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Diminished white matter integrity four decades after traumatic brain injury in Vietnam War veterans

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Abstract

Objective: Traumatic Brain Injury (TBI) and Post-Traumatic Stress Disorder (PTSD) are common in military veterans and have been associated with an increased risk of dementia. The mechanisms contributing to this relationship are poorly understood.

Main aim: This study investigated the effect of TBI and PTSD on white matter (WM) integrity, hippocampal and cortical volume within a cohort of Vietnam veterans.

Materials and methods: 87 male veterans in total. There were 31 with TBI (aged 69.0 ± 2.5 years), 35 with PTSD (aged 69.5 ± 2.6 years) and 21 controls (aged 70.1 ± 4.9 years) underwent 3Tesla Magnetic Resonance Imaging (MRI). The TBI cohort included 12 mild, 13 moderate and six severe injuries. WM integrity was assessed using tract-based spatial statistics and region-specific analyses of fractional anisotropy (FA) images. Automated processing of T1-weighted magnetisation-prepared rapid gradient-echo (MPRAGE) images resulted in hippocampal volumes and whole-brain cortical thickness estimation. Analyses were adjusted for IQ, Body Mass Index (BMI) and psychiatric comorbidities.

Results: The moderate-to-severe TBI group had significantly lower FA than controls in the genu ($F(3,36)=8.81$, $p<0.05$, partial $\eta^2 = 0.17$), and body ($F(3,36)=4.39$, $p<0.05$, partial $\eta^2=0.14$) of the corpus callosum, as well as in global WM ($F(3,36)=5.35$, $p<0.05$, partial $\eta^2=0.13$). The PTSD FA values did not differ from controls and neither the TBI nor PTSD group differed significantly from controls in hippocampal volume nor cortical thickness in Alzheimer's disease vulnerable regions.

Conclusion: These findings suggest that the widely reported loss of WM integrity observed after moderate to severe TBI persists throughout life but is not associated with hippocampal or grey matter atrophy after four decades. No PTSD-related structural or FA change was observed.

Keywords

Traumatic brain injury, PTSD, Veterans, Dementia, White matter integrity, MRI

INTRODUCTION

TBI is a major cause of lifelong disability worldwide, with males more than twice as likely to suffer a TBI (Frost et al., 2013), and up to two-thirds of sufferers acquiring their injury before the age of 25 (AIHW, 2007). Another population especially at risk of TBI includes members of the armed forces, who even whilst not deployed have a TBI rate 1.6-2.5 times greater than that of civilians (Ommaya et al., 1996). Amongst those deployed to contemporary war zones, advances in protective equipment and battlefield medical treatment have resulted in increased survival rates (Vasterling et al., 2009) and consequently, personnel are more likely to return home with injuries such as TBI. Within the combat environment, TBI rarely occurs alone, and it

has been argued that the co-occurrence of PTSD is what discriminates military from civilian TBI. For example, in a study of military deployment-related TBI, loss of consciousness (LoC) was associated with a 25% increase in soldiers meeting criteria for PTSD in comparison to soldiers with other injuries (Hoge et al., 2008). Over 350,000 US military service personnel have been diagnosed with a TBI since 2000 (VA, 2010), and PTSD is estimated to affect approximately 23% of veterans returning from the most recent Iraq conflicts (Fulton et al., 2015).

Both TBI and PTSD have been associated with a number of later-life sequelae, including major depressive disorder, anxiety, substance use disorder, cognitive deficits, hypertension, diabetes, obesity, and inflammation (Ahmadi et al., 2011; Hoofien et al., 2001; O'Donnell et al., 2004; Shalev et al., 1998; Vasterling et al., 2006). Of increasing concern is the mounting evidence that both TBI and PTSD may increase the risk for dementia. Epidemiological studies report that veterans with a TBI are 2-4 times more at risk of Alzheimer's disease (AD) than controls (Plassman et al., 2000), whilst PTSD has been reported to result in a two-fold increased risk of AD and other dementias (Yaffe et al., 2010). Further evidence comes from post-mortem studies that have found the major biomarkers of AD, β-amyloid plaques and neurofibrillary tangles, in nearly 30% of individuals up to 47 years after TBI, contrasting the minimal pathology observed in controls (Johnson et al., 2012; Roberts et al., 1994). Other studies report that TBI reduces time-to-onset of AD in those already at risk of developing the disease (Nemetz et al., 1999), and carriers of the apolipoprotein e4 (APOE e4) allele, an established risk factor for AD, are reportedly 10-times more at risk of AD after TBI than non-APOE e4 carriers (Mayeux et al., 1995). Complementing this work is an MRI study of Iraq and Afghanistan veterans that showed reduced cortical thickness in AD vulnerable regions amongst those who were at high genetic risk of the disorder and also had suffered a TBI (Hayes et al., 2017).

Structural MR imaging is a well-established and non-invasive tool for investigating morphological changes of neurodegeneration (Vemuri et al., 2009), and tissue loss in the hippocampus (Hua et al., 2009; Jack et al., 2004; Morra et al., 2009; Ridha et al., 2008; Thompson et al., 2004), corpus callosum (Elahi et al., 2015; Wang et al., 2006) and entorhinal cortex (Cardenas et al., 2011) correlates with cognitive deficits observed within AD. The hippocampus and corpus callosum are also especially vulnerable to TBI-induced lesions and atrophic change (Anderson & Bigler, 1994; Anderson et al., 1996; Bigler et al., 1997; Gale et al., 1993; Yount et al., 2002). Damage occurs due to the straining and shearing of axons, as the head undergoes acceleration-deceleration forces as well as the harming effects of excitatory neurotransmitters released following neural insult (Povlishock, 1993; Santhakumar et al., 2001). Chronic neuroinflammation following initial injury may also intensify corpus callosum volume loss (Johnson et al., 2013; Johnson et al., 2011), and atrophy may continue for years after injury (Tomaiuolo et al., 2012). Diffusion-weighted imaging (DWI) and post-mortem studies have confirmed abnormalities in the WM of those with TBI, specifically in the corona radiata, body, genu and splenium of the corpus callosum (Johnson et al., 2013; Kumar et al., 2010). However, much of this work investigates moderate-to-severe TBIs, and less is known about the effect of mild TBI (mTBI) or PTSD on risk for AD. There is some evidence from animal models to suggest PTSD-like trauma may drive AD pathogenesis (Justice et al., 2015) and generalised WM atrophy, including diminished integrity in the corpus callosum, which has been reported in those with chronic PTSD (Schuff et al., 2011; Villarreal et al., 2004; Villarreal et al., 2002). Reduced hippocampal volume has frequently been reported in studies of PTSD (Bonne et al., 2008; Bremner et al., 1995; Felmingham et al., 2009; Nutt & Malizia, 2004; Wang et al., 2006; Wang et al., 2010) however, it is not clear if this is a marker of neurodegeneration, a neurotoxic consequence possibly due to sustained overproduction of cortisol (Felmingham et al., 2009; Nutt & Malizia, 2004) or a predisposing factor for the development of PTSD (Gilbertson et al., 2002).

Main Aim And Hypothesis

A limitation of previous studies in this field has been the challenge of assembling a large cohort to study the long-term effects of TBI. We previously demonstrated cognitive deficits amongst Vietnam war veterans with PTSD (Elias et al., 2019), and with TBI, 30-50 years after injury (Cummins et al., in press). Therefore, the principal objective of the current study was to bridge the gap in the literature and build on this work, to determine the long-term effects of TBI and PTSD on WM integrity, hippocampal volume and cortical thickness in the same sample of Vietnam war veterans. A secondary aim was to determine the association between these structural effects and cognitive impairment in TBI. We hypothesised that when compared with a military, age-matched, control cohort, veterans with TBI or PTSD would exhibit diminished WM integrity in the corpus callosum, reduced grey matter volume in the hippocampus and reduced cortical thickness in AD vulnerable regions.

METHODS

Participants

Ex-military service personnel 60-85 years old (M=69.55, SD=3.22), were recruited through 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 Austin Health, Melbourne, Australia. Participants were allocated into one of three cohorts; the healthy control group, the TBI group or the PTSD group. To be included in the study, participants had to be free of any prior diagnosis of bipolar affective disorder, schizophrenia, dementia, mild cognitive impairment, any substance use disorder within the last five years, any immediate MRI contraindication, any major, unstable medical condition, and had not previously participated in clinical trials involving an amyloid targeting therapy.

To be included in the TBI cohort, participants had to have sustained at least one TBI between 16-40 years old. TBI severity was assessed based on criteria set down by the US Department of Defense (DoD) and Department of Veterans' Affairs (VA) – Management of Concussion/ mTBI Working Group, 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. Those with penetrating injuries were excluded. It was not possible to exclude participants with PTSD in addition to TBI, therefore the TBI group consisted of veterans with and without PTSD. Participants in the PTSD group were required to report no history of TBI, and meet a diagnosis of current, or past, service-related, PTSD. To be included in the control group, participants were required to report no prior history of TBI or PTSD.

Ethical approval for this study was obtained from the Austin Health Human Research Ethics Committee, the Human Research Protection Office of the US Army Medical Research and Material Command, and the Department of Veterans' Affairs Ethics Committee. All participants provided informed consent prior to participating, and there were no direct incentives offered for participation.

Procedure & Materials

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

Cognitive Functioning

The neuropsychological functioning of this cohort is described elsewhere (Cummins et al., in press) however, in brief, we 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 (Rey, 1964), the Rey Complex Figure Test (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-

Table 1. Criteria used by the US Department of Defense/Veterans' Affairs to categorise head injury severity.

	Mild	Moderate	Severe
Loss of consciousness (hours)	0 - 0.5	0.5 - 24	>24
Alteration of consciousness	A moment - 24 hrs	>24 hrs	>24 hrs
Post-traumatic amnesia (day/s)	0 - 1	1 - 7	>7
Glasgow Coma Scale	13 - 15	9 - 12	3 - 8
Structural imaging	Normal	Normal/abnormal	Normal/abnormal

Note. For moderate and severe head injuries, alteration of consciousness is based on additional criteria.

III), the Digit Span Task (Kaufman & Lichtenberger, 1999), the Clock Drawing Task (Kaplan, 1983), the Mini-Mental State Exam (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 Evaluation

The psychiatric evaluation consisted of several measures to assess PTSD severity, drug and alcohol use, sleep quality, overall psychological well-being and medical history. A PTSD diagnosis was allocated based on the Clinician Administered PTSD Scale (CAPS) (Aker et al., 1999) lifetime and current score, indicative of lifetime, and current PTSD severity. A lifetime CAPS score of over 40 was indicative of the individual having had 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/substance use, and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), sleep quality and disturbance. A score over five on the PSQI was indicative of poor sleep quality. 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 (CES) (Lund et al., 1984) to classify the level of wartime stressors experienced.

Image Acquisition and Processing

Participants underwent a 3-Tesla Siemens Trio whole-brain MRI scan, located at the Florey Institute of Neuroscience and Mental Health. A three-dimensional (3D) T1 MPRAGE sequence was acquired with the following parameters: FoV = 260 x 256 mm, 160 slices, 1.0 x 1.0 x 1.2 mm voxels, TR = 2300 ms, TE = 2.98 ms, flip angle = 9°. The 3D fluid-attenuation inversion recovery (FLAIR) images were obtained to assess WM hyperintensity (WMH) burden, and parameters were as follows: FoV = 234 x 250 mm, 176 slices, 0.976 x 0.976 x 0.9 mm voxels, TR = 6000 ms, TE=420 ms, flip angle = 120°. Diffusion-weighted images (DWI) were acquired for assessment of WM integrity. The following parameters were used: directions = 60, b value = 3000 s/mm2, FoV = 239 x 239 mm, 2.307 x 2.307 x 2.3 mm voxels, TR = 7600 ms, TE = 110 ms, flip angle = 90°, phase encoding along anterior-posterior. A single diffusion-weighted single image was acquired using the same parameters but reverse phase-encoding direction to assist image distortion correction.

Diffusion image analysis

Preprocessing of DWI images included intra-volume motion artifact removal, correction for head motion and eddy currents (Andersson & Sotiropoulos, 2016), bias field correction and skull stripping using FSL (Jenkinson et al., 2012). FA images were estimated from the preprocessed diffusion data using iteratively reweighted linear least squares (Veraart et al., 2013). Whole-brain group-wise analyses of FA images were carried out using the tract-based spatial statistics (TBSS) pipeline (Smith et al., 2006). In this pipeline, all FA images were first projected onto a common space to create a mean FA skeleton representing the centres of all tracts common to the group. Voxel-wise cross-subject statistics, correcting for covariates of age and BMI, were performed and corrected for multiple comparisons using threshold-free cluster enhancement with 5,000 random permutations.

The region of interest (ROI) analyses of FA images were conducted using the John Hopkins University (JHU) White Matter Parcellation Atlas as described in (Hayes et al., 2015). The ROIs constrained to the common WM tracts were defined based on the combination of the JHU atlas and mean FA skeleton mask, and were then transformed back into each participant's native image space. For each participant, the mean FA values were computed for corpus callosum and its subregions (the body, genu and splenium). These ROIs were hypothesised to be most vulnerable to TBI of varying severities and were in line with previous work.

Structural image analysis

The T1 weighted MPRAGE images for all participants were first segmented into grey matter, WM and cerebrospinal fluid using an implementation of expectation-maximisation algorithm (Van Leemput et al., 1999). Partial tissue classification and cortical thickness estimation were performed using CurAIBL (Acosta-Cabronero et al., 2011; Bourgeat et al., 2015). The hippocampus ROI was extracted using a multi-atlas approach based on the Harmonized Hippocampus Protocol (Boccardi et al., 2015). Cortical volumes were normalised by total intracranial volume (TIV). The WMH volume was quantified from FLAIR images using the HyperIntensity Segmentation Tool (Manjón et al., 2016), and subjects with excessive WMH burden (> 15 ml) were excluded in the following analyses.

Other measures

Participants self-reported their age, years of education, military-service history, cigarette smoking status and

medical history. The participants' height and weight were obtained and their BMI calculated and APOE genotype was determined by direct sequencing. The WTAR (Venegas & Clark, 2011) was employed as an estimation of premorbid intellectual functioning. The WTAR is a word pronunciation test, a type of measure reported to be relatively unaffected by neuropathological change (Russell, 1980) and reported to provide an accurate estimate of premorbid intellectual functioning in a variety of cognitively impaired populations (Wechsler, 2001; Dwan et al., 2015; Hanks et al., 2008; McGurn et al., 2004).

Statistical Analysis

An analysis of variance was used to compare the three groups on continuous demographic and clinical data. Percentages were calculated for categorical variables, which were then compared using chi-square. To investigate if the TBI or PTSD cohorts had reduced FA in the corpus callosum and subregions, or reduced hippocampal

Table 2. Demographics and participant characteristics.

	HC$_a$ (*n*=21)	TBI$_b$ (*n*=31)	PTSD$_c$ (*n*=35)	*df*	*F*	*p*
Demographics (Mean (SD))						
Age	70.1 (±4.9)	69.0 (±2.4)	69.5 (±2.6)	2	1.4	0.249
Years of education	13.3 (±2.7)	11.1 (±2.7)	11.7 (±3.0)	2	4.1	*0.020*$^{*}_{a\text{-}b}$
IQ	112.6(±4.9)	104.3 (±7.1)	106.2 (±7.5)	2	9.9	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
Body Mass Index	27.2 (±4.2)	30.4 (±4.5)	29.7 (±4.2)	2	3.7	*0.030*$^{*}_{a\text{-}b}$
Combat Exposure Scale	9.8(±7.6)	13.3 (±11.2)	16.5 (±8.8)	2	3.0	0.056
TBI history						
Mild TBI		38.7%				
Moderate TBI		41.9%				
Severe TBI		19.5%				
Age at TBI		23.5 (±4.9)				
Years since most severe TBI		44.6 (±4.9)				
Psychiatric history						
CAPS lifetime score	8.9 (±8.6)	54.0 (±28.1)	73.4(±14.5)	2	71.8	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c,\ b\text{-}c}$
Current psychiatric symptoms						
CAPS current score	6.4 (±6.5)	28.7 (±20.8)	44.0(±19.9)	2	28.5	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c,\ b\text{-}c}$
SLC-90						
Somatisation	54.7 (±11.8)	62.7 (±12.1)	65.9 (±10.0)	2	6.6	*0.002*$^{*}_{a\text{-}b,\ a\text{-}c}$
Obsessive-compulsive	54.8 (±12.3)	66.0 (±13.4)	71.9 (±9.7)	2	14.0	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
Interpersonal sensitivity	48.1 (±8.0)	62.6 (±12.5)	67.9 (±10.3)	2	22.8	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
Depression	51.7 (±11.6)	65.42 (±10.7)	70.7 (±9.0)	2	22.8	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
Anxiety	51.0 (±9.3)	61.6 (±14.4)	69.1(±11.1)	2	14.7	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c,\ b\text{-}c}$
Hostility	51.1 (±10.9)	62.5 (±12.4)	66.6 (±10.5)	2	12.6	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
Phobic anxiety	48.9 (±6.3)	63.4 (±12.2)	67.3 (±11.2)	2	20.4	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
Paranoid ideation	46.2 (±7.6)	57.6 (±13.2)	60.9 (±12.7)	2	10.4	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
Psychoticism	49.9 (±8.8)	62.3 (±11.6)	67.9 (±10.8)	2	18.8	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
Global severity index	51.5 (±13.1)	66.3 (±12.4)	72.1 (±9.4)	2	21.3	*<0.001*$^{*}_{a\text{-}b,\ a\text{-}c}$
PSQI	4.7 (±4.6)	7.5 (±4.1)	8.5 (±4.9)	2	4.5	*0.016*$^{*}_{a\text{-}c}$

Note. HC = healthy controls. TBI = traumatic brain injury. PTSD = post-traumatic stress disorder. IQ = Wechsler Test of Adult Reading US full scale predicted IQ. CAPS = Clinician Administered PTSD Scale. SLC-90 = Symptom Checklist 90-Revised. PSQI = Pittsburgh Sleep Quality Index.

volumes or cortical thickness when compared with healthy controls, a multiple linear regression was used to investigate the influence of covariates on the variables of interest, which 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 (R Core Team, 2016). A p-value of less than 0.05 was deemed statistically significant. The following R packages were installed: *lsr* (Navarro, 2015), *plyr* (Wickham, 2011), *reshape2* (Wickham, 2007), *ggplot2* (Wickham, 2009) and *car* (Weisberg, 2011).

RESULTS

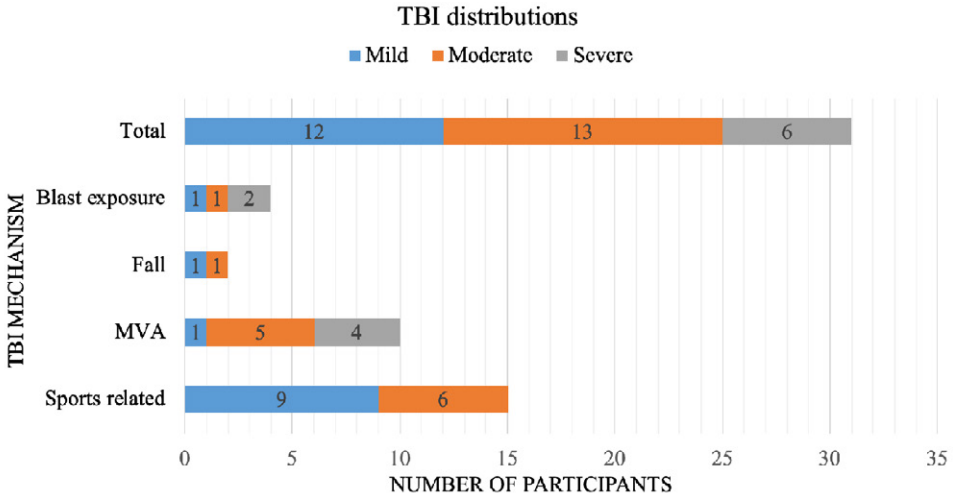
Demographics

There was no significant difference in age or in scores obtained on the CES between the three cohorts. Participants with a TBI had fewer years of education and a higher BMI than controls (see Table 2). Both the TBI and PTSD group had a mild but significantly lower level of premorbid intellectual functioning than the control group. Both the TBI and PTSD cohorts scored significantly higher than controls on all psychiatric measures, including current and past PTSD symptom severity (see Table 2).

Of the 31 participants in the TBI cohort, 12 had suffered a mild injury, 13 moderate, and six severe. The TBI groups did not differ from each other in terms of demographics or medical comorbidities. Injuries were sustained from a variety of mechanisms and further details are included in Figure 1. The average age at injury was 23.5 (± 4.9) years, and the average time since injury was 44.6 (± 4.9) years. The range for time since injury was 30-53 years.

White matter integrity

A whole-brain TBSS analysis, adjusted for age and BMI, revealed significantly decreased FA in moderate-to-severe TBI subjects mainly across the corpus callosum body, splenium and genu, bilateral anterior coronal radiata as well as right posterior thalamic radiation (Figure 2). In contrast, no significant differences in FA were observed between the full TBI cohort and controls or PTSD subjects and controls. A hierarchical linear regression was carried out to investigate the impact of possible confounders on global FA, as well as FA in the genu, body and splenium of the corpus callosum. Results indicated that BMI was a significant covariate and was controlled for in the subsequent analyse. An ANCOVA demonstrated that after controlling for BMI, there were no significant differences in FA values between the three cohorts. Those with mTBI were removed from the analysis to investigate the impact of more severe injuries (n=19) and compared to the control cohort. In contrast to the findings in the full TBI cohort, after controlling for BMI, moderate-to-severe injuries were found to have significantly reduced global FA ($F(3,36) = 5.35$, $p < 0.05$, partial $h^2 = 0.13$), in addition to reduced FA in the genu ($F(3,36)=8.81$, $p<0.05$, partial $h^2 = 0.17$) and body ($F(3,36) = 4.39$, $p < 0.05$, partial $h^2 = 0.14$) of the corpus callosum (Figure 3).



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 30minutes 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 injury mechanisms for TBI cohort

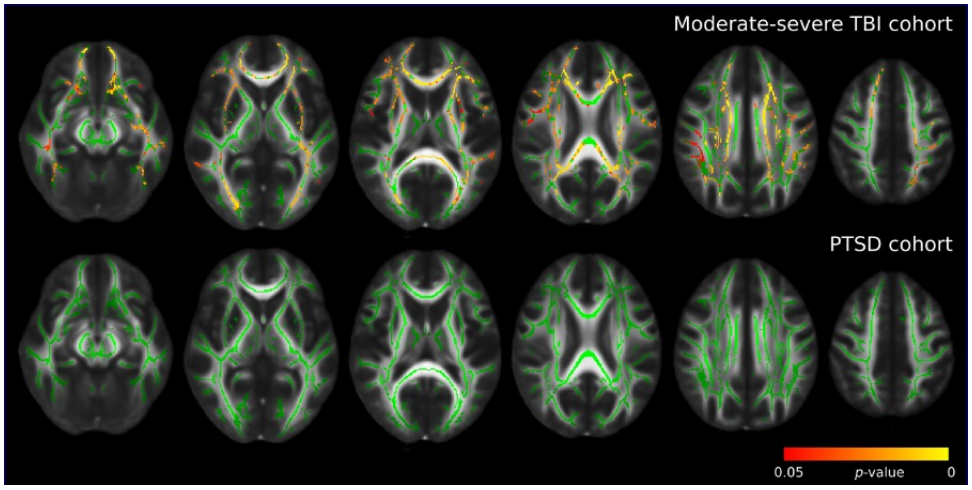


Figure 2. FA TBSS map showing statistically significant differences between TBI and PTSD groups compared to controls. Red-Yellow colour bar represents p-value.

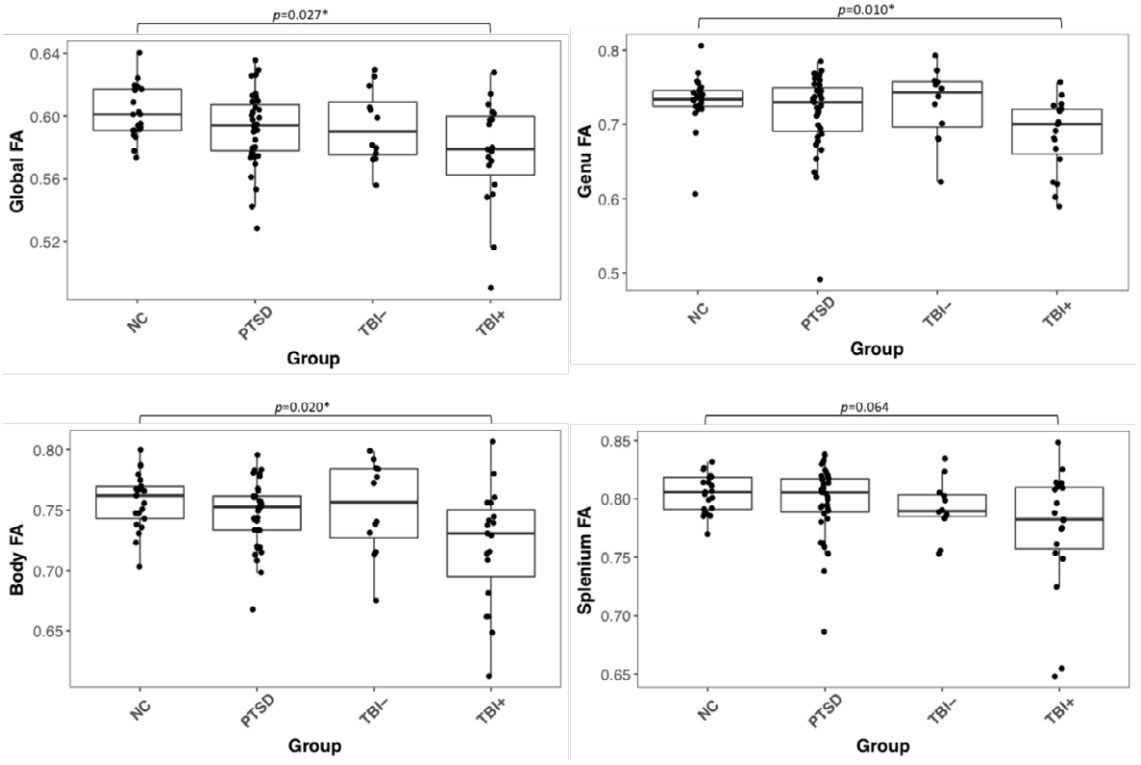


Figure 3. FA values for global white matter, genu, body and splenium of the corpus callosum. Groups consist of NC, PTSD, mTBI (TBI-) and moderate-to-severe TBI (TBI+) cohorts

Hippocampal volumes

Results from a hierarchical linear regression indicated that TIV and premorbid intellectual functioning were significant covariates of hippocampal volumes and were controlled for in the subsequent analyse. An ANCOVA revealed no significant differences in hippocampal volume between the three cohorts when TIV and premorbid intellectual functioning were controlled for. The mTBI were removed from analysis to investigate the effect of moderate-to-severe injuries. An ANCOVA showed there was no significant difference in hippocampal volume after controlling for

premorbid intellectual functioning and TIV (Figure 4).

Cortical Thickness

Multiple linear regression was carried out to investigate the impact of age, years of education, premorbid intellectual functioning, BMI and APOE status on cortical thickness in eight AD specific regions (Acosta-Cabronero et al., 2011; Bourgeat et al., 2015): fusiform gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, frontal lobe, precuneus, hippocampus, parietal lobe. None of the covariates were found to have a significant impact on cortical thickness in any of these regions. Further analysis revealed no significant differences between any of the groups in cortical thickness in any of the eight AD vulnerable regions.

White matter integrity and cognitive functioning

To assess the relationship between memory and learning, and attention and processing deficits amongst the TBI cohort, previously reported (Cummins et al., in press), Pearson product-moment correlation coefficients were computed between global FA values and FA in the genu, body and splenium of the corpus callosum, and composite scores for memory and learning and attention and processing speed. A significant positive correlation was found between memory and learning composites scores and splenium FA (r=0.24, p=0.025), as well as between attention and processing speed and splenium FA (r=0.22, p=0.04). No other significant correlations were observed between FA and cognitive scores. Results are summarised in Figures 5 and 6.

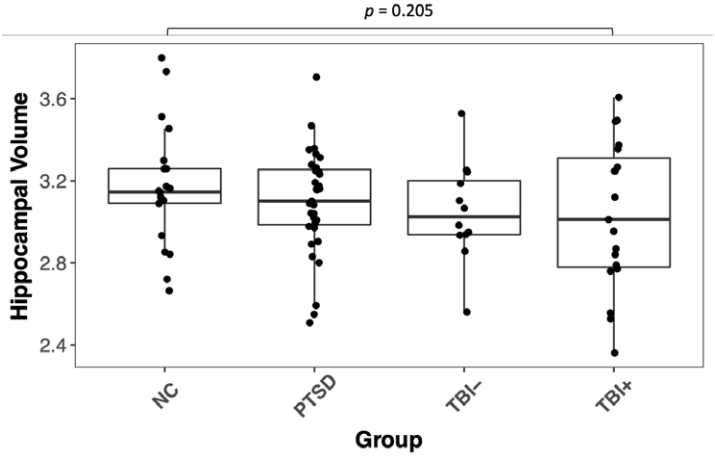


Figure 4. Hippocampal volumes (mm³) averaged across hemispheres. Groups consist of NC, PTSD, mTBI (TBI-) and moderate-to-severe TBI (TBI+) cohorts. Mean and upper and lower quartiles with 95% confidence interval.

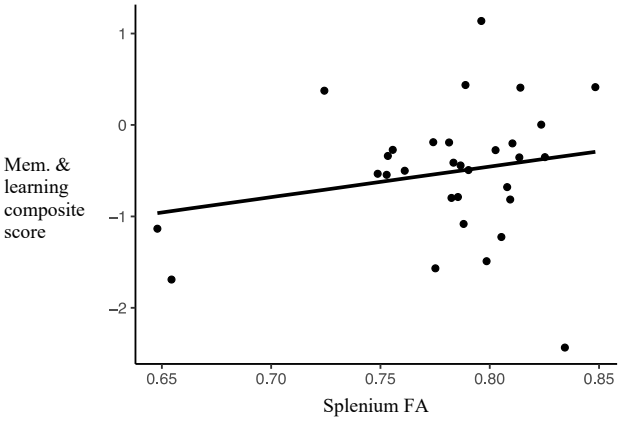


Figure 5. Correlation between TBI cohort memory and learning composite scores and splenium FA values.

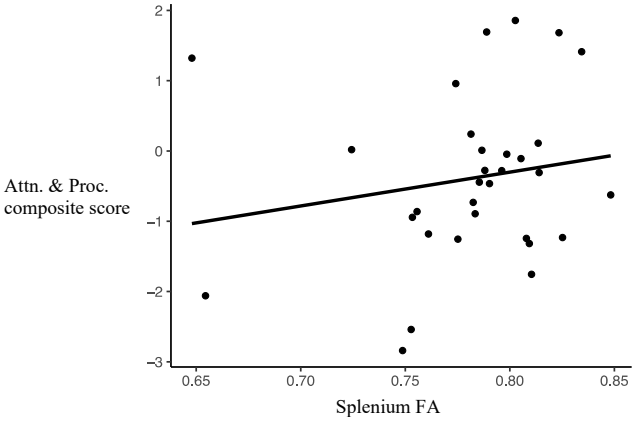


Figure 6. Correlation between TBI cohort attention and processing speed composite scores and splenium FA values.

DISCUSSION

Given the paucity of studies investigating the long-term consequences of TBI and PTSD on brain structure, the main aim of the current study was to examine the extent of WM degradation and neuronal loss in a homogenous cohort of veterans three-to-five decades after injury. A secondary aim was to determine the association between these structural effects and cognitive impairment. We hypothesised that when compared with a military, age-matched, control cohort, veterans with TBI or PTSD would exhibit diminished WM integrity in the corpus callosum, reduced grey matter volume in the hippocampus and reduced cortical thickness in AD vulnerable regions.

Diminished WM integrity in the whole brain and specifically in the corpus callosum subregions genu and body was identified amongst veterans who had suffered a moderate-to-severe TBI. However, no differences were observed between the mTBI and controls nor PTSD and controls. Neither the TBI and the control cohort, nor PTSD and control cohort demonstrated differences in hippocampal volume or cortical thickness.

Corpus callosum

The corpus callosum is especially vulnerable to the overstretching and shearing caused by acceleration and deceleration forces applied to the skull during a TBI. Previous structural MRI and DTI studies have reported corpus callosum volume loss and degradation following moderate-to-severe TBI; however, they have largely examined participants in the acute stages, in the weeks and months following injury (Anderson & Bigler, 1994; Anderson et al., 1996; Bendlin et al., 2008; Kumar et al., 2010; Yount et al., 2002). Whilst Johnson and team (Johnson et al., 2013) reported persistent damage to the corpus callosum up to 18 years after TBI, the time-since-injury within this heterogeneous group varied widely. We have built on and expanded previous work, providing evidence of diminished WM integrity in the genu and body of the corpus callosum only amongst veterans with moderate-to-severe TBI, three-to-five decades after injury. However, the results from the PTSD cohort are in contention with the handful of existing studies (Kitayama et al., 2007; Villarreal et al., 2004) that report reduced volume of the corpus callosum associated with PTSD. Given that these studies have investigated childhood trauma, as opposed to adult, combat-related trauma, it is possible that chronic stress affects the developing brain differently, thus explaining the conflicting results.

Hippocampal Volumes

Neither the TBI nor the PTSD cohort had reduced hippocampal volume when compared with the controls. This is in contrast to past research (Bigler et al., 1997; Gao et al., 2011; Povlishock, 1993). Whilst it was anticipated that the release of excitatory neurotransmitters immediately following TBI (Povlishock, 1993; Santhakumar et al., 2001) may result in long-lasting hippocampal damage, much of the literature was based on the acute period immediately following severe TBI. The range of injuries in the current study, alongside the modest sample size, may have limited the capacity of this study to identify a measurable volumetric difference. The negative findings within the PTSD group are contrasting to some previous research (Bonne et al., 2008; Bremner et al., 1995; Felmingham et al., 2009; Villarreal et al., 2002; Wang et al., 2010), but complementary to others (Golier et al., 2005; Yehuda et al., 2007). Few studies have assessed and controlled for premorbid intellectual functioning, as was the case in the current study. Hippocampal volume and premorbid intellectual functioning are negatively correlated (Andreasen et al., 1993), and it may be this key strength of the study that explains the discrepancies with prior studies.

Cortical thickness

After examining eight regions vulnerable to cortical thinning due to AD, it was found that none of the three groups differed significantly from each other. Whilst this is in contrast to prior research (Lindemer et al., 2013; Michael et al., 2015), it is important to note that the ROIs used for the current study were specific to AD, and varied from those used in previous work.

Other findings

We previously demonstrated cognitive deficits in domains of memory and learning, and attention and processing speed amongst Vietnam veterans with moderate-to-severe TBI (Cummins et al., in press). To understand whether WM injuries were associated with these cognitive deficits, FA values for the corpus callosum subregions and whole-brain FA correlations of FA values with cognitive functioning composite scores were performed. Although WM integrity in the splenium trended towards a difference between the cohorts ($p=0.064$), splenium FA did correlate significantly with cognitive performance in the domains of memory and learning and attention and processing speed. The splenium tissue integrity has previously been shown to be linked to memory impairment in addition to attention disorders (Huang et al., 2015).

Implications

The findings from this study could have significant implications both theoretically and clinically. Epidemiological studies suggest that veterans with TBI and/or PTSD are 2-4 times more at risk of AD and other dementias (Plassman et al., 2000; Yaffe et al., 2010), however, results from this study do not find evidence for this relationship. To account for the epidemiological findings, it is plausible that veterans with TBI and/or PTSD may be at risk of misdiagnosis of AD and other dementias. This could be due to the perceived similarity of cognitive (Bäckman et al., 2005; Cummins et al., in press; Elias et al., 2019), behavioural (Fernández et al., 2010; Fleminger, 2008; Jakupcak et al., 2007; Myers et al., 2012; Warriner & Velikonja, 2006), and somatic (Gormley & Rizwan, 1998; Ketcheson et al., 2018; Kornblith et al., 2020) symptoms associated with TBI, PTSD and AD.

Limitations

Medical records were not available to confirm TBI severity, therefore, we were reliant upon self-reporting, which may have led to an under or overestimation of injury severity. In addition, sample sizes were relatively small, which limited further investigation into the association of imaging parameters and injury severity. These modest sample sizes also restricted group separation by injury mechanism. This resulted in a mixture of single and repetitive injuries in the mTBI group, and blast injuries amongst the more severe TBIs. It was not possible to exclude participants with PTSD in addition to TBI and this may limit the applicability of these findings to a number of other TBI cohorts. The PTSD group all had a history of chronic PTSD, however, not all met diagnostic criteria for current PTSD. Due to recruitment difficulties, it was not possible to recruit only veterans with current PTSD symptomatology. Finally, given the cross-sectional nature of the study, it is not possible to accurately deduce if the reduction in WM was present from the time of injury or if it represents an ongoing process. Therefore, a longitudinal study of these veterans is necessary to determine if TBI has produced a progressive decline in WM integrity.

Future directions

Given the limitations of the cross-sectional nature of the study, future work should endeavour to assess defence personnel soon after injury and across their lifespan, ensuring quality data from longitudinal studies. Research on the current cohort must also be continued to understand if the findings are reflective of a static injury, or if WM damage represents an ongoing process. Further work is also required to understand if veterans with TBI and/or PTSD are more at risk of misdiagnosis of AD and other dementias due to overlapping symptoms.

Finally, this study included an all-male cohort. However, future research should expand to include female veterans in a bid to understand sex differences in the long-term effects of TBI and PTSD, and risk for AD and other dementias.

CONCLUSION

The long-term sequelae of TBI and PTSD is not only important to understand, but also extremely complex. Both TBI and PTSD are an all too common consequence of military service, however, the majority of the literature to date has focused on the immediate aftermath of injuries. This study provides reliable evidence that damage to the whole brain and corpus callosum WM is present many decades after TBI and correlates with injury severity. The absence of WM FA reduction in the PTSD cohort lends support to the hypothesis that this damage is TBI specific.

DECLARATIONS

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

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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: None to declare.
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