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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

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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 (A β) 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 A β plaques. Yet, these tau and A β 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 A β 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.					
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1. INTRODUCTION:

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 ($A\beta$) 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 $A\beta$ plaques. Yet, these tau and $A\beta$ 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 $A\beta$ plaques and tau NFTs in younger cohorts of military personnel and veterans and their relation to chronic behavioral and neurological symptoms is important. $A\beta$ 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 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 $A\beta$ 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 $A\beta$ 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:

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:

What were the major goals of the project?

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?

During the period of the award, we were able to adjust the SOW, according to delays, and included these adjustments in continuing reviews. The last updates related to the SOW are provided here.

Major Task 1: Institutional Review Board (IRB) Approvals

1) major activities:

- Review and execution of CRADA between HJF, WRNMMC and Life Molecular Imaging (LMI)
 - ***CRADA was signed by LMI, HJF, and WRNMMC in 09/2022.***
- Coordination with LMI regarding logistics and costs associated with LMI undertaking monitoring responsibilities
- Recruitment/hiring of key support positions needed to facilitate study coordination
 - ***Hiring of needed personnel (Clinical Research Coordinators) was completed on 09/2022.***
- No Cost Extension (NCE)
 - ***A 1-year NCE was requested and approved in 09/2022.***

2) specific objectives:

- Completion of legal/regulatory review needed to execute CRADA between HJF/WRNMMC and LMI
 - ***CRADA was signed and executed by LMI, HJF, and WRNMMC in 09/2022.***
- Coordination with research team at WRNMMC to begin execution of study procedures in 11/2022.

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

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?

We expect to have started to enroll participants and have collected data.

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

The primary significant challenge we faced this reporting period relates to the finalization/execution of the HJF/LMI/WRNMMC CRADA. However, the CRADA has now been signed by WRNMMC, LMI, and HJF and was fully executed 09/2022. We can now move forward with study procedures as planned. We have started to coordinate activities at WRNMMC to begin data collection 11/2099.

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

Issue 1: The need to resolve who would hold the IND (WR, HJF, NIH...) with the decision ultimately being made that LMI would hold the IND. LMI accepted this responsibility, as HJF was not able to identify a holder of an IND at Walter Reed. We were offered an option with HJF but it was in excess of for the duration of the study, and we did not have funding to support this additional cost. We worked with Walter Reed as well as NIH to try and gain the support required. NIH could not do so at an off-site, such as Walter Reed, and Walter Reed did not have an office to support INDs, nor did USUHS. HJF was not able to identify other options.

Response: To address this, we continued with LMI partner, Kathleen Findlin to assure that they would be able to hold the IND, as well as to oversee and conduct regulatory mandates for the IND. We had meetings at least once a month to continue to provide her and the company progress reports, and to maintain engagement.

Issue 2: Kathleen Findlin's (LMI VP and our primary point of contact) significant delay in providing the new quotes for the cost of the ligands and specifically for the cost of insurance which was needed since LMI would be the sponsor and functioning as the monitor for the study. She was not responsive, often for weeks up to months, even with frequent emails and calls, this occurred during 2021.

Response: Although she was not fully responsive, in 2020-2021, she was 100% supportive of holding the IND for the study, and we initiated site visits and ways to oversee reporting regulations. We planned to use LMI's infrastructure to hold the IND and oversee it with another study at Walter Reed, with a PI using the same ligand in a different population. When Kathleen visited the site, we were able to determine next steps, and to plan for logistical components for initiation of the study.

Kathleen Findlin's departure at the end of 2021 was not communicated to us directly, and we found this out through non-responsive emails, and then ultimately reaching out to colleagues who had worked with her previously. When we were able to determine her replacement, it was approximately 4/2022. Her replacement made it clear that she was not familiar with our study and asked if we could provide her with a copy of the protocol and any details on the status of the study as she was unable to currently locate any documents pertaining to our study. We began meetings with LMI employees that remained, and first they agreed to hold the IND, but wanted to vet the protocol and meet to ensure a collaborative relationship was formed. We met in 2022, and continued to meet, as we continued to develop the protocol and set up needed infrastructure.

Oversight by HJF with respect to ensuring regulatory forms (eIRB form and Form 1572) were filled out correctly, even though they were reviewed prior to submission. As you recall, these were forms that we filled out and returned to HJF who then returned them to LMI. At least 8 months passed until we were contacted about these forms not being filled out correctly. Once this was determined, LMI contacted us, and let us know of the error and the resulting delays. This occurred in Summer of 2022. We met with HJF about these errors, and there was an assurance of greater oversight to assure that this error and resulting delay would not occur again.

Issue 3: Finalization/execution of the HJF/LMI/WRNMMC CRADA. – As you recall, the CRADA was held up by every party involved but particularly LMI. It was apparently fully executed on 09/2022 (see below). This approval took at least 16 months, and was the major delay in initiating the study. At this point we were not able to develop a plan to initiate the study, as it would require basically starting the regulatory processes again from the beginning.

Response: In our last meeting with LMI, we were advised that they would no longer support our IND, as a result of the delays, and changes that occurred over 2022. This decision was in part likely related to our delays, but also likely, changes within company directions.

We informed HJF of this occurrence, and reviewed budgets and timelines. We were advised to close out the study early. For this reason we are engaged in study close down with HJF.

Changes that had a significant impact on expenditures

Nothing to Report.

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

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:

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

Journal publications.

Nothing to Report.

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

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

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

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

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

Nothing to Report.

- **Other Products**

No products or other outcomes have resulted from this award.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Jessica Gill
Project Role: PI
Nearest person month worked: 4
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. Coordination with Dr. Stone (UVA) to facilitate resources to advance protocol development and guide IND preparation are ongoing.

Name: Rael Lange
Project Role: PI
Nearest person month worked: 4
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: Samantha Baschenis
Project Role: Research Coordinator
Nearest person month worked: 3
Contribution to Project: Ms. Baschenis worked to coordinate efforts for protocols at Walter Reed to be developed and submitted.

Name: Christina Devoto
Project Role: Research Coordinator
Nearest person month worked: 12
Contribution to Project: Ms. Devoto worked to coordinate efforts for protocols at Walter Reed to be developed and submitted.

Name: Nathalie Jimenez
Project Role: Clinical Research Assistant I
Nearest person month worked: 10
Contribution to Project: Ms. Jimenez worked to coordinate efforts for protocols at Walter Reed to be developed and submitted.

Name: Chiara Racioppi
Project Role: Clinical Research Assistant I
Nearest person month worked: 9
Contribution to Project: Ms. Racioppi worked to coordinate efforts for protocols at Walter Reed to be developed and submitted.

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: