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TITLE: Determining the Role of Tau and Amyloid in Chronic Symptoms and Deficits in Military Personnel Following TBIs Through PET Imaging

PRINCIPAL INVESTIGATOR: Dr. Jessica Gill & Dr. Rael Lange

CONTRACTING ORGANIZATION: The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.
Bethesda, MD 20817-1891

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Dr. Jessica Gill & Dr. Rael Lange

E-Mail: gillj@mail.nih.gov ; rlange@dvbic.org

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The Henry M. Jackson Foundation for the
Advancement of Military Medicine, Inc.
6720-A Rockledge Dr, Ste 100
Bethesda, MD 20817-1891

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13. SUPPLEMENTARY NOTES

14. ABSTRACT (appr 200 words) Traumatic brain injuries (TBIs) are common in military personnel and are linked to high rates of chronic behavioral and neurological symptoms and deficits. However, the mechanisms underlying these symptoms and deficits remain elusive. Current research suggests a link between TBIs and Alzheimer's disease (AD) and AD-like dementia (ADRD). It may be that in some individuals, a TBI initiates a neurodegenerative process, that shares pathological features with AD and ADRD, including the presence of tau tangles and amyloid-beta (Aβ) plaques in the brain. Positron emission tomography (**PET**) studies report that tau neurofibrillary tangles (NFT) are present in athletes with multiple concussions, and that even a single TBI increases the risk for Aβ plaques. Yet, these tau and Aβ PET findings are not present in all TBI patients, and their role in chronic symptoms following a TBI remains largely unknown. In this study, we will use PET with ligands specific to amyloid and tau to determine if a TBI results in tau NFTs and Aβ plaques, 10-years following a TBI, in a young military cohort. We will then examine these PET changes have clinical implications 10-years post TBI. Finally, we will evaluate changes in blood based biomarkers implicated in AD to determine if these peripheral markers are related to neuronal changes. Results of these investigations will determine if there is an increased risk for AD-like pathology following a TBI in military personnel, and if PET findings have clinical implications to military personnel/veterans.

15. SUBJECT TERMS Traumatic brain injury; chronic traumatic encephalopathy; Alzheimer's disease; Alzheimer's disease-related dementias; neurodegenerative disorders; beta-amyloid, tau; tauopathy, diagnostic imaging; PET, positron emission tomography

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TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Traumatic brain injuries (TBIs) are common in military personnel and are linked to high rates of chronic behavioral and neurological symptoms and deficits, especially in those with multiple injuries and or more severe injuries. However, the mechanisms underlying these symptoms and deficits remain elusive. Current research suggests a link between TBIs and Alzheimer's disease (AD) and AD-like dementia (ADRD), but this relationship remains tentative. It may be that in some individuals, a TBI initiates a neurodegenerative process, that shares pathological features with AD and ADRD, including the presence of tau tangles and amyloid-beta (Aβ) plaques in the brain. Positron emission tomography (**PET**) studies report that tau neurofibrillary tangles (NFT) are present in athletes with multiple concussions, and that even a single TBI increases the risk for Aβ plaques. Yet, these tau and Aβ PET findings are not present in all TBI patients, and their role in chronic symptoms following a TBI remains largely unknown. Determining the presence of Aβ plaques and tau NFTs in younger cohorts of military personnel and veterans and their relation to chronic behavioral and neurological symptoms is important. Aβ plaques are linked to neuropsychological deficits and have been shown to predict conversion from mild cognitive impairment (MCI) to AD/ADRD in older civilian samples, but their contribution to symptoms and deficits in is younger individuals with TBIs remains unknown. Previously, we reported greater tau NFTs were present in athletes with multiple concussions and behavioral and neurological symptoms. Our group has also shown that military personnel with TBIs have (a) higher total tau in peripheral blood, (b) an altered Aβ 40/42 ratio, and (c) high levels of inflammation that persist for years following the injury, and that these biomarkers are related to chronic symptoms, including post-traumatic stress disorder and post-concussion symptoms as well as impaired neurocognitive performance within the first 12 months following a mild-moderate TBI, suggesting that these biomarkers relate to recovery from TBI. These findings have implications to understanding chronic symptoms in military personnel, as conversion from MCI to AD/ADRD has been linked to elevations of these proteins. In this study, we will use PET with ligands specific to amyloid and tau to determine if a TBI results in tau NFTs and Aβ plaques, 10-years following a TBI, in a young military cohort. We will then examine these PET changes have clinical implications 10-years post TBI. Finally, we will evaluate changes in blood-based biomarkers implicated in AD to determine if these peripheral markers are related to neuronal changes. Results of these investigations will determine if there is an increased risk for AD-like pathology following a TBI in military personnel, and if PET findings have clinical implications to military personnel/veterans.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

traumatic brain injury; chronic traumatic encephalopathy; Alzheimer's disease; Alzheimer's disease-related dementias; neurodegenerative disorders; beta-amyloid, tau; tauopathy; PET, positron emission tomography

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.

Major Task 1: Institutional Review Board (IRB) Approvals
Major Task 2: Data Collection in PET Studies
Major Task 3: Linking of clinical, neuropsychological functioning data, and neuroimaging data
Major Task 4: Analyses of already collected clinical and neuroimaging data with PET imaging data

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.

Major Task 1: Institutional Review Board (IRB) Approvals

1) major activities: During this period, we have faced significant administrative challenges in securing an IND and the logistics of conducting PET studies. However, despite these challenges, we have established the clinical infrastructure to undertake the study, including:

a) Amendment to the protocol and consent of the 15-year study (#353853) to have amyloid-ligand PET studies undertaken at NICoE.
   (These activities have led to the development of the protocol amendment that was approved by the WRNMMC IRB in 09/23/2019 of Q4 for the addition of the amyloid ligand within the parent study.)
b) We have developed an NIH protocol to conduct tau-ligand PET at the NIH. This step was undertaken to resolve issues with and surrounding the IND support needed for this and other ligand issues outlined in 4a.
c) We have established the pipeline that will be used for patient recruitment.
d) We have developed the methods that will be used to deliver the PET ligands and developed plans for trouble shooting issues related to PET delivery.

2) specific objectives:

a) Submission of NIH protocol for Scientific Review – The NIH protocol will be submitted for Scientific Review once the IND is close to execution (4-5 weeks).
b) We have obtained access to raw data from neuroimaging from all subjects within the parent, 15-year protocol.

3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative)

None

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.

Nothing to Report.

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.

Nothing to Report.

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.

By the next quarter, we expect to have the NIH protocol approved and ready to enroll participants. This will include the completion of the IND for the tau tracer and all other regulatory activities required for both protocols to be enrolling participants and collecting data.

4. **IMPACT:** D*escribe 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).

Nothing to report.

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.*

Nothing to Report.

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.*

Nothing to Report.

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:*

The submission of the IRB protocol has been delayed because we must secure FDA approval of the tau ligand prior to submission. FDA approval cannot be obtained until a sponsor for the IND application has been identified. We discussed with Henry M. Jackson Foundation whether they would hold the IND, but ultimately, they declined. We have worked through this issue, by developing the infrastructure to undertake the PET study with the tau ligand at NIH in the Clinical Center. NIH, and specifically NINR, will hold the IND, and oversee all regulatory activities required by the FDA for this. This has also meant the development of a new protocol for NIH use that encompasses patient recruitment and data linkage. An additional change is that we propose changing the tau ligand from the AVID version to the Piramal ligand (PI-2620). This is partly because of problems encountered when working with AVID regarding availability of the ligand due to shifting priorities within AVID. We have reviewed the data on PI-2620 and are impressed with this next-generation ligand, as well as the commitment of Piramal to provide this ligand formulation within our required budget.

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.

We do not anticipate any additional issues, and plan to proceed to initiate both protocols at Walter Reed National Military Medical Center as well as NIH.

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.

Nothing to Report.

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

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

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).*

Nothing to Report.

  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).*

Nothing to Report.

  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.*

Nothing to Report.

- **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.

Nothing to Report.

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

Nothing to Report.

- **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.

Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*

- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Jessica Gill
Project Role: PI
Nearest person month worked: 3
Contribution to Project: Dr. Gill has worked to coordinate efforts for both the NIH protocol development and the Walter Reed Amendment. She has also worked to resolve the IND issues as well as consult between AVID and Life Molecular to arrange the ligands for use in this project

Name: Rael Lange
Project Role: PI
Nearest person month worked: 3
Contribution to Project: Dr. Lange has been overseeing the protocol amendments and negotiations of data and workflow for Walter Reed. He has been working to resolve the IND issues as well.

Name: Cassandra Pattinson
Project Role: Postdoctoral Fellow
Nearest person month worked: 3
Contribution to Project: Dr. Pattinson worked to coordinate efforts for protocols at NIH and Walter Reed to be developed and submitted.

Name: Christina Devoto
Project Role: Research Coordinator
Nearest person month worked: 3
Contribution to Project: Ms. Devoto worked on the development of the NIH protocol for the tau ligand and needed IND submission.

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://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) 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.