

AWARD NUMBER: W81XWH-19-1-0746

TITLE: The Prevalence of Alzheimer's Disease Pathology After Traumatic Brain Injury in Veterans and Civilians: A Biomarker Study of Beta-Amyloid and Tau

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REPORT DATE: October 2022

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.				
1. REPORT DATE October 2022		2. REPORT TYPE Annual		3. DATES COVERED 01Sep2021-31Aug2022
4. TITLE AND SUBTITLE The Prevalence of Alzheimer's Disease Pathology After Traumatic Brain Injury in Veterans and Civilians: A Biomarker Study of Beta-Amyloid and Tau			5a. CONTRACT NUMBER W81XWH-19-1-0746	
			5b. GRANT NUMBER CDMRP Grant Agrmt Log# AZ180065	
			5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Christopher Rowe 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) University of Melbourne. Parkville, Victoria, Australia (Monash University. Clayton, Victoria, Australia Austin Health, Heidelberg, Victoria, 3084, Australia)			8. PERFORMING ORGANIZATION REPORT University of Melbourne	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012			10. SPONSOR/MONITOR'S ACRONYM(S)	
			11. SPONSOR/MONITOR'S REPORT NUMBER(S) NIIMRFR(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				
13. SUPPLEMENTARY NOTES				
14. ABSTRACT Background: Retrospective studies suggest that traumatic brain injury (TBI) increases the risk of Alzheimer's disease (AD) four-fold. This has not been supported by recent PET imaging studies including our previous work (Doré V, Cummins TL, et al. Tau, β -amyloid, and glucose metabolism following service-related Traumatic Brain Injury in Vietnam war veterans: The AIBL-VETS study. PREPRINT. https://www.medrxiv.org/content/10.1101/2022.03.10.22272230v1). PET scanning to measure the proteins Amyloid and Tau are the key predictors of future AD. This study investigates civilians and veterans with single TBI using the latest generation of more sensitive imaging biomarkers. Hypothesis: <i>That individuals with traumatic brain injury (TBI) have a higher prevalence of AD related pathology and neurodegeneration compared to age matched controls.</i> Study Design: We will use the latest generation of PET imaging and 7 Tesla MRI to measure AD pathology and chronic traumatic brain damage. We will study 150 elderly TBI subjects and 100 age-matched controls. In addition, psychological testing will be carried out such that the imaging results can be tested for correlation with clinical endpoints.				
15. SUBJECT TERMS Traumatic brain injury. Dementia. Amyloid. Tau. Positron emission tomography. Vietnam veterans. Motor vehicle accident. Alzheimer's disease.				
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 11
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified		
			19b. TELEPHONE NUMBER (include area code)	

TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	7
5. Changes/Problems	7
6. Products	9
7. Participants & Other Collaborating Organizations	10
8. Special Reporting Requirements	11
9. Appendices	11

1. INTRODUCTION:

Retrospective studies suggest that traumatic brain injury (TBI) increases the risk of Alzheimer's disease (AD) four-fold. This has not been supported by recent PET imaging studies in Vietnam War veterans. PET scanning to measure the proteins Amyloid and Tau are the key predictors of future AD. It is these abnormal protein deposits that define AD. However, PET TBI studies have had small cohorts and have not used the latest generation of more sensitive imaging biomarkers. We will use the latest generation of PET imaging and 7 Tesla MRI to measure AD pathology. We will study 150 elderly TBI subjects and 100 age-matched controls. In addition, psychological testing will be carried out such that the imaging results can be tested for correlation with clinical endpoints.

2. KEYWORDS:

Traumatic brain injury. Dementia. Amyloid. Tau. Positron emission tomography. Vietnam veterans. Motor vehicle accident. Alzheimer's disease.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The SOW had the following Tasks to be completed.

Major Task One: IRB amendments – **done and all approved**. Employ Research assistants – **done**.

Recruit 150 TBI and 100 controls over three years – **Behind schedule - 119 TBI and 84 controls recruited at end Yr 3**.

Major Task 2: 250 Tau and amyloid PET completed and transferred to FITBIR over 3 years – 119 TBI and 84 controls scanned to date. FITBIR transfer commenced. **Yr 3 target not achieved**. FITBIR transfer will be completed in the one year no cost extension period.

Major Task 3: 250 7T MRI over 3 years – **Yr 3 target not achieved due to covid** but scans have commenced. It is expected that a large proportion will be completed in the one year no cost extension period.

Major Task 4: Neuropsychological/psychological evaluations in 250 subjects over 3 years – 119 TBI and 84 controls evaluated to date. FITBIR transfer commenced. **Yr 3 target not achieved**. FITBIR transfer will be completed in the one year no cost extension period.

Major Task 5: Data Analysis, presentation and publication – Four publications achieved to date. PhD thesis awarded to A. Hicks for the work in the MVA cohort.

What was accomplished under these goals?

Major Activities – recruitment, amyloid and tau PET scans, 3T MRI scans and psychological/cognitive testing of subjects with TBI due to motor vehicle accident or military service and matching controls. Commence FITBIR data upload and 7T MRI.

Specific Objectives – achieve 100% of recruitment and assessment (target is 150 TBI and 100 controls) by end of year 3. Commence data analysis and present findings at conferences. Prepare manuscripts. PhD student (Amelia Hicks) to complete sufficient assessments to meet requirements for her PhD thesis.

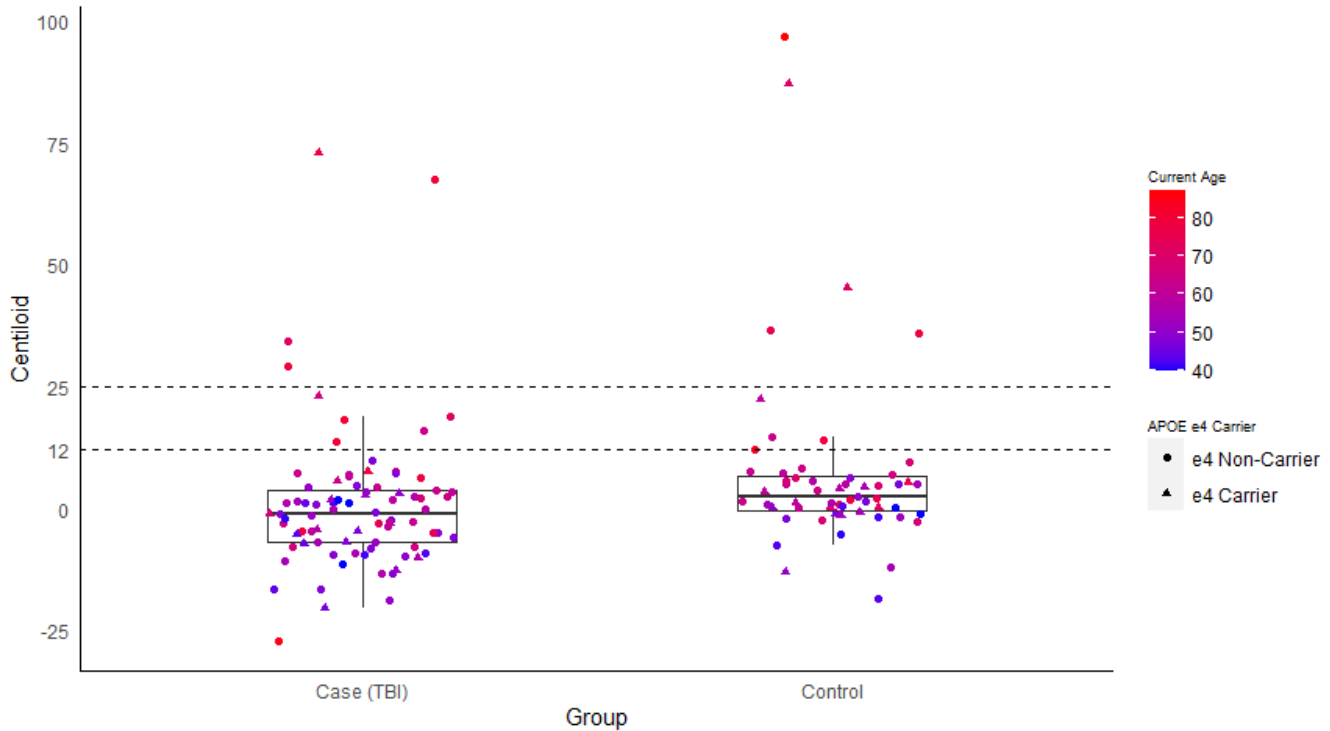
Key Outcomes – Due to Covid disruption, recruitment and completed assessments reached 119 of the 150 TBI target and 84 of the 100 controls target. PhD student had sufficient data to progress her PhD thesis and this was submitted in late 2021 and passed in March 2022. Analysis of the MVA TBI and TBI controls showed no increase in Alzheimer pathology on PET due to past moderate or severe TBI (Hicks A, et al. Neurology 2022).

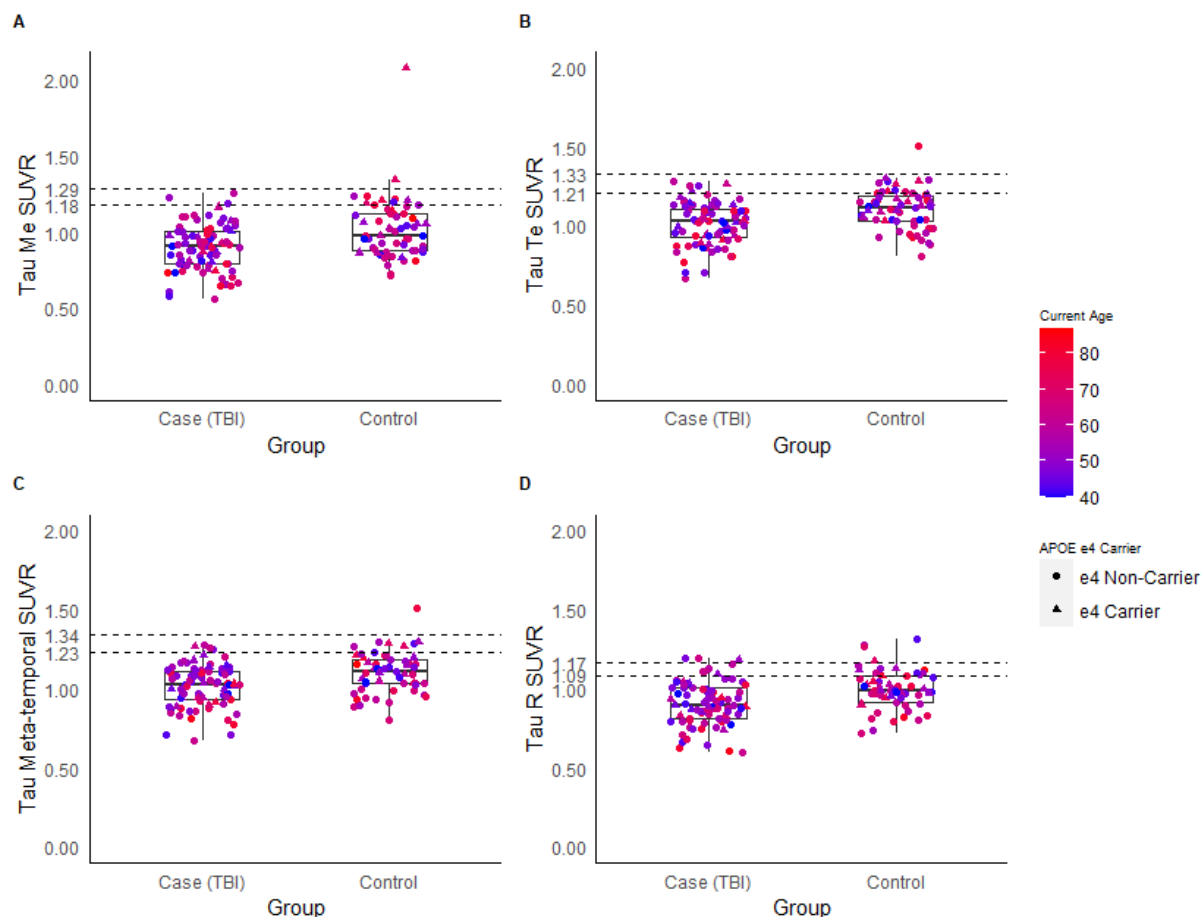
Publications:

Publication 1: Hicks AJ, Spitz G, Rowe CC, Roberts CM, McKenzie DP, Ponsford JL. Does cognitive decline occur decades after moderate to severe traumatic brain injury? A prospective controlled study. *Neuropsychol Rehabil.* 2021 Apr 15:1-20. doi: 10.1080/09602011.2021.1914674. Epub ahead of print. PMID: 33858304.

Publication 2: Amelia J Hicks, Jennie L Ponsford, Gershon Spitz, Vincent Doré, Natasha Krishnadas, Caroline Roberts, Christopher C Rowe. Amyloid- β and tau imaging in chronic traumatic brain injury: A case-control study. **Neurology** 2022. DOI: 10.1212/WNL.0000000000200857.

Selected figures from Publication 2 are shown below. Amyloid and tau PET results.





Amyloid and tau PET results are shown for the MVA TBI subjects recruited to date vs age matched healthy controls. There is no increase in tau or amyloid in the MVA TBI all of whom sustained moderate or severe non-penetrating TBI at least a decade before participation. See Publication 2. (Hicks A, et al. *Neurology* 2022)

Publication 3. Gershon Spitz, Amelia J. Hicks, Caroline Roberts, Christopher C. Rowe, Jennie Ponsford. Brain age in chronic traumatic brain injury. *NeuroImage: Clinical*, 2022; 35, <https://doi.org/10.1016/j.nicl.2022.103039>

Publication 4. Gershon Spitz, Amelia J. Hicks, Caroline Roberts, Christopher C. Rowe, Jennie Ponsford. Enlarged perivascular spaces in chronic moderate-severe traumatic brain injury. Under Review.

PhD thesis awarded and published. Amelia Hicks awarded PhD by Monash University for “Traumatic Brain Injury and Risk of Alzheimer’s Disease”. This thesis incorporated the MVA TBI data from this grant.

What opportunities for training and professional development has the project provided?

PhD candidate Amelia Hicks based her PhD on this study and submitted her thesis for assessment in late 2021 and it was passed in March 2022.
 PhD candidate Natasha Krishnadas MD has used some of the tau imaging data in her thesis on the role of tau imaging in Alzheimer’s disease. Thesis submitted and it was passed in July 2022.
 Final year medical student Robert Torode studied MRI findings in TBI for his research elective and drafted a paper on his findings.

How were the results disseminated to communities of interest?

Data has been presented to the Combat Sports council of Victoria, Australia. The project and early results have been discussed on a Melbourne morning radio show. Four publications in scientific journals to date.

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

During the one year no-cost extension we will complete the recruitment, analysis and publication of results. A new recruitment campaign has been launched through news media, Returned Services League clubs and Freemasons. However, to meet the target of 50 military veterans with service related TBI more than a decade ago, and complete the 7T MRI scans, an amendment to include non-Vietnam war military veterans has been necessary and has received ethics committee approvals.

4. IMPACT:

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

Analysis of data to date should reassure the general public and combat veterans that traumatic brain injury does not cause Alzheimer's disease. Alternative mechanisms for the reported increase in dementia in veterans and others with a history of TBI need to be explored. Possible explanations include loss of brain reserve/resilience so that dementia occurs in an earlier pathological stage of Alzheimer's disease or that non-AD pathology such as TDP-43 is increased by TBI.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Data will be available to other entities through FITBIR.

What was the impact on society beyond science and technology?

Analysis of data to date should reassure the general public and combat veterans that traumatic brain injury does not cause Alzheimer's disease.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Problems have arisen due to Covid. 1. Delay in recruitment of veterans with TBI. 2. Delay in commencement of 7T MRI as the facility was shut during prolonged lock-downs. More controls for the MVA TBI cohort were recruited (65 instead of 30) as the planned AIBL controls were too old to age match to the MVA TBI cohort. This required more PET scanning (the AIBL controls are previously scanned) but the cost has been accommodated within the existing budget and it has produced a better control population.

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

Covid pandemic closed the study for 9 months in 2020. The study returned to operation in early 2021 except at the 7T site but was closed again several months later as another Covid wave developed. Study recommenced in August 2021 for subjects who were fully vaccinated.

Consequently recruitment of veterans with TBI and 7T MRI scanning is behind schedule.

Changes that had a significant impact on expenditures

Covid has been markedly delayed expenditure on 7T MRI. Although amyloid and tau PET and neuropsychological evaluations are at 81% of the study target for TBI and controls, much of this work was done in the period between the date of grant application and the formal awarding of this grant, during the period of NHMRC funding. Consequently, invoicing for work done only since the grant award date is well below expectation. Permission to invoice for 55 tau PET scans performed in the year prior to the grant period in veterans and MVA subjects with past TBI who are included in this project within the 150 TBI study population and upload to FITBIR is requested as these scans were not covered by the NHMRC co-funding. These scans were in the approved grant budget so this will not increase the total grant funding. Without this approval the grant will be underspent.

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

Significant changes in use or care of human subjects

Nil.

Significant changes in use or care of vertebrate animals

Nil.

Significant changes in use of biohazards and/or select agents

Nil.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Publication 1: Hicks AJ, Spitz G, Rowe CC, Roberts CM, McKenzie DP, Ponsford JL. Does cognitive decline occur decades after moderate to severe traumatic brain injury? A prospective controlled study. *Neuropsychol Rehabil.* 2021 Apr 15:1-20. doi: 10.1080/09602011.2021.1914674. Epub ahead of print. PMID: 33858304.

Publication 2: Under Review. Amelia J Hicks, Jennie L Ponsford, Gershon Spitz, Vincent Doré, Natasha Krishnadas, Caroline Roberts, Christopher C Rowe. Amyloid- β and tau imaging in chronic traumatic brain injury: A case-control study. **Neurology** 2022. DOI: 10.1212/WNL.0000000000200857

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Publication 4. Gershon Spitz, Amelia J. Hicks, Caroline Roberts, Christopher C. Rowe, Jennie Ponsford. Enlarged perivascular spaces in chronic moderate-severe traumatic brain injury. Under Review.

Books or other non-periodical, one-time publications.

PhD thesis titled: Chronic effects of traumatic brain injury on cognition and Alzheimer's Disease pathology. Author Amelia Hicks Monash University.

Other publications, conference papers and presentations.

Nil

- **Website(s) or other Internet site(s)**

Nil

- **Technologies or techniques**

Nil

- **Inventions, patent applications, and/or licenses**

Nil

- **Other Products**

1. Cognitive, clinical, PET and MRI scans and data.
2. Blood samples in liquid nitrogen storage awaiting further analysis and available for collaborative research.
3. The Melbourne Brain Injury Questionnaire was developed to document and quantify TBI for former military personnel, contact sports participants and the general public.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Amelia Hicks
Project Role: PhD Student
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 20
Contribution to Project: Ms. Hicks has performed work in the area of recruitment, cognitive testing and analysis of the MVA TBI cohort.

Name: Vincent Dore PhD
Project Role: Senior Researcher
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 4
Contribution to Project: Dr. Dore has performed work in the area of PET data analysis.

Name: Natasha Krishnadas MD
Project Role: PhD Student
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 4
Contribution to Project: Dr. Krishnadas has performed work in the area of medical assessment of participants and analysis of the veterans and MVA TBI cohort data.

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

Nothing to report.

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: