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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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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 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.

Hypothesis: *That individuals with traumatic brain injury (TBI) have a higher prevalence of AD related pathology and neurodegeneration compared to age matched controls.*

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.

Progress: The Covid 19 pandemic and administrative and ethics requirements have delayed aspects of the study, in particular the 7T MRI imaging. Never-the-less, due to co-funding from the Australian NHMRC and the participating institutions good progress has been made. To date 41 Vietnam war veterans, 84 persons with moderate or severe TBI due to motor vehicle accident and 40 age matched controls have been studied. Comparative cognitive and scanning data from 275 cognitively normal controls, 114 persons with mild cognitive impairment and 102 persons with mild Alzheimer’s disease was obtained from the AIBL study of ageing.

Results: Analysis to date shows **no increase in amyloid or tau** in veterans or motor vehicle accident victims with TBI compared to controls. 7T MRI has not been acquired but all approvals for this are now in place and all participants are being re-consented for this and data sharing through FITBIR.

Conclusion and Significance: Results to date mirror those found in the first AIBL veterans study and the ADNI-DoD study. These results suggest that TBI does not result in increased development of Alzheimer’s disease. Acquisition and analysis of 7T MRI will enable correlation of long term damage from TBI with long term cognitive outcome and insight into whether reduction in cognitive reserve or direct traumatic damage might explain the increased risk of dementia reported from case record based epidemiological studies.

15. SUBJECT TERMS

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

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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: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The revised SOW of August 2019 had the following Tasks to be completed in year one.
Major Task One: IRB amendments – **done and all approved**. Employ Research assistants appointed – **done**
Recruit 150 TBI subjects and 100 controls over three years – **numbers exceeded for year one**
Major Task 2: 250 tau 250 Tau and amyloid PET completed and transferred to FITBIR over 3 years – **yr 1 target exceeded but not transferred to FITBIR yet**.
Major Task 3: 250 7T MRI over 3 years – **delayed due to covid**.
Major Task 4: Neuropsychological evaluations in 250 subjects over 3 years – **exceeded year one target**.
Major Task 5: Data Analysis, presentation and publication - Interim analysis done on PET results and MVA TBI cognition. **Publication on MVA TBI cognition under review**.

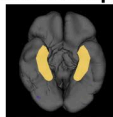
What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

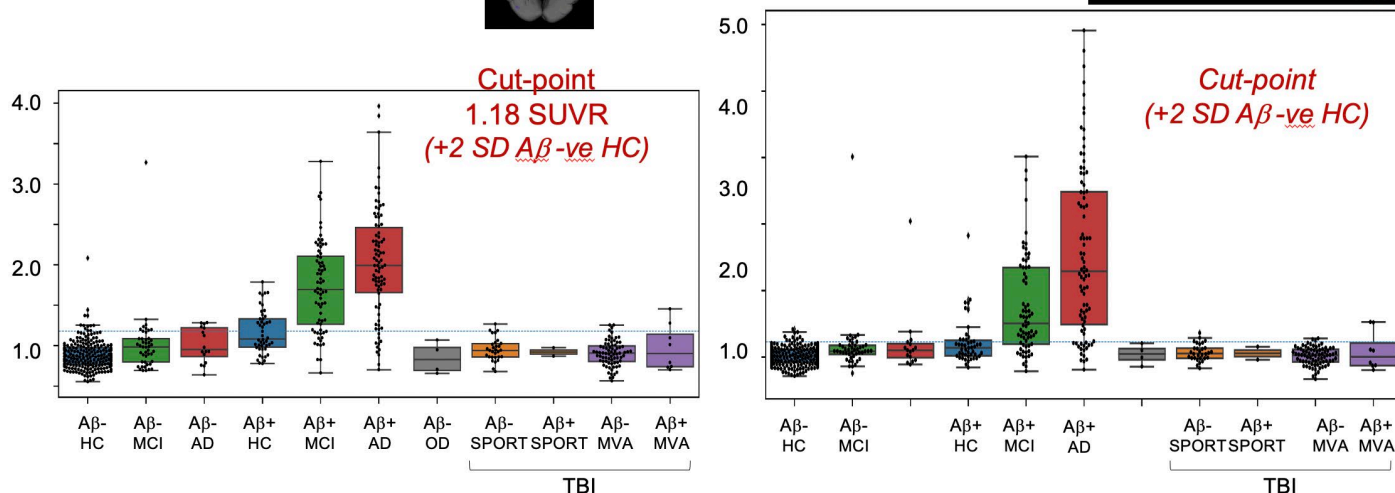
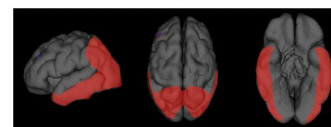
MK6240 Tau $SUVR_{Cb}$

275 HC 75.2 ± 5.7 yrs
 114 MCI 73.3 ± 7.6 yrs
 102 AD 70.3 ± 7.7 yrs
 83 MVA 60.0 ± 11.6 yrs
 34 Sports 53.8 ± 9.4 yrs

Mesial Temporal



Temporal



Tau PET results are shown for the MVA TBI subjects recruited to date vs other subjects (Healthy controls, MCI, AD). 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.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

PhD candidate has completed interim data analysis for her thesis and will submit in mid 2021.
 A second PhD student is including the tau PET data in her thesis and will submit at the end of 2021.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Data has been presented to the Combat Sports council of Victoria, Australia. Data has been discussed on a Melbourne morning radio show.

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

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Continue recruitment. A new recruitment campaign has been launched through news media, Returned Services League clubs and Freemasons.

4. IMPACT: *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

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

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Data will be transferred to FITBIR.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

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

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:*

Nothing to report.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Covid pandemic closed the study for 9 month in 2020. The study has been fully operational in 2021 due to elimination of community acquired Covid in Australia.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Covid has delayed expenditure on 7T MRI.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects *Nil*

Significant changes in use of biohazards and/or select agents

Nil.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

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

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nil.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nil

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nil

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

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nil

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nil

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

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nil

- **Other Products**

Data, blood samples in liquid nitrogen storage, questionnaire to document and quantify TBI for former military personnel, contact sports participants and 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: 10

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: 2

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: 2

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?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ebrap.org/eBRAP/public/index.htm> for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil/Pages/Resources.aspx>) should be updated and submitted with attachments.*

9. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*