

AWARD NUMBER: W81XWH-21-1-0963

TITLE: Expanding the Characterization and Application of Clinical MRI Markers in Gulf War Illness

PRINCIPAL INVESTIGATOR: Deborah M. Little PhD

CONTRACTING ORGANIZATION: University of Texas Health Science Center Houston

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14. ABSTRACT While MRI studies have identified diverse brain differences between GWI cases and controls, the applied use of such findings has been hindered by the fact that most are from a limited number of heterogeneous studies. There still exists relatively little concrete, consistent information, guidelines, or metrics that can be used clinically in assessing veterans with GWI-related brain pathology or for comparing findings across studies. Our overall objective is to develop and validate an evidence-based assessment tool to characterize the types and degree of brain pathology affecting GW Veterans. To do this we will develop a neuroradiologic checklist of potential pathology in GW Veterans; carry out a clinical radiologic assessment of the brains of GW Veterans; use the findings to create a checklist of pathology common to ill veterans, exposures, and symptoms and the validate this checklist in a separate group of veterans. We will also conduct standard research assessments of the MRIs to increase cross validation with the literature. To date we have created the checklist, begun neuroradiologic assessments of the first 100 MRIs of GW Veterans, completed volumetric assessment of the first 100 MRI's of GW Veterans. As the neuroradiologic assessment is not yet complete we have no findings at this time to report.					
15. SUBJECT TERMS Gulf War Illness; Veterans; Brain pathology; MRI					
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1. Introduction

Multiple MRI studies have identified diverse brain differences between GWI cases and controls, including overall reductions in white and/or grey matter and structural and functional alterations in different brain regions. These diverse studies have provided general consensus that CNS alterations are a prominent component of GWI. But applied use of such findings has been hindered by the fact that most are from a limited number of heterogeneous studies. There still exists relatively little concrete, consistent information, guidelines, or metrics that can be used clinically in assessing veterans with GWI-related brain pathology or for comparing findings across studies. Our experience and preliminary data indicate that GWI cases consistently exhibit specific types and patterns of brain pathology observable on MRI. This includes prominent atrophy in identified regions, an excessive burden of white matter lesions, and morphometric alterations of the corpus callosum. Preliminary analyses indicate these findings differ significantly from GW controls, are associated with GW exposures, and are independent of age-related cerebrovascular risk factors. Our overall objective is to utilize systematic neuroradiologic assessments of MRI scans in GWI cases and controls to develop and validate an evidence-based assessment tool, the Gulf War illness Brain Injury Scale (GW-BIS) to characterize the types and degree of brain pathology affecting GW Veterans. To do this we will conduct neuroradiological assessment of MRI scans from an initial, development sample (n=100) of GW Veterans randomly selected from MRIs obtained for the Boston-based Gulf War Illness Consortium (GWIC) multisite study. Specific findings that most reliably and consistently differentiate GWI cases from controls will form the basis of the initial GW-BIS (test scale). We will then evaluate the initial test scale in an independent validation sample (n=100) of GWIC and/or BBRAIN participants to finalize GW-BIS metrics and scoring. We will, in parallel, quantitatively validate GW-BIS scoring and subscale metrics in relation to MRI volumetric, morphometric, and lesion analyses. Finally, we aim to determine associations of GW-BIS metrics with GWI illness severity, symptom expression, cognitive decrements, and GW deployment exposures and to convene a GWI imaging expert panel to advise on GW-BIS items, validation, scale use, and application.

2. Keywords

Gulf War Illness; Veterans; Brain pathology; MRI

3. Accomplishments

What were the major goals under the project?

Although the data sharing agreements and subcontracts with Boston University (the source of the MRI scans) and Baylor College of Medicine were significantly delayed, we have made significant progress toward the work outlined in the SOW in the time since we obtained the MRI scans although we approached our 7 major tasks out of the order they were proposed in to achieve as much progress as possible during the first year.

There are 7 major tasks within this project as outlined in the SOW. Their estimated completion is included in parenthesis. Our progress to date is noted under each major task. These include:

1. Regulatory and Data Sharing Agreements (6 months)

We completed all human subjects requirements within the first month of the project. As indicated in Section 5, subcontracts and data sharing agreements were significantly delayed with Boston University not being executed until June of 2022 and Baylor College of Medicine until August of 2022). The role of Boston University was to provide the MRI scans required for Tasks 2-7. The role of Baylor College of Medicine relied upon the data created from Task 2. This task is now 100% complete.

2. Neuroradiologic Assessments and completion of the Initial Neuroradiologic Checklist (12 months)

Although we did not have access to data for the first 9 months of the award period, we completed the initial neuroradiologic checklist within the first three months. The neuroradiologic assessment of the first 100

scans is now underway and should be completed by Jan of 2023. We are approximately 60% complete on this task.

3. Testing of the scale derived from the Neuroradiologic Assessments (14 months)

We have made no progress toward this task.

4. Comparison of the Scale with Quantitative Data (14 months)

Since acquiring the MRI scans from Boston University, we have now completed the volumetric analysis for gray matter, white matter, and white matter hyperintensities for the first 100 scans. As we prioritized this once we had data, we estimate that we are 40% complete on this task as we have a number of analyses remaining.

5. Testing and Validation of the Scale relative to symptoms and exposures (16 months)

We have made no progress toward this task.

6. Testing and Validation of the Scale based upon the Expert Panel Feedback (22 months)

We have made no progress toward this task.

7. Evaluation and Data Sharing with the GW Community (24 months)

We have made no progress toward this task.

What was accomplished under these goals?

Due to the constraints placed on us by not obtaining the MRI data until 9 months into the award our accomplishments are somewhat limited with no specific results yet to report. At this time we have completed the initial neuroradiologic checklist of brain pathology. This checklist leverages the common data elements for head injury, MS, and cerebrovascular vascular diseases. From these CDEs we have included any presence of hematoma or hemorrhage. We observed evidence of past hematoma and hemorrhage in multiple GW Veterans when we scanned them for the Gulf War Illness Consortium here in Houston. We also have included a focus on brain atrophy (extent, location), damage to the brainstem, evidence of diffuse axonal injury (extent, location) given the number of GW Veterans who report a history of head injury, contusion (site), any evidence of ischemia or infarction as this cohort presents with significant cerebrovascular risk factors, and enlargement of perivascular spaces. We have also included an option for "any other findings". Our study neuroradiologists expect to complete their read of the first 100 scans by January of 2023.

In parallel, we jumped to Major Task 4 under the SOW which will allow us to examine the relationship between the validated scale with common research analysis and scales developed to assess certain areas that our preliminary data suggest are of greater vulnerability. These include preprocessing and postprocessing of the MRI data in Freesurfer to extract volumes, a scale to examine white matter lesion distribution and extent, atrophy of the corpus callosum, and atrophy of the fronto-temporal lobes (visual scale). We have just completed extraction of all volumetric data and are in the process of formatting this data so that it can be sent to Dr. Steele at Baylor College of Medicine for analysis.

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

During the first year of the award I have been mentoring and training our Research Assistant on the project to assist him with movement toward a goal of graduate education. Our Research Assistant is a combat Veteran who served for 10 years in the Air Force including deployments in Iraq. Although a steep learning curve, helping Mr. Atwater move toward his professional goals is a tremendous honor. I look forward to

more progress so that he can get additional exposure in presenting at professional conferences and in contributing to manuscripts

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?

Now that all goals are in place we plan to move forward as stated in the SOW with the exception of continuing to conduct research analysis of the images in parallel with the other major tasks.

4. Impact

What was the impact on the development of the principal discipline 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

Nothing to report.

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

Data sharing agreements with Boston University (the source of the MRI scans) and Baylor College of Medicine were significantly delayed. The Boston University Subcontract was executed in June of 2022 and the subcontract with Baylor College of Medicine was executed in August of 2022. This caused a delay of 9 months before we could begin any of the MRI analysis on the data. These problems are now resolved.

Changes that had a significant impact on expenditures

Due to the delay in obtaining a subcontract with Boston University and the MRI scans that Boston University was to provide the PI reduced effort/salary on the grant until we were able to begin the research as proposed.

Funds were also not used to support the subcontracts until they were executed. As such, funds are maintained in the event a no cost extension is required.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

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

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.

7. Participants & Other Collaborating Organizations

Name:	Deborah M. Little PhD
Project Role:	PI
Researcher Identifier:	https://orcid.org/0000-0003-4498-4649
Nearest person month worked:	2.52
Contribution to the Project:	Regulatory, Development of Neuroradiologic Checklist, Training of Staff on Methods,

	Collaboration Across Sites
Funding Support:	NA

Name:	Emanuel Atwater
Project Role:	Research Assistant
Researcher Identifier:	NA
Nearest person month worked:	12
Contribution to the Project:	Data transfer, Volumetric analysis, quality assurance
Funding Support:	NA

Name:	Hande Christensen
Project Role:	Sr. Data Analyst
Researcher Identifier:	NA
Nearest person month worked:	3.6
Contribution to the Project:	Volumetric analysis, quality assurance
Funding Support:	NA

Name:	Roy Riascos-Casteneda MD PhD
Project Role:	Co-I
Researcher Identifier:	
Nearest person month worked:	1.2
Contribution to the Project:	Neuroradiology Reads
Funding Support:	NA

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

Yes, there have changes in active other support since the grant was awarded. Current other support is listed below. Current support for 2022 is 10.27PM. Current support for 2023 is 9.12PM. There is no current pending support.

Title: Glucocorticoid modulation of contextual processing and its neurocircuitry: Testing a new model of PTSD pathophysiology

Project Number: R01MH113574

Name of PD/PI: Acierno, Ronald

*Source of Support: NIH

Project/Proposal Start and End Date: 10/2021 – 07/2025

* Total Award Amount (including Indirect Costs): \$61,734

* Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2022	0.40 calendar
2. 2023	0.48 calendar

*Title: Building Resilience in Caregivers Trauma Survivors

Project Number: W81XWH-17-1-0690

Name of PD/PI: Little, Deborah M.

*Source of Support: DOD/USAMRAA

*Primary Place of Performance: UT Health, Houston

Project/Proposal Start and End Date: 03/2018 – 08/2023 (NCE)

* Total Award Amount (including Indirect Costs): \$1,887,757

* Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2022	4.8 calendar
2. 2023	4.8 calendar

*Title: Defining And Characterizing GWI Pathobiology Using Longitudinal Brain Imaging Biomarkers Of White Matter Integrity And Hemodynamic Response

Project Number: W81XWH-19-1-0767

Name of PD/PI: Sullivan, Kimberly

*Source of Support: DOD/AMRAA

*Primary Place of Performance: UT Health, Houston

Project/Proposal Start and End Date: 09/2019 – 09/2022

* Total Award Amount (including Indirect Costs): \$177,085

* Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2022	1.11 calendar

*Title: Expanding the Characterization and Application of Clinical MRI Markers in Gulf War Illness

*Major Goals: To characterize brain health and/or injury in Gulf War Veterans who meet the case definition for Gulf War Illness.

Project Number: W81XWH-21-1-0963

Name of PD/PI: Little, Deborah M.

*Source of Support: DOD/USAMRAA

*Primary Place of Performance: UT Health, Houston

Project/Proposal Start and End Date: 09/2021 – 09/2023

* Total Award Amount: \$960,372

* Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. 2022	2.52 calendar
2. 2023	2.64 calendar

*Title: ALTO-100-001, An Open-Label of Alto-100 in adults with major depressive disorder and/or posttraumatic stress disorder

Project Number: W81XWH-14-1-0622

Name of PD/PI: Little, Deborah M.

*Source of Support: Alto Neuroscience

*Primary Place of Performance: UT Health, Houston

Project/Proposal Start and End Date: 05/2022 – 05/2023

* Total Award Amount: \$ 302,880

* Person Months (Calendar/Academic/Summer) per budget period.

Year Person Months

1. 2023 0.24 calendar

*Title: ARPA Funding SB 8, Section 8, TCHATT – UT Health’s Trauma and Resilience Center, Child Services Expansion

Project Number: None

Name of PD/PI: Taylor, Leslie

*Source of Support: ARPA/UT System

*Primary Place of Performance: UT Health, Houston

Project/Proposal Start and End Date: 01/2022 – 12/2023

* Total Award Amount: \$2,002,638

* Person Months (Calendar/Academic/Summer) per budget period.

Year Person Months

1. 2022 1.2 calendar

2. 2023 1.2 calendar

What other organizations were involved as partners?

Organization Name: Boston University

Location of Organization: Boston, MA

Financial Support:

In-Kind Support: NA

Facilities: NA

Collaboration: Subcontract; selecting and providing MRI scans thus far.

Personnel Exchanges: NA

Other: NA

Organization Name: Baylor College of Medicine

Location of Organization: Houston, TX

Financial Support:

In-Kind Support: NA

Facilities: NA

Collaboration: Subcontract executed August 29, data analysis

Personnel Exchanges: NA

Other: NA

8. Special Reporting Requirements

NA

9. Appendices

Quad Chart (separate file uploaded)