnormal	Normal/abnormal

reporting in an interview with the study psychiatrist.

DATA ANALYSIS

To allow for a meaningful comparison of cognitive performance with the veteran population, Z-scores were created by calculating mean and standard deviations (SD) for all continuous variables of interest within the veteran control group. A Z-score was created for each measure, by subtracting the control cohort's average score from each individual's score and dividing that by the SD of the control cohort. The Z-scores thus reflected the extent to which a participant's neuropsychological performance deviated from that of their healthy, age-matched peers. Based on previous research, (Kaup et al., 2017) and to minimise multiple comparisons, five cognitive domain composite scores were created from individual Z-scores, resulting in overall scores for: memory and learning, executive function, language, attention and processing speed, and visuospatial functioning. Z-scores were then created for these domains. Composites Z-scores were created by summing the individual test Z-scores, subtracting the control cohort's averaged summed Z-score and dividing that by the summed Z-score SD of the control cohort. Specifically, measures of memory included the delayed paragraph recall from the Logical Memory Test II (story A only), RAVLT, the sum of trials 1-5, 30-minute delayed recall and RAVLT recognition, and the RCFT, 3-minute delay, 30-minute delay and recognition task. Executive function was measured by the Trail Making Test, part B and language was assessed with the 30-item version of the Boston Naming Test and the Category Fluency Test. The WAIS-III Digit Span Task and Trail Making Test, part A, formed the attention and processing speed domain, whilst the visuospatial domain included the RCFT copy task and the Clock Drawing Task. In addition, measures of global cognition included the MMSE and the MoCA, and premorbid intellectual functioning was assessed using the WTAR.

Percentages were calculated for categorical variables. Participant characteristics and neuropsychological performance was compared between individuals in the TBI cohort and the veteran control group using T-Tests for continuous variables and chi-square for categorical variables, as well as Cohen's d to measure effect size. To compare the healthy veteran controls with an age-matched civilian cohort from the AIBL study, participant characteristics and neuropsychological raw scores were compared using T-Tests. Hierarchical regressions were used to investigate the influence of covariates. Those that had a significant effect on the outcome variable were then controlled for in an analysis of covariance (ANCOVA). All analyses were conducted using the statistical program R: A Language and Environment for Statistical Computing (RStudio, 2016) The following R packages were installed: lsr (Navarro, 2015), plyr (Wickham, 2011), effsize (Delaney, 2000), reshape2 (Wickham, 2007), ggplot2 (Wickham, 2009). A p-value of less than 0.05 was deemed statistically significant.

RESULTS

DEMOGRAPHICS

The healthy veterans' control group showed no significant group differences from the AIBL cohort in either demographics or neuropsychological performance indicating that they were representative of the general community who volunteers for cognitive research studies (see table 2). Of note, both groups had above average estimated IQ (mean 112 vs 111 respectively).

The TBI and veterans' control group were largely similar in terms of demographics and medical comorbidities. However, participants with a TBI were significantly younger (68 vs 70 years), had fewer years of education (11 vs 13), lower predicted IQ (105 vs 112), higher Body Mass Index (BMI) (30 vs 27), and were more likely to report a previous diagnosis of sleep apnoea (see table 3). The TBI cohort also reported higher symptoms of depression, anxiety, interpersonal sensitivity, paranoia, psychoticism, sleep disturbance and greater current and lifetime PTSD symptom severity. Of the TBI cohort, 37.5% had suffered a mild injury (n=15), 40% moderate (n=16), and 22.5% severe (n=9). The TBI groups did not differ from each other in terms of demographics or medical comorbidities (see tables 3 and 4). Injuries were sustained from a variety of mechanisms and further details are included in figure 1. The most common cause of injury, across all severities, was sports related, followed by motor vehicle accidents. The average age at injury was 24.0 (±5.4) years, and the average time since injury was 44.2 (±5.3) years. The range for time since injury was 30-53 years.

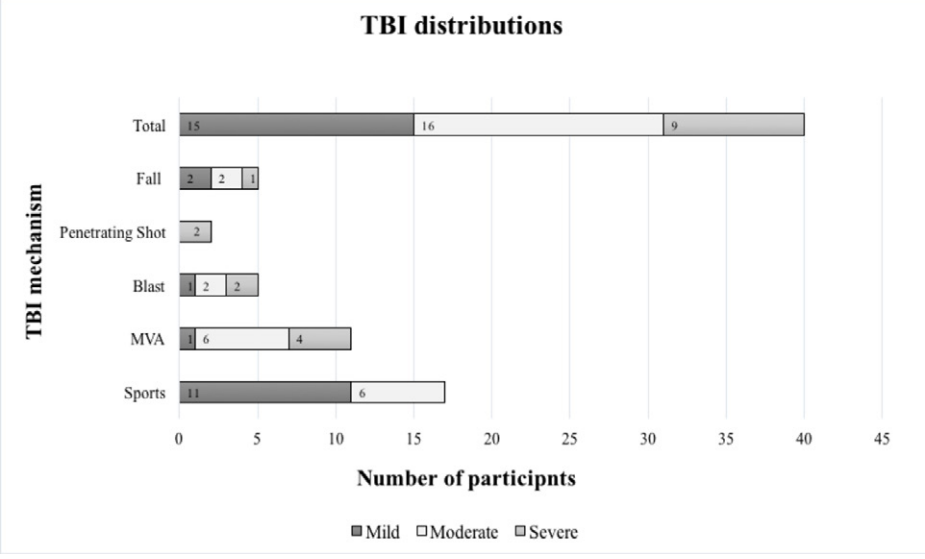
Cognition

After examining demographic, medical and psychiatric covariates, results from a hierarchical linear regression indicated that age and premorbid intellectual functioning were the only significant covariates, and were controlled for in the subsequent analysis. A series of ANCOVAs were carried out, controlling for the significant covariates identified in the hierarchical regressions. After adjustment for age and premorbid intellectual functioning, a significant difference in memory and learning was found between the TBI and HC groups ($F(2,66) = 5.95$, $p < 0.05$, partial $\eta^2 = 0.14$). No other differences were observed between

Table 2. Demographics & raw neuropsychological assessment scores for veteran healthy controls and AIBL healthy controls.

	HC (n=28)	AIBL HC (n=27)	p-value
demographics			
age, years	70.0 (±5.4)	71.48 (±7.7)	0.425
education, years	12.9 (±3.0)	13.7 (±3.7)	0.381
Cognition – raw scores			
MMSE	28.5 (±1.1)	29.0 (±1.3)	0.121
GDS	1.4 (±1.7)	1.6(±1.9)	0.673
Digit_FW_plus_BW	17.9 (±4.0)	18.0 (±4.1)	0.87
LM1	14.1(±4.1)	12.8 (±3.4)	0.211
LM2	11.2 (±4.2)	11.6 (±5.0)	0.755
RCFT_copy	30.2 (±2.3)	31.3 (±3.1)	0.115
RCFT_3min	17.5 (±6.2)	19.0(±6.0)	0.375
RCFT_30min	16.6 (±5.9)	18.9 (±6.2)	0.158
RCFT_recog	20.6 (±1.8)	20.7 (±1.7)	0.922
Clock	9.4 (±1.7)	9.8 (±0.6)	0.155
BNT	28.5 (±1.6)	28.5 (±1.8)	0.995
Animal_plus_boys	42.6 (±7.3)	40.9 (±8.6)	0.422
WTAR_IQ	111.9 (±5.6)	110.6 (±7.3)	0.44

Abbreviations: Healthy Controls (HC), Australian Imaging, Biomarker and Lifestyle study of ageing (AIBL), Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Digit Span Task (Digit_FW_plus_BW), Logical Memory (LM), the Rey Complex Figure Test (RCFT), Boston Naming Test (BNT), Category Fluency Test (CFT_Animal_plus_boys), Wechsler Test of Adult Reading (WTAR).



Classifications: fall from height (fall), received penetrating bullet wound through brain tissue (Penetrating Shot), received blast injury (Blast), Motor Vehicle Accident (MVA), sports-related TBI (sports).
Mild: Loss of consciousness (LoC) under 30 minutes and/or alteration of consciousness (AoC) under 24 hours and/or post-traumatic amnesia (PTA) less than one day. Moderate: LoC for more than 30 minutes but under 24 hours and/or AoC over 24 hours and/or PTA for more than one day but less than seven days. Severe: LoC for more than 24 hours and/or PTA for more than seven days.

Figure 1. Breakdown of causes of TBI across the cohort.

the groups in performance in MMSE, MoCA, language, executive functioning, or attention and processing speed after controlling for the significant covariates (see table 5).

Effect of injury severity

To investigate the impact of injury severity, the TBI cohort was subdivided into mTBI (n=15) and moderate-to-severe TBI (n=25), in line with guidelines set forward by the Mayo Clinic (Friedland, 2013). Results from a hierarchical linear regression indicated that premorbid intellectual functioning and years of education were significant covariates, and were controlled for in the subsequent analyse. After adjustment for premorbid intellectual functioning and years of education, an ANCOVA showed there were no significant differences in any of the cognitive domains between the mTBI and HC groups.

Amongst the moderate-to-severe and HC groups, the hierarchical linear regression indicated that premorbid intellectual functioning and age were significant covariates, and were controlled for in the subsequent analyses. After adjustment for premorbid intellectual functioning and age, an ANCOVA indicated there was a significant difference between the moderate-to-severe TBI cohort and controls in memory ($F(1,52) = 4.53$, $p<0.05$, partial $\eta^2 = 0.08$) and attention and processing scores ($F(2,51) = 4.84$, $p<0.05$, partial $\eta^2 = 0.15$). No other group differences were found (see figure 2).

DISCUSSION

TBI has been associated with a number of later-life health issues and of particular concern is the increased risk of dementia. However, there is limited longitudinal research

Table 3. Demographics and participant characteristics.

Mean (SD) or %	HC (*n*=29)	TBI (*n*=40)	test statistic	p-Value	Effect size (Cohen's d)
demographics					
age, years	70.1 (±5.3)	68.0 (±2.5)	t=2.15 (67)	*0.03**	0.52
education, years	13.0 (±3.0)	11.2 (±2.6)	t=2.61 (67)	*0.01**	0.64
WTAR US predicted full scale IQ	111.8 (±5.6)	104.6 (±6.9)	t=4.63 (67)	*<0.001**	1.13
military service, years	12.1 (±12.6)	7.8 (±8.8)	W=696	0.14	
CES	10.46 (±8.3)	13.8 (±11.0)	t=-1.31 (59)	0.2	
TBI history					
mild TBI		37.5% (n=15)			
moderate TBI		40.0% (n=16)			
severe TBI		22.5% (n=9)			
age at TBI		24.2 (±5.5)			
time since most severe TBI, years		44.1 (±5.3)			
medical history					
hypertension	41.4%	50.0%	Fisher's exact test	0.48	
ischemic heart disease	10.3%	20.0%	Fisher's exact test	0.28	
stroke	3.4%	0.0%	Fisher's exact test	0.24	
diabetes	10.3%	22.5%	Fisher's exact test	0.19	
current smoking	3.4%	7.5%	Fisher's exact test	0.48	
migraine	17.2%	27.5%	Fisher's exact test	0.32	
sleep apnoea	11.0%	38.0%	Fisher's exact test	*0.02**	0.62
BMI	27.0 (±3.8)	30.4 (±5.1)	t=-3.01 (67)	*0.003**	0.73

Abbreviations: Healthy Controls (HC), Traumatic Brain Injury (TBI), Wechsler Test of Adult Reading (WTAR), Combat Exposure Scale (CES), Body Mass Index (BMI) Classifications: Mild: Loss of consciousness (LoC) under 30 minutes and/or alteration of consciousness (AoC) under 24 hours and/or post-traumatic amnesia (PTA) less than one day. Moderate: LoC for more than 30 minutes but under 24 hours and/or AoC over 24 hours and/or PTA for more than one day but less than seven days. Severe: LoC for more than 24 hours and/or PTA for more than seven days

Table 4. Participant psychiatric data.

Mean (SD) or %	HC (*n*=29)	TBI (*n*=40)	test statistic	p-Value	Effect size (Cohen's d)
psychiatric history					
lifetime PTSD severity (CAPS lifetime)	9.1 (±8.5)	51.9 (±27.0)	t=-8.07 (67)	*<0.001**	-1.97
met clinical threshold for prior PTSD	0%	73%			
current psychiatric symptoms					
depressive symptoms (GDS)	1.3 (±1.7)	4.3 (±3.7)	W=277	*<0.001**	0.98
current PTSD severity (CAPS current)	6.5 (±6.0)	29.1 (±20.2)	t=-5.82 (67)	*<0.001**	1.42
somatization (SLC-90)	54.9 (±12.2)	63.2 (±11.9)	t=-2.84 (67)	*0.006**	0.69
obsessive-Compulsive (SLC-90)	56.1 (±11.9)	66.3 (±13.8)	t=-3.22 (67)	*0.009**	0.78
interpersonal sensitivity (SLC-90)	49.2 (±9.0)	62.0 (±13.4)	t=-4.47 (67)	*<0.001**	1.09
depression (SLC-90)	53.2 (±12.3)	64.7 (±11.4)	t=-3.97 (67)	*<0.001**	0.97
anxiety (SLC-90)	51.7 (±9.7)	61.3 (±14.5)	t=-3.10 (67)	*0.003**	0.75
hostility (SLC-90)	52.5 (±11.9)	61.8 (±13.3)	t=-3.00 (67)	*0.004**	0.73
phobic anxiety (SLC-90)	48.9 (±6.0)	63.4 (±12.2)	t=-5.89 (67)	*<0.001**	1.44
paranoid ideation (SLC-90)	47.7 (±8.4)	57.6 (±12.6)	t=-3.67 (67)	*<0.001**	0.89
psychoticism (SLC-90)	51.4 (±9.4)	61.9 (±12.0)	t=-3.91 (67)	*<0.001**	0.95
overall psychological distress (SLC-90: GSI)	53.1 (±13.9)	66.2 (±13.9)	t=-3.85 (67)	*0.001**	0.94
sleep disturbance (PSQI)	4.7 (±4.4)	7.3 (±4.2)	t=-2.15 (52)	*0.036**	0.59
met clinical threshold for current PTSD	0%	30%			

Abbreviations: Healthy Controls (HC), Traumatic Brain Injury (TBI), Clinician Administered PTSD scale (CAPS), Geriatric Depression Scale (GDS), Symptom Checklist-90 (SLC-90), Global Severity Index (GSI), Pittsburgh Sleep Quality Index (PSQI).

Table 5. Descriptive statistics for performance in cognitive domains, before controlling for covariates.

	Mean (SD)				**Effect size**
	HC (n=29)	TBI (*n*=40)	t	p-value	(Cohen's d)
MMSE	28.51 (±1.09)	27.60 (±1.58)	2.69	0.009	0.65
MoCA	27.52 (±2.60)	25.73 (±2.15)	3.13	0.003	0.76
memory & Learning		-0.55 (±0.69)	2.86	0.006	0.31
executive function		-0.29 (±1.20)	1.21	0.229	0.26
language		-0.94 (±1.17)	3.55	<0.001	0.85
attention & Processing		-0.40 (±1.19)	1.49	0.140	0.36
visuospatial function		-0.21 (±1.20)	0.53	0.596	0.19

Abbreviations: Healthy Controls (HC), Traumatic Brain Injury (TBI), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA).

regarding the neuropsychological impact of injury and the long-term effects of injury remain unclear. We examined the neuropsychological and medical profile of Vietnam veterans with and without TBI, many decades after the injury, in a bid to objectively document the long-term effects on cognition of TBI. An added challenge, given the population, was to untangle the effects of TBI from those of comorbid PTSD, which was attempted using data gathered from an extensive psychiatric assessment. Based on prior work, it was hypothesised that veterans with a history of mild, moderate or severe TBI would perform worse on measures of cognitive function when compared with healthy veteran controls.

When examined as a full group, significant differences were found between the TBI and control cohorts in memory and learning. However, when the TBI cohort was subdivided into mild and moderate-to-severe, deficits in memory and learning as well as in attention and processing speed were observed but only amongst the moderate-to-severe group.

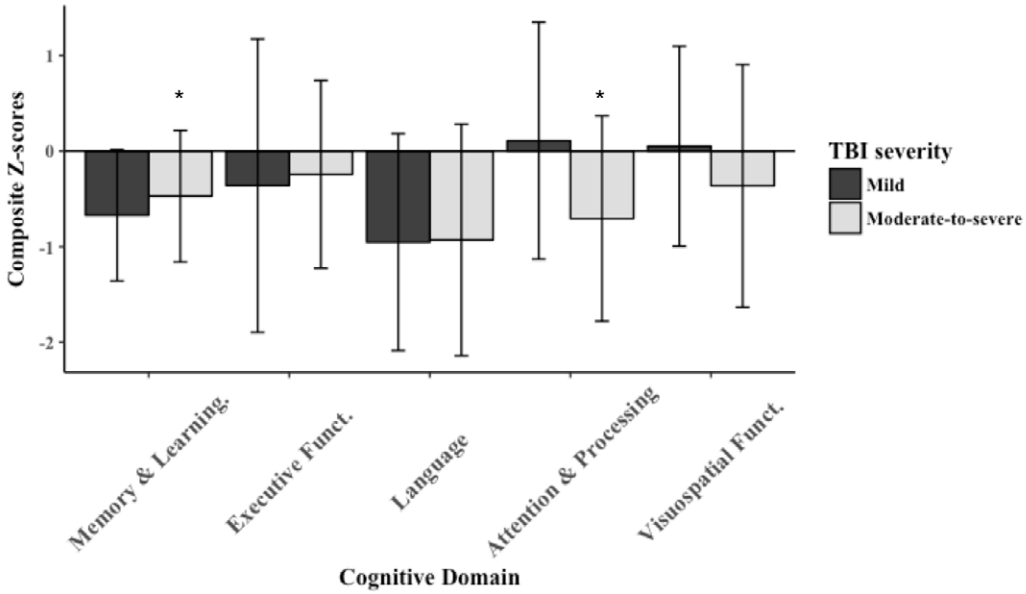


Figure 2. Neuropsychological profile of TBI cohort. Results are compared against normative data from the HC. The graph represents mean cognitive domain composite scores and *p<0.05 after controlling for baseline differences between the cohorts. Bars represent +/- standard deviation.

No differences were detected between the mTBI group and controls, though the study may be underpowered to address this question. Interestingly, all three TBI severities had a significantly lower level of premorbid intellectual functioning than controls and also completed fewer years of education. Whilst the explanation for this reduced premorbid intellectual functioning is unknown, it is a characteristic that accounted for many variations between the groups in cognitive performance, and was subsequently controlled for. The TBI cohort was found to endorse a greater number of psychiatric comorbidities, including: anxiety, somatisation, obsessive-compulsive behaviours, interpersonal sensitivity, depression, hostility, paranoid ideation, psychoticism, lifetime and current PTSD symptomology, and poor-quality sleep. Rating the severity of psychiatric disorders, such as PTSD, enabled us to untangle deficits due to these comorbidities, and those due to TBI. This was complemented by earlier work by the team (Elias et al., 2019).

Interestingly, despite the presence of these comorbidities, the TBI cohort did not report a higher level of combat exposure than controls. However, the prevalence of psychiatric disorders has been reported as higher amongst those who have suffered a TBI than the general population (Ashman et al., 2004; Koponen et al., 2002), which may account for this finding. Finally, the TBI cohort not only had a higher BMI than controls but the group also contained a larger proportion of individuals reporting a prior diagnosis of sleep apnoea. This difference in BMI is likely due to the psychological distress suffered by those in the TBI cohort, which subsequently increased risk of sleep apnoea.

Cognitive domains particularly vulnerable to a TBI include memory and learning, attention and processing speed and executive function (Belanger & Vanderploeg, 2005; Carroll et al., 2004; Frencham et al., 2005; Schretlen & Shapiro, 2003), with more severe injuries resulting in additional motor and complex language deficits (Levin, 1993; Millis et al., 2001). Our findings complement and extend prior work by providing objective evidence demonstrating deficits in memory and learning, and attention and processing speed, decades after moderate-to-severe TBI in veterans. Whilst diminished executive function was not observed in the TBI group, this may reflect the fact that only one neuropsychological test was used to measure executive function, in a bid to keep the testing session succinct. Further testing may have revealed some impairment in this area. This is also true for the language domain, measures for which were sensitive to Alzheimer's type of dementia-related processes but not necessarily sensitive or comprehensive enough for TBI-related impairment. Cognitive decline observed amongst survivors of TBI has been argued to be qualitatively different from the early signs of AD (Himanen et al., 2006; Senathi-Raja et al., 2010). Given the reported transient nature of mTBI symptoms (Belanger & Vanderploeg, 2005), it is perhaps unsurprising that cognitive deficits were not observed in this group. Discrepancies with some

prior work may be due to methodological factors, as those that reported cognitive impairment years after mTBI relied upon self-rated questionnaires and hospital reports, and did not conduct a thorough neuropsychological examination of patients (Dagher et al., 2013; Guskiewicz et al., 2005; Guskiewicz et al., 2003).

Based on previous research, both in the acute and chronic timeframes after TBI (Belanger et al., 2005; Belanger & Vanderploeg, 2005; Levin, 1993; Schretlen & Shapiro, 2003), it is likely that the impairments observed amongst the moderate-to-severe TBI group in memory and learning, attention and processing speed, is a direct result of the injury, likely present soon after the event. These deficits observed amongst the more severe injuries are likely to indicate diffuse axonal injury, as previously suggested (Spitz et al., 2013), and do not represent a neurodegenerative process. However, given the cross-sectional nature of this study, it is not possible to confirm these observations and a longitudinal study is required to investigate if these deficits get worse with age. It is unclear if the lower level of premorbid functioning observed in the TBI cohort is related to injury or an unintentional selection bias, however, it highlights the importance of controlling for such variation in future studies, in a bid to isolate the impact of TBI. Other confounders that must be carefully considered include PTSD and other psychiatric disorders, which commonly occur alongside military-related TBI. This makes studying TBI amongst veterans particularly complex and redacts from the applicability of results to other TBI cohorts. With this in mind, the homogenous group of veterans assessed in this study, whilst unique in some respects, enables the results to be applied directly to serving personnel affected by TBI. The study was further strengthened by comparing the control cohort, a group of healthy veterans who had all undergone combat exposure, to civilian controls from the AIBL study. This ensured there was no masking of any differences that could be evident if the TBI group were compared to a non-trauma-exposed cohort.

Limitations

The current study has some limitations. Unfortunately, medical records were not available to confirm TBI severity, therefore, the study team were reliant upon self-reporting, which may have led to an under or over-estimation of injury severity. In addition, sample sizes were relatively small, which limited further investigation into the presence of a dose-response relationship between injury severity and cognitive deficits. These modest sample sizes may have accounted for the lack of findings when the TBI group was divided by injury severity, and restricted group separation by injury mechanism and further exploration of the relationship with psychiatric comorbidities. This resulted in a mixture of single and repetitive injuries in the mTBI group, and blast and penetrating injuries amongst the more severe TBIs. It was not possible to exclude participants with TBI in addition to PTSD, and this may limit the applicability of these findings to a number of other TBI cohorts. Finally, whilst this cross-sectional study has given a snapshot of later-life cognitive function many years following TBI, a longitudinal study of these veterans is necessary to confirm whether TBI has accelerated an ageing process.

CONCLUSION

The long-term sequelae of TBI amongst veterans is not only important to understand, but also extremely complex. The results from this study provide an interesting insight into the long-term effects of TBI amongst Vietnam war veterans many years after injury. Deficits in memory and learning, attention and processing speed amongst moderate-to-severe injuries are suggestive of long-term damage likely due to diffuse axonal injury at the time of insult, but unlikely to reflect typical AD pathological neurodegeneration. In addition to the higher incidence of sleep apnoea, increased BMI and psychiatric symptomatology amongst those with TBI, the results from this study highlight an ageing population of veterans who face substantial and complex medical challenges as a result of their service. Future work will include follow-up neuropsychological assessments of this cohort, alongside neuroimaging to further investigate the long-term effects of TBI.

DECLARATIONS

Co-author contributions: FL completed the neuropsychological assessment, and AE completed psychiatric evaluations. FL, JLP and MH contributed towards manuscript preparation.

Funding: This study was supported by the United States Army Medical Research and Development Command, award number W81XWH-14-1-0418, and the Sir Edward 'Weary' Dunlop Medical Research Foundation. In addition, the authors acknowledge the financial support of the Yulgilbar Alzheimer's Research Program, and the Cooperative Research Centre (CRC) for Mental Health. The CRC programme is an Australian government initiative. The funding sources had no input into the design of the study, analysis of the data or writing of the manuscript.

Ethical approval: Ethical approval was obtained from the Austin Health Human Research Ethics Committee (Ref: H2013/04947).

Informed consent: All participants provided informed consent prior to participating, and there were no direct incentives offered for participation. The consent process included a 45-minute face-to-face discussion with a member of the research team to ensure participants understood the nature of the study as well as any risks or benefits.
Conflict of interest: There is none to declare.
Study registration: N/A. Registration of observational studies is not mandatory in Australia.

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