

AWARD NUMBER: W81XWH-14-2-0137

TITLE: Blood Biomarker Profile of TBI-Associated Cognitive Impairment Among Old and Young Veterans

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGEForm 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 2016		2. REPORT TYPE Annual		3. DATES COVERED 30Sep2015 - 29Sep2016	
4. TITLE AND SUBTITLE Blood Biomarker Profile of TBI-Associated Cognitive Impairment Among Old and Young Veterans				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-2-0137	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Kristine Yaffe, MD email: Kristine.Yaffe@ucsf.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Northern California Institute for Research and Education 4150 Clement Street (151 NC) San Francisco, CA 94121-1545 Henry Jackson Foundation for the Advancement of Military Medicine 6720A Rockledge Drive, Suite 100 Bethesda, MD 20817-1805				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The goal of this project is to define the biomarker profile of TBI-associated cognitive impairment (CI) in veterans and compare it to that of veterans with Alzheimer's Disease (AD) and to age-matched controls. Our overall hypothesis is that TBI-associated CI involves a unique biomarker profile that has features distinguishable from AD and normal aging. Specifically, we hypothesize that: 1) patients with TBI associated CI will have higher phospho-tau/total tau ratio than controls who have not had a TBI, and that 2) TBI-associated CI will be associated with elevations in inflammatory markers compared to controls and 3) a decrease in b-amyloid measures compared to controls but not as low as in the setting of AD. We currently have data collection ongoing at both sites. As of 30-SEP-2016, data from 134 participants has been collected (65 TBI, 48 controls, and 21 with AD and no TBI). Once data collection is complete, we will examine the biomarker profile of the groups. This study will refine our understanding of the underlying mechanisms in TBI-associated CI, help predict who is at greatest risk of developing CI in veterans with TBI, and identify who may benefit from interventions and treatment for CI and its prevention.					
15. SUBJECT TERMS Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), blood biomarkers, aging, cognitive impairment (CI), Alzheimer's Disease (AD)					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			USAMRMC
			Unclassified	11	19b. TELEPHONE NUMBER (include area code)

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Introduction

Military personnel are at high risk for traumatic brain injury (TBI). Two well-recognized and important adverse outcomes of TBI are cognitive impairment (CI) and dementia. While most studies report a 2-3 times increased risk of dementia associated with TBI, the underlying mechanism and type of dementia associated with TBI remains unclear. Some studies link TBI to Alzheimer disease (AD) while others suggest the TBI-associated dementia is more similar to chronic traumatic encephalopathy (CTE). The goal of this project is to define the biomarker profile of TBI-associated CI in veterans and compare it to that of veterans with AD and to age-matched controls. Our overall hypothesis is that TBI-associated CI involves a unique biomarker profile that has features distinguishable from AD and normal aging. Specifically, we hypothesize that: 1) patients with TBI associated CI will have higher phospho-tau/total tau ratio than controls who have not had a TBI, and that 2) TBI-associated CI will be associated with elevations in inflammatory markers compared to controls and 3) a decrease in b-amyloid measures compared to controls but not as low as in the setting of AD. This study will refine our understanding of the underlying mechanisms in TBI-associated CI, help predict who is at greatest risk of developing CI in veterans with TBI, and identify who may benefit from interventions and treatment for CI and its prevention.

Key Words

Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), blood biomarkers, aging, cognitive impairment (CI), Alzheimer's disease (AD)

Accomplishments

- **What were the major goals of the project?**
 - Planning, study design, and regulatory approval: Months 1-6
 - Study protocols were approved at both sites in the first quarter of the project. The study protocol, measurements and operations manual were completed in the first six months as planned.
 - Identify and enroll 80 older veterans with TBI and 80 normal controls at Armed Forces Retirement Home (AFRH), Washington, DC, and Veterans Home of California-Yountville (VHC-Y), Yountville, CA: Months 6-18
 - Data collection is currently ongoing. We have data from 65 veterans with TBI and 48 normal controls.
 - Enroll 80 veterans with mild Alzheimer Disease (AD) at AFRH and VHC-Y: Months 18-30
 - We have enrolled 21 participants with AD and no TBI and are continuing to recruit participants and collect data for this group.
 - Identify blood biomarker profile of TBI and compare to that of AD and controls: Months 24-36
 - Nothing to report

- **What was accomplished under these goals?**

We have made good progress on our project's data collection, which was the focus of our Year 2 goals as detailed in our Statement of Work.

As of 30-SEP-2016, data has been collected on a total of 134 participants at both study sites: 48 cognitively normal veterans with no TBI history (controls), 65 veterans with a history of TBI, and 21 veterans with AD and no past head injuries. The breakdown of participants by site is as follows:

AFRH: Total = 47

Controls: 18

TBI: 18

AD: 11

Yountville: Total = 87

Controls: 30

TBI: 47

AD: 10

Total = 134

Controls: 48

TBI: 65

AD: 21

In addition, we had regular conference calls and e-mail contact with the sub-site USUHS/AFRH regarding study progress and future plans and will continue this close working relationship into Year 3.

- **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?**
 - In the next reporting period we will continue data collection on all participants, particularly focusing on those with AD to increase the size of that group. Once we complete enrollment we will finalize our biomarker assays with Quanterix and run them.

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

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**
 - Subject recruitment and enrollment at the Yountville site has been going well. The AFRH site has encountered a delay in subject running due to a change in leadership and staffing. Dr. Diaz-Arrastia, the PI, left USUHS in June to take a position at the University of Pennsylvania and Dr. Kenney took over as PI. Beginning in July, a new research associate was hired and trained; however, significant delays were encountered in getting her Common Access Card (CAC). Until the CAC is received, the AFRH site is not able to run subjects for this project. Once all approvals are in place, Dr. Kenney and the AFRH site plan to work full-time to make up for the lost months. They have demonstrated an ability to make up lost time quickly after past administrative delays.
- **Changes that had a significant impact on expenditures**
 - Expenses on the AFRH subcontract have been on hold during the data collection delay at AFRH. We anticipate that, due to this delay, we may need to request a NCE to complete the project as originally designed.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
 - Nothing to report

Products

- **Publications, conference papers, and presentations**
 - **Journal publications.**

Related Publications:

1. Gardner RC, Peltz CB, Kenney K, Covinsky KE, Diaz-Arrastia R, Yaffe K. Remote traumatic brain injury is associated with motor dysfunction in older military veterans. (Submitted).
2. Peltz CB, Gardner RC, Kenney K, Diaz-Arrastia R, Kramer JH, Yaffe K. Neurobehavioral Characteristics of Older Veterans with Remote Traumatic Brain Injury. *J Head Trauma Rehabil* 2016 Jun 17. [Epub ahead of print]
3. Kaup AR, Peltz C, Kenney K, Kramer JH, Diaz-Arrastia R, Yaffe K. Neuropsychological Profile of Lifetime Traumatic Brain Injury in Older Veterans. *J Int Neuropsychol Soc* 2016, 22, 1-9.

- **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**
Nothing to report

Participants and other collaborating organizations

- **What individuals have worked on the project?**

Name:	<i>Kristine Yaffe</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>KYAFFE</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Yaffe provides leadership and oversees research and data collection at both sites.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Ramon Diaz-Arrastia</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>RDIAZA</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Diaz-Arrastia provided leadership and oversaw data collection at the AFRH site until June 30, 2016, when he left USUHS for a position at the University of Pennsylvania.</i>
Funding Support:	<i>Federal employee, salary contained through his appointment.</i>

Name:	<i>Joel Kramer</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>JKRAMER</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Kramer provides cognitive testing expertise and oversees the neuropsychological testing.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Kimbra Kenney</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>KKENNEY</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Kenney provides neurological expertise and oversees the data collection and neurological battery at the AFRH site. Beginning on July 1, 2016, Dr. Kenney took over the leadership position at the AFRH site from Dr. Diaz-Arrastia.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Carrie Peltz</i>
Project Role:	<i>Project Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Dr. Peltz coordinates the project at both sites and monitors the day-to-day progress at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Kim Kelley</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>5</i>
Contribution to Project:	<i>Ms. Kelley collects data at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Dan Freimer</i>
Project Role:	<i>Research Associate</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Mr. Freimer assists with project coordination and data collection at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Erika Silverman</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>3</i>
Contribution to Project:	<i>Ms. Silverman collects data at the AFRH site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Cora Davis</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>3</i>
Contribution to Project:	<i>Ms. Davis collects data at the AFRH site.</i>
Funding Support:	<i>n/a</i>

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

Dr. Yaffe:

Summary: Dr. Yaffe had two grants begin in the past year.

Title: Doris Duke Fund to Retain Clinical Scientists (Yaffe: PI)

Time Commitment: 0.12 calendar months

Supporting Agency: Doris Duke Charitable Foundation

Performance Period: 01/01/2016-12/31/20

Level of Funding:

Title: Risk and Resiliency for Dementia: Comparison of Male and Female Veterans (Yaffe: PI)

Time Commitment: 1.2 calendar months

Supporting Agency: DOD

Performance Period: 08/15/16-08/14/19

Level of Funding:

Dr. Diaz-Arrastia

Summary: Dr. Diaz-Arrastia had three grants end.

Title: TBI Endpoints Development (TED) (Diaz-Arrastia: Co-PI)

Time Commitment: 1.0 calendar month

Supporting Agency: DoD/USAMRAA

Performance Period: 09/01/2014-08/31/2016

Level of Funding:

Title: Fieldable Multiplex Test for TBI Assessment (Diaz-Arrastia: PI)

Time Commitment: 0.3 calendar months

Supporting Agency: DoD

Performance Period: 10/1/2013-3/30/2016 (NCE)

Level of Funding:

Title: Dopamine Receptor Imaging to Predict Response to Stimulant Therapy in Chronic TBI (Diaz-Arrastia: PI)

Time Commitment: 0.3 calendar months

Supporting Agency: USUHS/CNRM

Performance Period: 7/1/2013-6/30/2016

Level of Funding:

Dr. Kenney:

Summary: Dr. Kenney had one grant begin and one end.

Title: Super G Grant BA 150704 (Ho Vincent (PI), Kenney K (Collaborator)

Time Commitment: 1.0 calendar months

Supporting Agency: USAMRAA/General Electric

Performance Period: 7/1/2016-5/31/2018

Title: Dopamine Receptor Imaging to Predict Response to Stimulant Therapy in Chronic TBI, (Diaz-Arrastia- PI)

Time Commitment: 0.3 calendar months

Supporting Agency: USUHS/CNRM

Performance Period: 7/1/2013 – 6/30/2016

Level of Funding:

Dr. Kramer:

Summary: Dr. Kramer had one grant begin and one grant end.

Title: The Hillblom California Brain Health Registry Network (Kramer: Co-Investigator)

Time Commitment: 0.12 calendar month

Supporting Agency: Hillblom Foundation

Performance Period: 01/01/2016-12/31/2019

Level of Funding:

Title: TBI Endpoints Development (TED) (Kramer: Co-Investigator)

Time Commitment: 0.36 calendar month

Supporting Agency: DoD/USAMRAA

Performance Period: 09/01/2014-08/31/2016

Level of Funding:

- **What other organizations were involved as partners?**
 - Nothing to report

Special Reporting Requirements

Nothing to report