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

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14. ABSTRACT

Background:

Studies suggest an increased risk of Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) after traumatic brain injury (TBI). Greater understanding of the chronic effects of TBI may lead to new therapies. This proposal will add a TBI cohort, tau PET imaging and 7T-MRI to the Australian Imaging Biomarkers and Lifestyle - Veterans study (AIBL-VETS) of post-traumatic stress disorder and neurodegeneration. AIBL researchers have an outstanding international record in the development of tau and amyloid PET imaging.

Hypothesis:

1: veterans with war related TBI have increased tau and AD biomarkers, compared to veterans without TBI.
2: the acute clinical severity of TBI will relate to the extent of positive biomarkers and areas with evidence of focal brain trauma will show more tau and beta-amyloid.
3: veterans with TBI will demonstrate focal and widespread changes in white matter integrity.
4: 7T-MRI will reveal more extensive microhemorrhage than seen on 3T-MRI and this will relate to traumatic axon injury and cognitive impairment.

Rationale:

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 and CTE.

Specific Aims:

1. To determine if veterans with TBI are more likely to have AD or CTE markers such as beta-amyloid or tau.
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 prospective study of the pathological and neurodegenerative effects of TBI in veterans.

Relevance:

Better understanding of the chronic consequences of TBI will lead to the development of treatment and prevention strategies for cognitive decline and dementia in veterans and in the general population.

15. SUBJECT TERMS					
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1. Introduction

The project will utilize 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. Greater understanding of the chronic effects of TBI will lead to better care of veterans and potentially to new therapies to prevent dementia.

The specific aims of this work are:

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 and timing 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

What were the major goals and objectives of the project?

First Year Goals

Study to commence upon signing of funding agreement. Estimate is 25th September 2014.

- ***Milestone 1:*** Hire and train Research assistant; submit amendments to existing veterans' protocol and PICF, to include TBI cohort, tau imaging and 7T MRI; Place advertisements for veterans with history of TBI in veterans' publications.
  Estimated completion: December 2014

- ***Milestone 2:*** recruitment, clinical & cognitive evaluation of 20% of TBI (n=10).
  Estimated completion: March 2015

- ***Milestone 3:*** Recruitment, clinical & cognitive evaluation of 50% of TBI (n=25)
  Estimated completion: June 2015

What was accomplished under these goals?

- All paperwork was finalized and local IRB and HRPO granted final ethics approval on 26th March 2015.
- Three separate veteran organizations (Returned Services League; Vietnam Veterans' Association of Australia; Totally & Permanently Incapacitated Federation) published a call for volunteers in their quarterly publications.
- Of proposed 50, 8 veterans with a history of head injury were recruited, passed screening and are now undergoing PET & MRI scans.
- Of proposed 50, 35 veterans with PTSD were recruited, passed screening and are now undergoing PET & MRI scans.
- Of proposed 50, 20 veteran controls were recruited, passed screening and are undergoing PET & MRI scans.
- 35 of the proposed 150 participants have attended a tau PET scan: 12 controls; 20 PTSD; 3 TBI.
- 17 participants are undergoing screening, 6 of these participants have reported a history of TBI.

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

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

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

- A call for volunteers has been submitted to 3 veteran publications, *Peacekeeper* magazine, *Chin-Up*, *FSB-Vic*, all due to be published in December.
- The Department of Veterans Affairs in Australia has been approached to discuss the possibility of organizing a mail-out to suitable veterans with a TBI. Ethics approval from the DVA's local IRB must first be sought. This is due to be submitted in January.
- The PI & study coordinator attended a weekly event at a local veteran organization, whereby the PI gave a short presentation to attract volunteers. Similar events will be scheduled for the coming year.

4. Impact

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

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. Changes / problems

Changes in approach and reasons for change

Nothing to report.

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

It has been difficult recruiting veterans with a history of TBI. To overcome this, a call for volunteers has been placed in veteran publications, specifically targeting veterans with head injury. These articles have also included brief descriptions on what constitutes a TBI.

Changes that had a significant impact on expenditures

A cost was incurred whilst advertising the study.
Publication: Mufti
Organization: Returned and Services League
Cost: $1 741.61 USD

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

Nothing to report.

6. Products

Conference presentations

Conference: Human Amyloid Imaging conference
Date: 13-15 Jan 2016
Location: Miami, Florida
Title: In vivo assessment of markers of Aβ & tau 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.

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
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 overseas 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.
Funding support: NHMRC grant

Name: Robert Williams
Project Role: Technician
Researcher identify: ORCID no. 0000-0001-6060-5042
Nearest person month worked: 2
Contributions to project: Mr Williams is chief PET technician at the Florey institute of neuroscience and mental health. His main role is acquisition of PET images, and assisting with image analysis.
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 pharmaceuticals 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: Laura Margison
Project Role: research nurse
Researcher identify: N/A
Nearest person month worked: 3
Contributions to project: Ms Margison assists the PET technician on scanning days, administering radiotracer doses, and completing data entry. On other occasions, Ms Margison assists with administrative duties.
Funding support: USAMRMC grant

Name: Paschal Alexander
Project Role: medical officer
Researcher identify: N/A
Nearest person month worked: 1.8
Contributions to project: Dr Alexander provides medical cover during the scanning days, and carries out medical duties on other occasions.
Funding support: USAMRMC grant

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

What other organizations have been involved as partners?

Nothing to report

8. Appendices

Conference abstract:

In vivo assessment of markers of Aβ & tau pathology in Vietnam war veterans with chronic Post-Traumatic Stress Disorder

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.

Background: Epidemiological studies indicate a nearly twofold increase in risk of dementia associated with Post Traumatic Stress Disorder (PTSD) in military cohorts; however mechanisms contributing to this relationship are poorly understood. The aim of this study was to investigate if Vietnam war veterans without mild cognitive impairment or dementia, but with chronic combat related PTSD show evidence of Alzheimer's disease (AD) pathological markers, as assessed by amyloid and tau imaging with PET.

Methods: Sixty-seven male participants -30 veterans with chronic PTSD (aged 67.9±2.6 years) and 37 controls (aged 74.3±8.3 years)- underwent both tau and amyloid PET imaging scans with ^{18}F-AV1451 and ^{18}F-florbetaben or ^{18}F-flutemetamol, respectively. While ^{18}F-AV1451 SUVR was calculated using the cerebellar cortex as reference region, the whole cerebellum and the pons were used as reference regions for ^{18}F-florbetaben and ^{18}F-flutemetamol, respectively.

Results: Despite the PTSD cohort being significantly younger than the controls, there was a significant difference in ^{18}F-AV1451 retention between the PTSD and control groups in the temporoparietal (1.21±0.12 vs. 1.13±0.13, p=0.017) and frontotemporal (1.14±0.12 vs. 1.06±0.13, p=0.018) regions. A similar, albeit not significant, trend was observed in the mesial temporal cortex (1.19±0.12 vs. 1.12±0.17, p=0.058). There was no significant difference in A□ burden between the groups

Conclusions: Our preliminary findings suggest that chronic PTSD might be associated with higher neocortical tau deposition later in life. More studies to confirm these results are warranted.