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TITLE: Incidence of Mild Cognitive Impairment in Gulf War Veterans

PRINCIPAL INVESTIGATOR: Linda Chao

RECIPIENT: Northern California Institute for Research and Education (NCIRE)
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14. ABSTRACT

The goal of this project is to evaluate whether Gulf War Veterans are developing Mild Cognitive Impairment (MCI) earlier, and at a higher than expect rate. On the continuum of cognitive decline, mild cognitive impairment (MCI) is considered the transition between cognitive impairment associated with normal aging and the more serious decline associated with dementia. The project's specific aims are to cross-validate preliminary findings of a higher than expected rate of MCI, hippocampal atrophy, and parietal cortex thinning in the Gulf War Illness Consortium (GWIC) cohort; (2) to examine global white matter hyperintensities (WMH) volume from the MRIs of GW veterans with and without MCI from the San Francisco Veterans Administration and GWIC cohorts; and (3) to investigate whether GW veterans with MCI fit the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework characterization of Alzheimer's disease (AD) by examining levels of A-beta.

15. SUBJECT TERMS

Gulf War Illness (GWI), Mild Cognitive Impairment (MCI), cognition, Gulf War Veterans

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1. INTRODUCTION:

The goals of this study are twofold. First, we will cross-validate preliminary findings of a higher-than-expected rate of mild cognitive impairment (MCI) in deployed GW Veterans from the Boston Gulf War Illness Consortium (GWIC) cohort. We will also compare hippocampal volume and parietal cortex thickness in Gulf War (GW) Veterans with and without MCI in the GWIC cohort. Second, we will investigate the underlying cause of MCI in deployed GW Veterans in the SF VA and GWIC cohorts. Alzheimer's disease (AD) is most common cause of MCI and dementia; amyloid β (Aβ) is one of the molecular biomarkers of AD neuropathology. Vascular dementia is the second most common cause of MCI and dementia. Cerebrovascular disease, characterized by white matter hyperintensities (WMH) on magnetic resonance images (MRI), is a primary cause of clinical deficits in vascular MCI and vascular dementia. We will investigate whether GW Veterans with MCI have AD or non-AD pathology by (1) examining level of Aβ to determine whether GW Veterans with MCI fit the National Institute on Aging and Alzheimer's Association research framework characterization of AD and (2) quantifying WMH volumes from the MRI scans to determine the cerebrovascular disease burden in the brains of GW Veterans with and without MCI.

2. KEYWORDS:

Gulf War Illness (GWI), Mild Cognitive Impairment (MCI), Gulf War Veterans, cognition, dementia

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Prepare regulatory documents and research protocol.
    a. Milestone 1: obtain local IRB approval
    b. Milestone 2: obtain HRPO approval
2. Coordinate with Boston University for CRADA, MOU and MTAs.
3. Ascertain prevalence of MCI in GWIC cohort
4. Compare hippocampal volume and parietal cortex thickness in MRIs from GW veterans with and without MCI in both SF and GWIC cohorts
5. Identify white matter hyperintensities (WMH) in MRIs from GW veterans with and without MCI in both SF and GWIC cohorts

What was accomplished under these goals?

Major activities and achievements:

A. Obtained local IRB approval from UCSF on 8/24/2021
    1. The study qualified for expedited review under the revised Common Rule. As such, the study will not expire.
B. Obtained DOD HRPO approval on 10/29/2021
C. Obtained DUA and MTA from Boston University for GWIC neuropsychological data and MR images on 11/2/2021
D. Obtained IRB approval from Boston University on 1/24/2022
E. Obtained neuropsychological data from GWIC on 2/19/2022
F. Obtained neuroimaging data from GWIC on 3/5/2022
G. Ascertained prevalence of MCI in GWIC dataset
    1. 16% (44/269) of GW veterans in the GWIC cohort met the actuarial criteria for MCI
    2. The mean age of veterans with MCI in the GWIC cohort at the time of testing was 55 $\pm$ 8 years.
    3. This is comparable to the 12% of GW veterans with MCI, who on average were 48 years old at the time of testing, in the San Francisco cohort.
    4. These findings continue to suggest that GW veterans are exhibiting a higher rate of MCI at a younger age than the civilian population. The American Academy of Neurology Practice estimates that prevalence of MCI in the general population is 6.7% for ages 60-64, 8.4% for 65-69, 10.1% for 70-74, 14.5% for 75-59, and 25.2% for ages 80-84.
H. Obtained neuroimaging data from GWIC on 3/8/2022

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 are processing the imaging data from the GWIC cohort in our image analysis pipelines so it can be combined and analyzed together with the imaging data from the San Francisco cohort.
- We are exploring avenues for ascertaining plasma Aβ levels from GW veterans with and without MCI in both the San Francisco and GWIC cohorts.

4. IMPACT:

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

The preliminary neuropsychological findings support our hypothesis that GW Veterans are aging and experiencing cognitive decline more rapidly than the civilian population.

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

We originally proposed to use magnetic immunoassay to ascertain plasma Aβ levels from a subset of GW veterans with and without MCI. The commercial laboratory that offered this biomarker service, MagQu LCC, is a Taiwanese company that had a laboratory in the US (in Arizona). Unfortunately, the MagQu closed their US laboratory during the pandemic. Currently, if we wish to use MagQu for biomarker magnetic immunoassay assays, we need to send the frozen plasma samples to Taiwan for analyses. Due to uncertainties with overseas shipping, we are exploring other commercial biomarker assay options.

Presently, the most promising marker for plasma Aβ 42/40 is immunoprecipitation coupled with mass spectrometry (IPMS). This assay is commercially available through the laboratory C2N, founded by Dr. Randy Bateman at Washington University in St. Louis. Because C2N and Dr. Batemen are trying to patent the IPMS technique, they have a lengthy Research Service Agreement (RSA) for the biomarker services. The San Francisco VA and NCIRE have been reviewing the RSA for the past three months. If the SFVA, NCIRE, and C2N cannot come to an agreement over the language in the RSA, we will explore other options for plasma Aβ assays.

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

Imaging data from a handful of GW Veterans from the Boston GWIC cohort did not transfer properly. We are exploring reasons for the failures in file transfer and will try to obtain the full set of imaging data via other methods if these files continue to be problematic with FTP.

Changes that had a significant impact on expenditures

N/A.

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

There are no significant deviations or changes in approved protocols for the use of human subjects. The current IRB approval dates are:

SF VAMC site: initially approved: 08/24/2021, no expiration date
Boston University site: approved 2/10/2022, no expiration date

Significant changes in use or care of vertebrate animals.

N/A

Significant changes in use of biohazards and/or select agents

N/A

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.

List the URL for any Internet site(s) that disseminates the results of the research activities.

Nothing to report.

- **Technologies or techniques**

Nothing to report.

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

Nothing to report.

- **Other Products**

N/A

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Linda Chao
Project Role:	PI
Researcher Identifier:	0000-0002-8593-2434 (eRA Commons: lindachao)
Nearest person month worked:	0.88 calendar months
Contribution to Project:	Dr. Chao has work closely with Dr. Sullivan to coordinate the transfer of cognitive and neuroimaging data from GWIC.
Name:	Khadri, Tahir
Project Role:	Staff Research Associate
Nearest person month worked:	3.2 calendar months
Contribution to Project:	Mr. Khadri has worked under Dr. Chao's supervision processing and analyzing neuroimaging data from the GWIC and SF cohorts.

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

Name:	Linda Chao
Changes:	1. Dr. Chao was awarded a VA Research Career Scientist award (K6CX002552-05) on 04/01/2022. This award supports 100% of Dr. Chao's VA FTE. 2. Dr. Chao's SF VA appointment has increased from 7/8th to 8/8th 3. Dr. Chao's UCSF and the San Francisco VA has increased from 26.5% FTE to 50% FTE. Her combined UCSF and SFVA effort is now 150%. 3. Dr. Chao's effort on VA Merit award "An Investigation of the Relationship between Toxicant Exposures during Gulf War Deployment and Prodromal Parkinson's Disease" (2I01CX00079805) has been decreased to "as needed." 4. Dr. Chao is now PI of VA Merit award "Preventing Loss of Independence through Exercise in Community Living Centers (PLIE-CLC)" (1I01HX002764). Her effort on this project as "as needed." 5. DOD/CDMRP/PRARP grant "Using Multimodal Imaging to Examine the Neural Mechanism of an Integrative Exercise Program in Individuals with Mild Cognitive Impairment" has ended. 6. DOD/CDMRP/GWIRP grant "Examination of plasma PON1 paraxonase activity and genotype in Gulf War Veterans" has ended. 7. DOD/CDMRP/PRARP grant "MOTION: Moving Online Together: Investigation Of Neurocognition" has been awarded. Dr. Chao is PI at 0.96 calendar months. 8. DOD/CDMRP/GWIRP grant "Pilot Test of Apnea and Insomnia Relief for Veterans with Gulf War Illness" has been awarded. Dr. Chao is PI at 1.2 calendar months. 9. DOD/CDMRP/GWIRP grant " Generational and Family Health in Veterans with Gulf War Illness; Address Longstanding Questions about Effects of Gulf War Service on Birth Outcomes, Reproductive Health, and Health Conditions Affecting Veterans' Spouses and Children" has been awarded. Dr. Chao is co-investigator at 0.3 calendar months. 10. DOD/CDMRP/GWIRP grant " Enrichment of Data Collection for the Boston Biorepository and Integrative Network for GWI: The Non-Exclusionary Wave (NEW BBRAIN) Cohort" has been awarded. Dr. Chao is co-investigator at 0.3 calendar months.

Name:	Kimberly Sullivan
Changes:	1. Effort on DOD/CDMRP grant "Boston Biorepository, Recruitment and Innovative Network (BBRAIN) for GWI" increased from 8% to 20%. This grant received a NCE, and a second NCE is planned. New end date will be 8/31/23. 2. DOD/CDMRP grant "Examination of Neuroimaging, Cognitive Functioning, and Plasma Markers in a Longitudinal Cohort of Gulf War Deployed Veterans: The Fort Devens Cohort" has ended. 3. DOD/CDMRP grant "Investigating Gene-Environment Interactions in Multiple Cohorts of 1990-1991 Gulf War Veterans" will end on 8/31/2022. 4. DOD/CDMRP grant "Identification of Epigenetic Signatures as Biomarkers of Gulf War Illness" has ended. 5. DOD/CDMRP grant "Understanding Gut-Microbiome links to Gulf War Illness persistence and development of gut dysbiosis targeted therapy" has ended 6. DOD/CDMRP grant "Novel Combinatorial screening for Neurotrophins, Neuropoietic cytokines, Matrix Metalloproteinases and Complement components in relevance to Neuronal Autoantibodies in the serum and CSF of Veteran with Gulf War illness" has ended. 7. DOD/CDMRP grant "Microtubule-Based Therapy for Neurodegeneration in Gulf War Illness: Studies with hiPSC-Derived Neurons from Gulf War Veterans" has ended. 8.Effort on DOD/CDMRP grant "The Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC)" has increased from 7% to 10%. 9. Effort on DOD/CDMRP grant "Identifying Objective Diagnostic Markers of Gulf War Illness: Salivary and Plasma Autoantibodies Against Neural Proteins Validated With Brain Imaging" has increased from 5% to 10%. This grant also has a new end date of 4/30/24. 10. VA grant "A Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness" has ended. 11. DOD/CDMRP/GWIRP grant "Tracking Neuroinflammation in GWI from Brain Derived Extracellular Vesicles" has been awarded. Dr. Sullivan is co-investigator at 7.5%. 12. DOD/CDMRP/GWIRP grant "Validating Novel Brain Imaging Biomarkers for classifying mild Traumatic Brain Injury (TBI) and subsequent risks of Alzheimer's Disease (AD) in Gulf War Veterans" has been awarded. Dr. Sullivan is co-investigator at 5%. 13. DOD/CDMRP/GWIRP grant "Identifying Gaps in Patient Provider Communication and Improving Care for Veterans with Gulf War Illness" has been awarded. Dr. Sullivan is co-investigator at 5%. 14. DOD/CDMRP/GWIRP grant "Validating Blood Biomarkers of Brain Immune and Metabolic Dysfunction in GWI" has been awarded. Dr. Sullivan is co-investigator at 5%. 15. DOD/CDMRP/GWIRP grant "Incidence of Mild Cognitive Impairment in Gulf War Veterans" has been awarded. Dr. Sullivan is co-investigator at 10%.

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What other organizations were involved as partners?

Name:	Kimberly Sullivan
Organization Name:	Boston University
Project Role:	Site PI
Researcher Identifier:	0000-0001-7940-6123
Nearest person month worked:	0.85 calendar months
Contribution to Project:	Dr. Sullivan has provided cognitive and imaging data from the Department of Defense-funded (GW120037) multi-site Gulf War Illness consortium (GWIC) for study analysis.

Describe partner organizations that were involved with the project.

8. SPECIAL REPORTING REQUIREMENTS: N/A

9. APPENDICES: N/A