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PRINCIPAL INVESTIGATOR: Kristine Yaffe, MD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education
San Francisco, CA 94121

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Kristine Yaffe, MD

EMAIL: cgawards@ncire.org

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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

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13. SUPPLEMENTARY NOTES

14. ABSTRACT The goal of this project is to define the biomarker profile of TBI-associated cognitive impairment (TBI-CI) in veterans and compare it to that of veterans with TBI with no CI (TBI), veterans with no TBI and CI (noTBI-CI), and to age-matched controls. Our overall hypothesis is that TBI-associated CI involves a unique biomarker profile that has features distinguishable from CI without TBI and normal aging. Examining biomarkers in exosomes from the central nervous system, we found multiple blood-based biomarkers that differed significantly between the four 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)

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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 CI and no TBI history and to controls. Our overall hypothesis is that TBI-associated CI involves a unique biomarker profile that has features distinguishable from CI without TBI 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)

Accomplishments

- **What were the major goals of the project?**
    - Planning, study design, and regulatory approval
        - 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 older veterans with TBI and normal controls at Armed Forces Retirement Home (AFRH), Washington, DC, and Veterans Home of California-Yountville (VHC-Y), Yountville, CA
        - Data collection is complete. We have data from 57 normal controls and 68 veterans with TBI (35 with CI, and 30 without CI)
    - Enroll veterans with CI but no TBI history at AFRH and VHC-Y
        - Data collection is complete. We have data from 33 veterans with CI but no history of TBI.
    - Identify blood biomarker profile of TBI and compare to that of and controls
        - Across the four groups (Control, noTBI-CI, TBI-noCI, and TBI-CI) we found significant differences in multiple biomarkers. Analyses to further examine these results are nearing completion.

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

  In the past year, we have worked diligently to examine the results of the data we've collected over the previous years. All the blood samples from both sites were sent to Dr. Jessia Gill's lab at NIH for analysis. The preliminary results were presented in a TBI symposium at the Alzheimer's Association International Conference (AAIC) in July. We have completed a few further analyses and now are writing up the manuscript for publication.

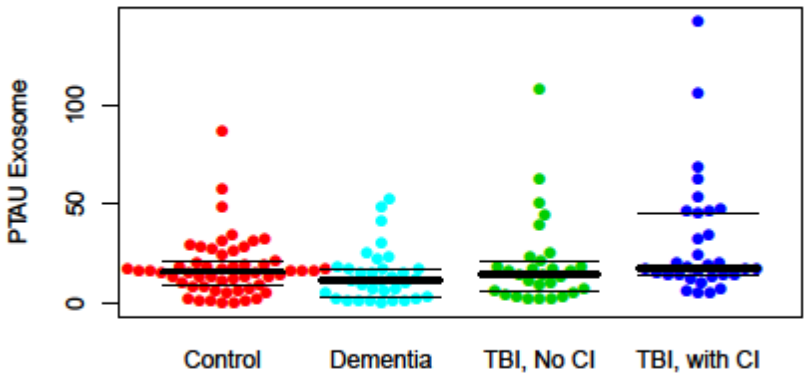
  The analysis focuses on our veteran participants separated into four groups: Control (n=57), noTBI-CI (n=33), TBI-noCI (n=30), and TBI-CI (n=35). We compared proteins [neurofilament light (NFL), total tau (TAU), glial fibrillary acidic protein (GFAP), and ubiquitin carboxyl-terminal hydrolase (UCHL1), alpha synuclein (aSYN) and phosphorylated tau (pTAU)] and cytokines [human tumor necrosis factor alpha (TNFa), interleukin 6 (IL-6) and interleukin 10 (IL-10)] between the groups. We examined the levels of the proteins and cytokines in neuronal-derived exosomes from peripheral blood using ultrasensitive immunoassay technology (Quanterix Simoa).

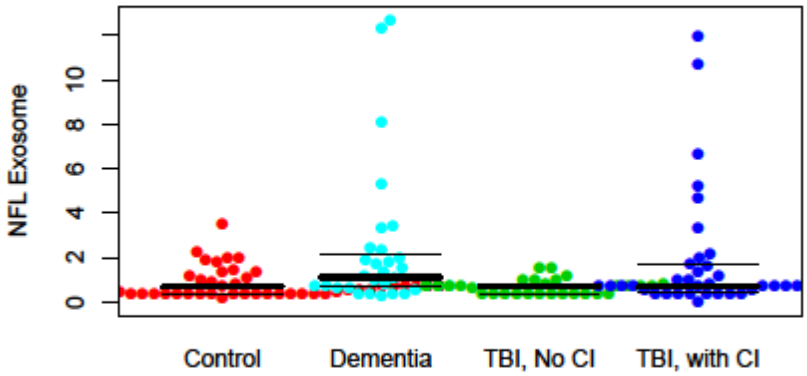
  Veterans were, on average, 79 years old, mostly male, and had completed 15 years of education. The Table below shows group differences on demographics and medical and psychiatric history. Within the participants with TBI, 78% reported loss of consciousness, and 35% had a history of moderate/severe TBI. Mean interval from first TBI to study visit was 51 years, and 88% of veterans had remote TBI (>2 years before visit).

	Control N = 57	**noTBI-CI** N = 33	**TBI-noCI** N = 30	**TBI-CI** N = 35
% or mean (SD)				
Demographics				
Age, years	78.5 (8.9)	82.0 (9.3)	79.7 (9.6)	76.6 (10.1)
Sex (% male)	86.0	87.9	86.7	100
Race (% Minority)	10.5	15.2	6.7	8.6
Education, years	15.1 (2.0)	13.9 (3.1)	15.3 (2.4)	14.5 (2.4)
Medical Comorbidities				
Hypertension	71.9	90.9	63.3	80.0
Stroke	10.5	15.2	6.9	20.0
TIA	3.5	9.1	3.4	2.9
Diabetes	29.8	36.4	23.3	31.4
Psychiatric Comorbidities and General Cognition				
Depression	24.6	30.0	34.5	50.0
Anxiety	15.8	15.6	16.7	20.0
PTSD	10.7	9.1	6.7	14.3
Substance Abuse	22.8	18.2	23.3	37.1
GDS	1.2 (1.8)	1.4 (1.7)	0.8 (1.3)	2.9 (5.0)
MMSE	28.8 (1.4)	26.6 (2.4)	28.9 (1.3)	27.2 (2.2)

TIA = transient ischemic attack; PTSD = post-traumatic stress disorder; GSD = Geriatric Depression Scale; MMSE = Mini-Mental State Examination

In analyses adjusting for age and sex, we found that the four groups differed on several of the biomarkers (PTAU, NFL, IL-6, and TNFa; all $p<0.05$). GFAP was marginally significant ($p = 0.06$). The figures below show a few of the biomarker differences between the groups (Dementia = noTBI-CI group).





Contrast analyses comparing Control subjects to the other three groups showed that the Control group and the TBI-noCI group did not differ on any of the biomarkers. However, both CI groups differed from the control group in several biomarkers. Compared to Controls, TBI-CI had higher levels of IL-6, NFL, GFAP, and pTAU ($p < 0.10$ in age- and sex-adjusted analyses). Compared to Controls, noTBI-CI had higher levels of NFL and IL-6 (both $p < 0.05$ in age- and sex-adjusted analyses).

Our results suggest that both groups without CI differ from the groups with CI. However, those with TBI-CI seem to have a biomarker profile that's different than the noTBI-CI group on levels of proteins and inflammatory cytokines associated with acute TBI. Further investigation of other markers may help determine the underlying pathology of remote TBI and related CI.

We are currently finalizing our analyses and are writing the results up into a manuscript. As the manuscript writing process continues, we are meeting with Dr. Gill's lab and Dr. Kenney's group in conference calls and are in frequent e-mail contact.

- **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 final reporting period we will work closely with Dr. Gill and Dr. Kenney as we write up the manuscript and submit for publication.

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**
  - As reported in our quarterly reports, and our last annual report, the AFRH site experienced delays and difficulties in receiving permission to continue to perform research at AFRH. They were unable to resolve these issues and thus, additional recruitment was done at the VHC-Y site. Due to the delay, we requested and received a 2nd Extension Without Funds (EWOF).
- **Changes that had a significant impact on expenditures**
  - Due to the delay at AFRH, we requested and received a second EWOF 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. Williams, S. M., Peltz, C., Yaffe, K., Schulz, P., Sierks, M. R. (In Press). CNS Disease Related Protein Variants as Blood-Based Biomarkers in Traumatic Brain Injury. *Neurology.* 2018; 91(15): 702-709.
2. Freimer D, Peltz C, Kaup A, Xia F, Yaffe K. Olfaction as a Marker of Cognitive Impairment in Older Veterans. Under Review.
3. 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. *J Gerontol Ser A-Biol Sci Med Sci.* 2017; 72(9):1233-1238.
4. 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.* 2017; 32(1): E8-E15.
5. Kaup AR, Peltz C, Kenney K, Kramer JH, Diaz-Arrastia R, Yaffe K. Neuropsychological Profile of Lifetime Traumatic Brain Injury in Older Veterans. Journal of the International Neuropsychological Society. 2017; 23(1):56-64.
6. Kaup AR, Yaffe K. Reassuring News About Football and Cognitive Decline?: Not So Fast. JAMA Neurology. 2017; 74(8): 898-899.

    - **Books or other non-periodical, one-time publications.** Nothing to report
    - **Other publications, conference papers, and presentations.**

1. Yaffe K, Peltz C, Kenney K, Gill J. Blood-Based Biomarker Profile of Older Veterans with Remote TBI. Symposium Presentation at the *2018 Alzheimer's Association International Conference, Chicago, IL*.
2. Williams SM, Schulz P, Peltz C, Yaffe K, Sierks MR. Neurodegenerative Disease Associated Protein Variants as Potential Blood-Based Biomarkers to Assess Severity of Traumatic Brain Injury. Presented at the 2017 *Society for Neuroscience Conference, Washington, DC.*

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

Name:	*Kimbra Kenney*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*KKENNEY*
Nearest person month worked:	1 (WOC)
Contribution to Project:	*Dr. Kenney provides neurological expertise and oversees the data collection and neurological battery at the AFRH site.*
Funding Support:	*n/a*

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

Name:	*Carrie Peltz*
Project Role:	*Project Coordinator*
Researcher Identifier (e.g.	*n/a*

ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	*Dr. Peltz coordinates the project at both sites and monitors the day-to-day progress at the VHC-Y site.*
Funding Support:	*n/a*

- **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 one grant end and three begin in the past year.

End
Title: Study of Osteoporotic Fractures
(Multiple PI: Yaffe/Cummings)
Time Commitment: 0.24 calendar months
Supporting Agency: NIH: National Institute on Aging
Performance Period: 09/11 – 05/18NCE
Level of Funding:

Begin
Title: Leveraging New Data on Cognitive Aging & Dementia from Around the World
(Multiple PI: Yaffe/Kenney)
Time Commitment: 0.48 calendar months
Supporting Agency: Global Brain Health Institute
Performance Period: 06/15/18 – 6/14/20
Level of Funding:

Title: Connection Between Depressive Symptoms and Dementia: When Best to Intervene?
(Multiple PI: Yaffe/Zeki Al-Hazzouri)
Time Commitment: 0.48 calendar months
Supporting Agency: Alzheimer Drug Discovery Foundation
Performance Period: 06/01/18 - 5/31/20
Level of Funding:

Title: Multi-domain Alzheimer's Risk Reduction Study (SMARRT)
(Multiple PI: Yaffe/Larson)
Time Commitment: 1.2 calendar months
Supporting Agency: NIH: National Institute on Aging
Performance Period: 09/17 – 04/21

Level of Funding:

Dr. Kenney:
Summary: Dr. Kenney had two grants end and two begin in the past year.

End
Title: Cerebrovascular Reactivity (CVR) Assessed with Functional Near InfraRed Spectroscopy (fNIRS) as a Biomarker of Traumatic Micro Vascular Injury (TVI) Measured (MNCoE)
(Kenney PI)
Time Commitment: 0.6 calendar months
Supporting Agency: USUHS
Performance Period: 8/01/2011-12/31/2017
Level of Funding:

Title: Cerebrovascular reactivity as a marker for traumatic vascular injury in the chronic stage after TBI
(Kenney-Collaborator/Key Personnel) (Chapman-PI) Washington Veteran Administration
Time Commitment: 1.2 calendar months
Supporting Agency: CDMRP
Performance Period: 07/01/2015-06/30/2018
Level of Funding:

Begin
Title: Ultrasensitive Blood Tests for Investigating Pathogenesis of Post-Concussive Neurologic Conditions
(Debad J, MSD PI, Kenney K, key personnel)
Time Commitment: 0.6 calendar months per annum
Supporting Agency: CDMRP, DoD
Performance Period: 10/01/2017-09/30/2019
Level of Funding:

Title: TRACK TBI Precision Medicine – Pathomechanistic Classification of Traumatic Brain Injury: The Bridge to Targeted Therapies
(Overall PI: Geoff Manley MD PhD; Kenney K, USUHS PI)
Time Commitment: 0.6 calendar months per annum
Supporting Agency: CDMRP, DoD
Performance Period: 10/01/2017-09/30/2020
Level of Funding:

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

Title: Lifestyle Intervention for early Alzheimer's disease
(PI: Kramer)

Supporting Agency: Preventive Medicine Research Institute
Performance Period: 07/01/2018 – 12/31/2019
Level of Funding:

Title: Neurobiological Basis of Emotion Regulation Trajectories
(PI: Sturm; Kramer Co-I)
Supporting Agency: NIH/NIA
Performance Period: 09/15/2017 – 05/31/2022
Level of Funding:

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

Special Reporting Requirements

Nothing to report