

AWARD NUMBER: W81XWH-14-1-0418

TITLE: Tau and Beta-Amyloid Deposition, Micro hemorrhage and Brain Function after Traumatic Brain Injury in War Veterans

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REPORT DATE: December 2017

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE		<i>Form Approved</i> <i>OMB No. 0704-0188</i>	
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1. REPORT DATE December 2017	2. REPORT TYPE Final report	3. DATES COVERED 25 th Sept 2014 - 24 th September 2017	
4. TITLE AND SUBTITLE Tau and Beta-Amyloid Deposition, Micro hemorrhage and Brain Function after Traumatic Brain Injury in War Veterans		5a. CONTRACT NUMBER W81XWH-14-1-0418	5b. GRANT NUMBER 13267002
		5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Prof. Christopher Rowe Ms. Tia Cummins E-Mail: Christopher.rowe@austin.org.au		5d. PROJECT NUMBER	
		5e. TASK NUMBER	
		5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) AND ADDRESS(ES) University of Melbourne Grattan street Parkville Australia VIC 3052		8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSOR/MONITOR'S ACRONYM(S) USAMRMC	
		11. SPONSOR/MONITOR'S NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited			
13. SUPPLEMENTARY NOTES			

14. ABSTRACT

Background:

Studies suggest an increased risk of Alzheimer's disease (AD) after traumatic brain injury (TBI). However, this is largely based on retrospective reports and clinical diagnosis without biomarker confirmation. The development of brain imaging techniques for in-vivo examination of tau, amyloid and structural integrity now allows study of the chronic effects of TBI and its relationship to AD.

Specific Aims:

1. To determine if Vietnam War veterans with TBI are more likely to have positive AD biomarkers such as beta-amyloid or tau deposition on PET scans than veteran controls.
2. To determine the relationship between the severity, location and timing of TBI to the extent of positive markers for tau and beta-amyloid.
3. To establish a cohort for long-term study to confirm prognostic significance.

Study Design:

A case control longitudinal study of the pathological and neurodegenerative effects of TBI in Australian veterans of the Vietnam war. Persons with an existing diagnosis of mild cognitive impairment or dementia were excluded.

Results:

Over 3 years, 40 veterans with TBI (68.0 ± 2.5 yrs), 55 with PTSD (69.5 ± 2.6 yrs) and 32 with no history of TBI or PTSD (70.1 ± 5.3 yrs) were recruited into the study. The TBI cohort included 15 mild, 16 moderate, and 9 severe TBI. The majority of TBI were due to contact sport or motor vehicle accidents during the time of active military service. After adjustment for identified covariates, veterans with moderate-to-severe TBI performed significantly worse than controls on composite measures of memory and learning ($M = -0.55 \pm 0.69$, $t(67) = 2.86$, $p=0.006$, $d=0.70$) and attention and processing speed ($M = -0.71 \pm 1.08$, $t(52) = 2.53$, $p=0.014$, $d=0.69$). There were no differences in cognitive performance between veterans with mild TBI and controls. Veterans with PTSD did not show significant cognitive deficits after correction for covariates. Neither TBI or PTSD cohorts showed hippocampal or gray matter reduction nor increased amyloid or tau binding compared to controls. Moderate to severe TBI showed reduced white matter integrity as measured on MRI by fractional anisotropy (FA), especially in the corpus callosum, and medial temporal hypometabolism on FDG PET.

Conclusions:

The findings do not support a substantially increased risk of Alzheimer's disease after TBI or with chronic PTSD as previously suggested by retrospective clinical studies. However, post hoc power analyses based on scan results in the controls indicate the study had insufficient sample size to exclude a mild increase in AD biomarkers and therefore long term AD risk. A larger cohort study is required to more confidently exclude increased prevalence of AD biomarkers after TBI. Given the difficulty recruiting large numbers of veterans in the target age range with TBI, it would necessary to include civilian TBI participants in a larger study. Longitudinal follow-up is required to determine if the cognitive deficits, the reduced FA in white matter and the medial temporal lobe hypometabolism are due to progressive non-AD related neurodegeneration and could lead to dementia or are a static consequence of direct TBI.

15. SUBJECT TERMS					
None listed					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER <i>(include area code)</i>
Unclassified	Unclassified	Unclassified	Unclassified	21	

Standard Form 298 (Rev. 8-98)

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1. Introduction

The project utilized tau, amyloid and FDG PET imaging, and MRI as well as clinical and neuropsychological tools to identify war veterans at risk of Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) as a result of traumatic brain injury (TBI) sustained during military service.

Specific aims:

1. To determine if veterans with TBI are more likely to have markers of AD or tau based disorders such as CTE.
2. To determine the relationship between the severity of TBI to the extent of positive markers for tau and beta-amyloid and the extent of chronic damage including white matter disruption, microhaemorrhage, brain hypometabolism and atrophy, and cognitive impairment.
3. To establish a cohort for long-term study to confirm the prognostic significance of our findings.

2. Keywords

Traumatic Brain Injury, Alzheimer's, Tau, Beta Amyloid, PET, 7T-MRI

3. Accomplishments

Two PhD students, one a psychiatrist (Alby Elias BMBS, FRANZCP) who concentrated on the impact of PTSD and has undertaken the PhD studies on a part-time basis, and the other a psychologist (Tia Cummins BSc) who focused on TBI and was a fulltime PhD student, worked on this project. Both have completed manuscripts reviewing existing literature and on cognitive, MRI, and PET findings. Ms. Cummins has submitted a PhD thesis for examination.

One hundred and twenty seven Australian Vietnam war veterans were recruited into the study: 40 veterans with a TBI, 55 veterans with PTSD, and 32 veteran controls. Data has been analysed and presented at major international meetings and submitted for publication.

De-identified data continues to be uploaded to the FITBIR data centre for the use of approved researchers world-wide. Estimated completion: Late 2018. The FITBIR data upload has to be done manually and has proven very slow and laborious. A data entry person has been employed one day per week on this for 3 years and still has much work to do. FITBIR upload was imposed post award of the grant and so there was no budget for it. This process needs to be reviewed by USAMRMC and better automated.

The cognitive data showed that after adjustment for age, premorbid intellectual functioning and psychiatric co-morbidities, veterans with moderate to severe TBI performed significantly worse than controls on

composite measures of memory, learning, attention and processing speed. There were no differences in cognitive performance between veterans with mild TBI and controls.

MR image analysis (cortical thickness, white matter tract integrity, microhemorrhage at 3T and 7T) is ongoing but completed work on brain volumes found no reduction in hippocampal or other brain regions in TBI. Analysis of white matter tract integrity found loss of FA signal generally and especially in the corpus callosum in the moderate to severe TBI subjects but no changes in mild TBI.

Analysis of the PET data found no differences between veteran controls and the TBI cohort in levels or distribution of amyloid plaques or tau aggregates. FDG (brain metabolism marker) uptake was reduced in the medial temporal regions in the TBI cohort. These preliminary findings suggest that whilst TBI is associated with later-life cognitive deficits, these deficits are not associated with AD pathology.

Power analysis conducted based on the findings in the veteran control cohort showed that the TBI sample size was not sufficient to reliably exclude differences of 0.5 standard deviation or less (i.e. mild to moderate effect size). The PET data will be combined with that obtained by the ADNI DOD veterans study to reduce the risk of false negative findings of mild to moderate degree. To this end, the PET data has been exchanged with Susan Landau of the ADNI DOD Imaging core for independent processing and cross validation before merging of the data sets.

Follow-up of the veteran controls and TBI cohorts has commenced with the interval between assessments ranging from 2-3 years. Though beyond the scope of this grant, PET imaging is being repeated with new, more sensitive tracers for amyloid and tau (F-18 NAV4694 and F-18 MK6240 respectively). These newer tracers have superior imaging characteristics and sensitivity than the tracers available when the study was originally designed. This may increase the ability to detect mild to moderate differences due to TBI if any exist.

What opportunities for training and professional development did the project provide?

PhD candidate and study coordinator, Tia Cummins, presented data at the Australasian Neuroscience Society conference, in Hobart, Australia, at the 2017 Alzheimer's Association International Conference, in London, UK, the 2017 Frontiers in TBI conference in London, and the 2018 Alzheimer's Association International Conference in Chicago. Ms Cummins also visited Brisbane, Australia on a number of occasions to collaborate with the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in MR image analysis.

PhD candidate Dr Alby Elias attended and presented data at the 2017 Alzheimer's Association International Conference, in London, and at the 2017 American Psychiatric Association annual meeting, in Atlanta, USA.

How were the results disseminated to communities of interest?

Data was presented at National and International meetings as listed above plus at the 2017 International Conference on Alzheimer's Disease and Parkinson's Disease.

Publications are pending and will be distributed to the veterans organizations that assisted with recruitment, relevant government departments and the participants.

What do you plan to do during the next reporting period to accomplish the goals and objectives?

- Not applicable as this is the final report. However, data merge with ADNI Veterans study and follow-up assessments of the cohorts are underway. FITBIR data entry continues.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

The study provides evidence that TBI does not result in an increase in the neuropathological markers of AD 40 years post injury. This adds to a growing body of biomarker evidence that AD is not the cause of the reported increase in dementia after TBI. We are now undertaking a study of civilian persons several decades after moderate to severe TBI from motor vehicle accidents to further evaluate this question of TBI predisposing to AD.

What was the impact on other disciplines?

The study also found no increase in AD biomarkers in war veterans with chronic PTSD 40 years post the PTSD trigger event.

It also showed that Vietnam veterans with PTSD or TBI have impaired cognitive test scores compared to Vietnam veteran controls but that the majority of this difference is due to baseline lower IQ estimated from the Weschler Test of Adult Reading.

Our findings reinforce the need for correction of data for baseline intelligence and education and all other potential confounding factors such as age and depression. Veteran controls, and probably control cohorts in general, recruited by advertisement are likely to be more educated, altruistic, community engaged and healthy than disease cohorts and consequently perform better on cognitive testing and other measures.

What was the impact on technology transfer?

Due to the development of methods throughout the current study, the investigators have been invited to join consortia investigating traumatic brain injury, and its impact on risk for dementia.

What was the impact on society beyond science and technology?

It is still too early to tell. If ADNI veterans and other AD biomarker studies (including our on-going AIBL Veterans and new MVA studies) continue to show no relationship to TBI, there may be a reduction in community concern over the long term impact of TBI on the brain. This could affect sporting and professional guidelines and practice or direct research towards none-AD related neurodegeneration post TBI and markedly different treatment.

5. Changes / problems

Changes in approach and reasons for change

Recruitment of veterans proved arduous and slow. Consequently our future TBI research will include civilian cohorts of motor accident and sporting related head trauma. We have also changed our PET tracers for amyloid and tau as the newer tracers should increase the likelihood of detection of mild to moderate changes (i.e. increase binding by 0.2-0.5 standard deviation of control group binding) if present.

Actual or anticipated problems or delays and actions or plans to resolve them

It has been difficult recruiting veterans with a history of TBI, as well as veteran controls. The request to place all data in FITBIR after the grant was awarded but without extra funding proved onerous, requiring the employment of a part-time data entry person for several years.

Changes that had a significant impact on expenditures

There was an increase in staffing costs due to the extended duration of recruitment required to reach acceptable study numbers and the need for a FITBIR data entry person. Consequently the project has run over budget.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6. Products

Publications

T.L. Cummins, A. Elias, F. Lamb, J.L. Ponsford, M. Hopwood, F., V. L. Villemagne, C. C. Rowe. *Long-term neuropsychological sequela of Traumatic Brain Injury in Australian Vietnam war veterans.* **In Review.**

A. Elias, T.L. Cummins, M. Hopwood, J.V. Rosenfeld, V. Doré, F. Lamb, R. Williams, V.L. Villemagne, C.C. Rowe. *Long-term cognitive impairment in Vietnam veterans.* **In Review.**

Award No: W81XWH-14-1-0418 **PI:** Professor Chris Rowe **Document:** Final report
Title: Tau and beta-amyloid deposition, microhemorrhage and brain function after traumatic brain injury in war veterans.

A. Elias, T.L. Cummins, M. Hopwood, J.V. Rosenfeld, V. Doré, F. Lamb, R. Williams, V.L. Villemagne, C.C. Rowe. *Beta-amyloid and tau imaging in obstructive sleep apnoea*. **In Review.**

T.L. Cummins, A. Elias, M. Hopwood, V. Doré, F. Lamb, R. Williams, O. Salvado, C. Masters, V. L. Villemagne, C. C. Rowe. *In vivo assessment of markers of Alzheimer's Disease pathology in Vietnam war veterans with Traumatic Brain Injury*. **Manuscript Prepared.**

T.L. Cummins, Y. Xia, A. Elias, K. Pannek, P. Raniga, J. Fripp, V. Doré, F. Lamb, M. Hopwood, O. Salvado, V. L. Villemagne, C. C. Rowe. *White matter integrity in the corpus callosum following Traumatic Brain Injury in Australian Vietnam war veterans*. **In review.**

Conference presentations

Conference: The Alzheimer's Association International conference

Date: 21-26 July 2018

Location: Chicago, USA

Title: Tau, A β -Amyloid, Brain Structure and cognitive function following service-related Traumatic Brain Injury in Australian Vietnam war veterans

Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Guzman, R., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: The Australasian Neuroscience Society conference

Date: 4-7 Dec 2016

Location: Hobart, Australia

Title: Neuropathological markers of Alzheimer's disease in Vietnam war veterans with Traumatic Brain Injury & Post-Traumatic Stress Disorder

Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: Alzheimer's & Parkinson's Diseases Congress

Date: 29 March-2 April 2017

Location: Vienna, Austria

Title: In-vivo assessment of markers of Alzheimer's disease pathology in Vietnam war veterans with chronic Post - Traumatic Stress Disorder

Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Margison, L., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: The Frontiers in TBI conference

Date: 13-14 July 2017

Location: London, UK

Title: Tau, A β -Amyloid, and cognitive function following service-related Traumatic Brain Injury in Vietnam war veterans

Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Guzman, R., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: The Alzheimer's Association International conference

Date: 15-20 July 2017

Location: London, UK

Title: Tau, A β -Amyloid, and cognitive function following service-related Traumatic Brain Injury in Vietnam war veterans

Authors: Cummins, T.L., Elias, A., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Guzman, R., Salvado, O., Masters, C.L., Villemagne, V.L., Rowe, C.C.

Conference: The Alzheimer's Association International conference

Date: 15-20 July 2016

Location: Toronto, Canada

Title: PTSD and Risk of Alzheimer's Disease in Australian Vietnam Veterans: Amyloid and Tau PET Findings from AIBL - VETS

Authors: Elias, A., Cummins, T.L., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Villemagne, V.L., Rowe, C.C.

Conference: The Alzheimer's Association International conference

Date: 15-20 July 2016

Location: Toronto, Canada

Title: Ab-Amyloid and Tau Imaging in Obstructive Sleep Apnoea: Australian Imaging Biomarkers and Lifestyle-Veterans Study (AIBL-VETS)

Authors: Elias, A., Cummins, T.L., Hopwood, M., Rosenfeld, J.V., Doré, V., Lamb, F., Williams, R., Villemagne, V.L., Rowe, C.C.

7. Participants & other collaborating organizations

What individuals have worked on the project?

Name: Christopher Rowe

Project Role: PI

Researcher identify: ORCID no. 0000-0003-3910-2453

Nearest person month worked: 1.2

Contributions to project: As PI, Prof. Rowe has been responsible for the overall management and study integrity, including management and monitoring of collaborative relationships, finances, personnel, ethical compliance & all other aspects of the study.

Funding support: Hospital salary & NHMRC fellowship

Name: Victor Villemagne

Project Role: Co-PI

Researcher identify: N/A

Nearest person month worked: 0.6

Contributions to project: A/Prof Villemagne has had substantial intellectual input, assisted with data analysis, publication and presentation of results.

Funding support: NHMRC fellowship

Name: Malcolm Hopwood

Project Role: Co-PI

Researcher identify: ORCID no. 0000-0001-6004-4521

Nearest person month worked: 0.6

Contributions to project: Prof. Hopwood has had intellectual input into data analysis, publication and presentation of results.

Funding support: University of Melbourne

Name: Tia Cummins

Project Role: Graduate Student & study coordinator

Researcher identify: ORCID no. 0000-0003-3592-0838

Nearest person month worked: 12

Contributions to project: Ms. Cummins handles day-to-day management of the study. She oversees recruitment, bookings, grant applications, ethics submissions, liaising between study team and collaborators, data entry, and maintenance of study records. In February 2015, Ms Cummins began her PhD on the study, Tau and beta-amyloid deposition, micro hemorrhage and brain function after traumatic brain injury in war veterans.

Award No: W81XWH-14-1-0418 **PI:** Professor Chris Rowe **Document:** Final report
Title: Tau and beta-amyloid deposition, microhemorrhage and brain function after traumatic brain injury in war veterans.

Funding support: NHMRC grant

Name: Robert Williams

Project Role: PET Technician

Researcher identify: ORCID no. 0000-0001-6060-5042

Nearest person month worked: 2

Contributions to project: Mr Williams is PET technician at the Florey Institute of Neuroscience and Mental Health. His main role is acquisition and reconstruction of PET images.

Funding support: University of Melbourne

Name: Alby Elias

Project Role: Graduate student

Researcher identify: ORCID no. 0000-0002-7494-1028

Nearest person month worked: 6

Contributions to project: Dr. Elias carries out psychiatric assessment of participants, and is a PhD student working with the data obtained from the PTSD cohort. The title of his thesis is Post-Traumatic Stress Disorder and Risk of Alzheimer's Disease

Funding support: Piramal Imaging grant

Name: Fiona Lamb

Project Role: Neuropsychologist

Researcher identify: N/A

Nearest person month worked: 4.8

Contributions to project: Dr Lamb's main role on the study involves cognitive assessment, and clinical review of each participant. In addition, Dr Lamb assists with data interpretation and intellectual input.

Funding support: USAMRMC grant

Name: Regan Tyrrell

Project Role: research nurse

Researcher identify: N/A

Nearest person month worked: 3

Contributions to project: Ms Tyrrell took over as study coordinator in March 2017.

Funding support: USAMRMC grant

Award No: W81XWH-14-1-0418 **PI:** Professor Chris Rowe **Document:** Final report
Title: Tau and beta-amyloid deposition, microhemorrhage and brain function after traumatic brain injury in war veterans.

Has there been a change in the other active support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report. More funding has been received from the NHMRC of Australia for the TBI AD Biomarker research.

What other organizations have been involved as partners?

Name: Commonwealth Scientific and Industrial Research Organisation

Contribution: In-Kind support, facilities, collaboration, personnel exchange.

Name: Austin Health (a Victorian State Government funded hospital)

Contribution: Production of radiopharmaceuticals

8. Appendices

Abstracts of Articles Under Review:

1. Long-term neuropsychological sequela of Traumatic Brain Injury in Australian Vietnam war veterans

Cummins TL, Elias A, Lamb F, Ponsford JL, Hopwood M, Villemagne VV, Rowe CC.

Abstract

Since 2000, over 350,000 US military personnel have been diagnosed with a Traumatic Brain Injury (TBI).¹ Whilst epidemiological studies report up to a 4-fold increased risk for dementia associated with brain injury amongst veterans,² there is limited controlled research into the long term neuropsychological burden of injury. The aim of this study was to determine whether Australian Vietnam war veterans with service related TBI were more likely to exhibit cognitive deficits, thirty-to-fifty years after injury, when compared to healthy veteran controls.

Sixty-nine male veterans, aged 60-85 years, underwent psychiatric and neuropsychological assessment; forty with a TBI (mean age = 68.0 ± 2.5) and twenty-nine without (mean age = 70.1 ± 5.3). The TBI cohort included 15 mild, 16 moderate, and 9 severe TBI.

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

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.

2. Tau, A β -amyloid, and glucose metabolism following service-related Traumatic Brain Injury in Vietnam war veterans

Tia L. Cummins, B.Sc.,^{1,2} Alby Elias, M.D.,⁴ Fiona Lamb, D. Psych,² Vincent Doré, Ph.D.,³ Robert Williams,¹ Prof. Malcolm Hopwood, M.D.,⁴ A/Prof. Victor V. Villemagne, M.D.,^{2,5} Prof. Christopher C. Rowe, M.D.^{2,5}

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³The Australian eHealth Research Centre, CSIRO, Brisbane, Australia

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Abstract

Background: Traumatic Brain Injury (TBI) is common amongst military veterans and has been associated with an increased risk of dementia. It is unclear if this is due to increased risk for Alzheimer's disease (AD) or other mechanisms. This case control study sought evidence for AD as defined by the 2018 NIA-AA research framework [1] by measuring tau, A β -amyloid and glucose metabolism using positron emission tomography (PET) in veterans with service-related TBI.

Methods: Sixty-nine male Vietnam war veterans - 40 with TBI (aged 68.0 \pm 2.5 years) and 29 controls (aged 70.1 \pm 5.3 years) - underwent, A β -amyloid (¹⁸F-Florbetaben), tau (¹⁸F-AV1451) and ¹⁸F-FDG PET. The TBI cohort included 15 participants with mild, 16 with moderate, and 9 with severe injury. PET Standardized Uptake Value Ratios (SUVR) were calculated using the cerebellar cortex as reference region. Analyses were adjusted for age, ApoE-e4, vascular risk factors, medical and psychiatric comorbidities.

Results: There were no significant differences in ¹⁸F-Florbetaben or ¹⁸F-AV1451 uptake, or ¹⁸F-FDG retention amongst the two groups. When the mild injuries were removed from analyses, the moderate-to-severe TBI group had significantly lower ¹⁸F-FDG retention than controls in the mesial temporal region (p=0.013).

Conclusions: These findings suggest that TBI is not associated with the later life accumulation of the neuropathological markers of AD. Isolated mesial temporal hypometabolism suggests another mechanism may be responsible for the reported association of TBI with dementia.

3. Diminished white matter integrity four decades after Traumatic Brain Injury in Vietnam War veterans

Tia L. Cummins, B.Sc.,^{1,2} Ying Xia, Ph.D.,³ Alby Elias, M.D.,⁴ Fiona Lamb, D. Psych.,² Kerstin Pannek, Ph.D.,³ Vincent Doré, Ph.D.,³ Pierrick Bourgeat, Ph.D.,³ Olivier Salvado, Ph.D.,³ Jurgen Fripp, Ph.D.,³ Prof. Malcolm Hopwood, M.D.,⁴ Prof. Jennie L. Ponsford⁵, A/Prof. Victor V. Villemagne, M.D.,^{2,6} Prof. Christopher C. Rowe, M.D.^{2,6}

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Abstract

Background: Traumatic Brain Injury (TBI) and Post-Traumatic Stress Disorder (PTSD) are common in military veterans and have been associated with increased risk of dementia. The mechanisms contributing to this relationship are poorly understood. This study investigated the effect of TBI and PTSD in veterans on white matter integrity, hippocampal and cortical volume.

Methods: Eighty-seven male veterans - 31 with TBI (aged 69.0±2.5 years), 35 with PTSD (aged 69.5±2.6 years) and 29 controls (aged 70.1±4.9 years) underwent 3Tesla MRI. The TBI cohort included 12 mild, 13 moderate, and 6 severe injuries. White matter integrity was assessed using tract-based spatial statistics and region-specific analyses of fractional anisotropy (FA) images. Automated processing of T1-weighted MPRAGE images resulted in hippocampal volumes and whole brain cortical thickness estimation. Analyses were adjusted for IQ, Body Mass Index 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 white matter ($F(3,36)=5.35$, $p < 0.05$, 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 AD vulnerable regions.

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

4. COGNITIVE FUNCTION AND BRAIN VOLUMETRY IN VIETNAM VETERANS WITH POST TRAUMATIC STRESS DISORDER

Alby Elias^{a,e}, Tia Cummins^a, Regan Tyrrell^a, Fiona Lamb^a, Vincent Dore^b, Robert Williams^c, Jeffrey Rosenfeld^d, Malcolm Hopwood^e, Victor L Villemagne^a, Christopher C Rowe^a

Abstract

Cognitive dysfunction and reduced cortical and hippocampal volume have been reported in post traumatic stress disorder (PTSD) but little is known about the very long-term impact of PTSD on these measures. This study was a cross sectional assessment of cognition and brain volumes in Vietnam War veterans with and without PTSD. Clinician's Administered PTSD Scale (CAPS) was used to assess PTSD. Comprehensive neuropsychology assessment was performed. 3T T1 MP-RAGE MRI and an automated program for gray matter volumes (CurAIBL) was used for volumetric analysis. Existing diagnosis of dementia or mild cognitive impairment, traumatic brain injury, current substance abuse, unstable medical condition and psychotic or bipolar affective disorder were exclusion criteria. 30 veterans with and 30 without PTSD completed neuropsychological assessment of which 24 with and 25 without PTSD completed MRI. Compared with the veteran controls, those with PTSD had significantly lower premorbid intelligence (predicted IQ 102 vs 112; $p < 0.001$) and total intracranial volume (1565 cm^3 vs. 1614 cm^3 ; $p = 0.005$) and scored mildly but significantly lower on a global measure of cognition, the Montreal Cognitive Assessment (MoCA) (25.3 vs 27.4; $p = 0.024$). However the group difference in MoCA lost significance with adjustment for premorbid IQ or depression. There were no differences between the groups in regional brain volumes. The

results suggest that PTSD in older veterans is not independently associated with cognitive impairment or atrophy of structures involved in cognition. Rather cognitive performance is reflective of premorbid IQ and current affective state.

5. Risk of Alzheimer's Disease in Australian Vietnam Veterans with Post-Traumatic Stress Disorder.

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Key Points

Question: Is posttraumatic stress disorder (PTSD) in older Vietnam veterans associated with cognitive impairment, beta-amyloid and tau deposition and regional hypometabolism?

Findings: Posttraumatic stress disorder was associated with lower level of education, predicted premorbid intelligence and cognitive impairment. The association between PTSD and cognitive impairment was not independent of years of education or predicted premorbid intelligence. PTSD was not with increased beta-amyloid or tau deposition or regional hypometabolism.

Meaning: Posttraumatic stress disorder is not associated with increased risk of Alzheimer's disease. Cognitive reserve, a factor that may delay the onset of Alzheimer's dementia, is relatively low in posttraumatic stress disorder and this could explain the previously reported relationship between PTSD and Alzheimer's dementia.

Abstract

Importance: Epidemiological studies suggested an association between post-traumatic stress disorder (PTSD) and Alzheimer's dementia, but these studies did not investigate brain β -amyloid (A- β), tau and regional glucose metabolism, the biomarkers of Alzheimer's disease (AD).

Objective: To determine whether there is an association between PTSD and cognitive impairment along with pathological biomarkers of AD.

Design, setting and participants: Community based sample of Vietnam Veterans participated in the study. Clinician's Administered PTSD scale (CAPS) score 40 and above defined the PTSD group and 30 and below defined the control group.

Main outcome measurements: Comprehensive neuropsychological test battery along with amyloid and tau deposition and regional glucose metabolism as measured by Specific Uptake Value Ratio (SUVR) of ¹⁸F-Florbetaben, ¹⁸F-AV-1451 and ¹⁸F-fludeoxyglucose respectively on positron emission tomographic (PET) scan.

Results: Between March 2014 and June 2017, 85 male Vietnam Veterans (controls, n=31, lifetime PTSD, n=54, lifetime and current PTSD, n=33) completed the assessments. Compared to veterans without PTSD those with current PTSD had significantly lower level of education and predicted premorbid Intelligent Quotient (IQ) and performed poorly on attention, working memory, immediate visual recall, executive function and global cognitive function as measured by Montreal Cognitive Assessment. However, the group differences in cognitive outcomes did not remain when education and predicted IQ were adjusted in multilinear regression model. There was no significant difference between the two groups in ¹⁸F-florbetaben, ¹⁸F-AV-1451 or ¹⁸F-fludeoxyglucose SUVRs. There was a significant interaction between PTSD and positive ¹⁸F-Florbetaben in predicting impaired executive function, but not independent of education or premorbid IQ.

Conclusions and relevance: PTSD is not associated with increased risk of Alzheimer's disease. In view of the protective effect of high cognitive reserve against onset of dementia and relatively low cognitive reserve in PTSD whether this disorder represents potential risk of increased predisposition to dementia in individuals with A- β deposition cannot be ruled out.

Accepted Manuscript: Journal of Alzheimer's Disease, August 2018

Risk of Alzheimer's Disease in Obstructive Sleep Apnoea Syndrome: Amyloid- β and Tau Imaging.

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Abstract

Background: An association between obstructive sleep apnoea (OSA) and Alzheimer's dementia has been suggested but little is known about amyloid- β and tau deposition in this syndrome.

Objective: To determine amyloid and tau burden and cognitive function in OSA in comparison to those without a diagnosis of OSA.

Methods: The status of OSA was determined by asking participants about history of polysomnographic diagnosis of OSA and the use of Continuous Positive Airway Pressure (CPAP). A comprehensive neuropsychological battery measured cognitive function. Positron emission tomography (PET) was used to measure standardised uptake value ratio (SUVR) of ^{18}F -florbetaben and ^{18}F -AV1451, to quantify amyloid and tau burden.

Results: 119 male Vietnam veterans completed assessment. Impairment in visual attention and processing speed and increased body mass index (BMI) were seen in subjects with OSA compared with those without a diagnosis OSA. The cortical uptake of ^{18}F -florbetaben was higher in the OSA group than in the control group (SUVR: 1.35 ± 0.21 vs. 1.27 ± 0.16 , $p = .04$). There were more apolipoprotein E e4 allele (APOE e4) carriers in the OSA group than in the control group. In multilinear regression analysis, the significance of OSA in predicting ^{18}F -florbetaben uptake remained independent of age and vascular risk factors but not when BMI or APOE e4 was adjusted. The reported use of CPAP had no effect on cognitive or amyloid PET findings. There was no significant difference in ^{18}F -AV1451 uptake between the two groups.

Conclusions and relevance: Obstructive sleep apnoea is associated with Alzheimer's disease pathology, but this relationship is moderated by apolipoprotein E e4 and BMI.