

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

REPORT DATE: OCTOBER 2023

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form 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 2023		2. REPORT TYPE Annual		3. DATES COVERED 30 Sep 2022 - 29 Sep 2023	
4. TITLE AND SUBTITLE Expanding the Characterization and Application of Clinical MRI Markers in Gulf War Illness				5a. CONTRACT NUMBER W81XWH-21-1-0963	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Deborah M. Little Ph.D. E-Mail: Deborah.M.Little@uth.tmc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Texas Health Science Center Houston UTHealth 7000 Fannin St. Houston TX 77030-5400				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development 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 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					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	11	19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Key Words	4
3. Accomplishments	4
4. Impact	7
5. Changes/Problems	8
6. Products	8
7. Participants & Other Collaborating Organizations	9
8. Special Reporting Requirements	11
9. Appendices	11

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)

Completed and data is included.

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

Initial analysis is complete. Correlation with symptoms and severity is pending.

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

This has been completed. Comparison with symptoms and severity, relative to quantitative data is pending.

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?

There were delays at the beginning of the project of 9 months into the award due to contracting. 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. To date we have accomplished:

1. All regulatory work.
2. The initial checklist for the study neuroradiologists.
3. A no cost extension due to the significant delays.
4. Neuroradiological reads of 100 veterans including 21 GW controls and 79 GW cases.
5. Research based (Freesurfer) volumetric analysis of all 100 veterans.
6. Assessment of global cortical atrophy using the standardized Global Cortical Atrophy Scale using two reviewers with interrater reliability of greater than 0.90.
7. Assessment of white matter damage associated with cerebrovascular risk factors using the Fazikas Scale with 2 raters with interrater reliability of greater than 0.90.

A discussion of the findings for items 4-7 follows.

4. Neuroradiological reads of 100 veterans including 21 GW controls and 79 GW cases.

Two board certified neuroradiologists have been involved in the research. The “primary” neuroradiologist completed the primary read (assessment). A second neuroradiologist read every 10th to confirm reliability. Reliability was calculated at above 0.90. The first global assessment was simply to assess whether the scan was normal or abnormal. This is a global read and simply indicates if there is an overall read of the scan per patient being abnormal. The data is presented in Figure 1. About a quarter of controls had an overall read of abnormal while over 90% of cases had their MRIs read as abnormal.

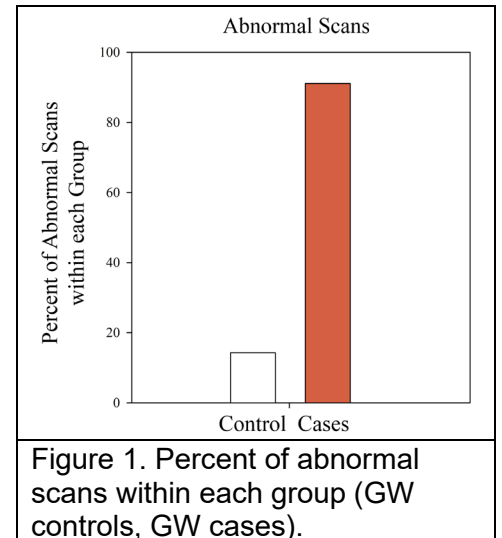


Figure 1. Percent of abnormal scans within each group (GW controls, GW cases).

5. Neuroradiological Assessment of Cortical Atrophy

Neuroradiologists were asked to assess atrophy by major lobe including frontal, parietal, temporal and occipital. They were also asked to assess deep gray and hippocampal regions. Figure 2 demonstrates the results of comparisons of the major cortical lobes.

Because of differences in subjects numbers for each group (Controls: 21; Cases:79), we calculated the percent of each group for which the study neuroradiologists indicated atrophy per regions. For example, if all 21 controls showed atrophy in the frontal lobe, this would represent 100% on the graphs.

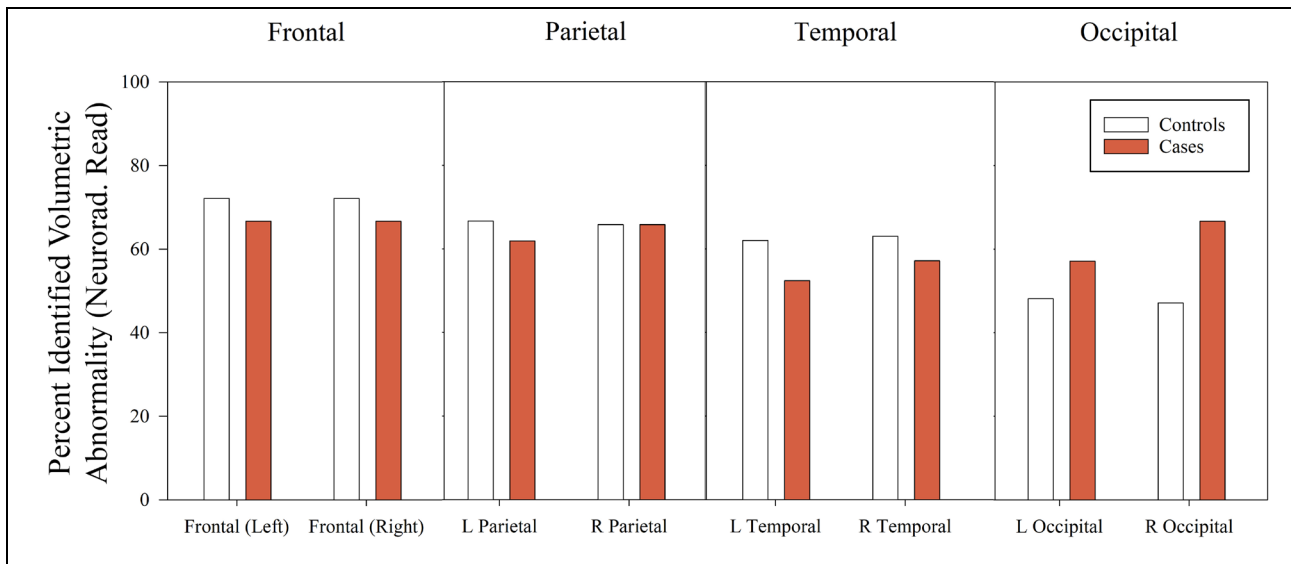


Figure 2. Percent of veterans (GW controls: white; GW Cases: orange) for which the study neuroradiologist indicated atrophy in the left or right of the frontal (far left), parietal (second to the left), temporal (second to the right) and occipital lobe).

What is interesting is that this **clinical read** showed no differences in atrophy between groups in these areas. This conflicts with research reporting. However, what stood out, is the differences identified by the neuroradiologists for deep gray matter and the hippocampus. In both areas, cases averaged 55% of neuroradiologists identifying clinically significant atrophy (deep gray matter) and 65% (hippocampus) while controls showed less than 6% scans with atrophy in the GWI cases. While the hippocampus is not surprising the finding of such significant and clinically relevant atrophy in the deep gray matter is the first finding of it's kind in GW cases.

6. Assessment of global cortical atrophy using the standardized Global Cortical Atrophy Scale using two reviewers with interrater reliability of greater than 0.90.

The global atrophy scale is a standardized measure used across sites and studies largely in dementia. Two raters were used to independently grade each scan. These data are presented in Figure 3. Raters were asked to assess atrophy in the anterior cingulate, the orbito-frontal and fronto-insula regions. Cases has

significantly higher GCA scores in the anterior cingulate and orbito-frontal regions than controls. The differences between cases and controls in the fronto-insula region did not reach significance.

7. Assessment of white matter damage associated with cerebrovascular risk factors using the Fazikas Scale with 2 raters with interrater reliability of greater than 0.90. Given the age of our veterans and their cerebrovascular risk factors we also examined white matter damage using the Fazikas Scale for all 100 veterans. This data is shown in Figure 4. While there appears to be a trend toward cases having a higher Fazikas Score (higher is worse), this is not significant suggesting that white matter involvement, at least from both the neuroradiological read and the standardized Fazikas Scale.

Overall, there are a number of different areas that are ripe for further analysis and integration with symptoms and exposures. From this, we should shortly be able to draft a second draft of the neuroradiology scale.

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. We added a first year medical student to the team (rater 2 on the Fazekas Score) and a M3 (rater 2 on the Global Cortical Atrophy Scale). Both medical students are going through medical school as part of the Army program and will be active duty following medical school. We will continue to look for training activities for veterans and active duty service members. All three will be on manuscripts and given the wealth of data being collected there will be more than sufficient for multiple manuscripts.

How were the results disseminated to communities of interest?

Nothing yet 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.

8. 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.

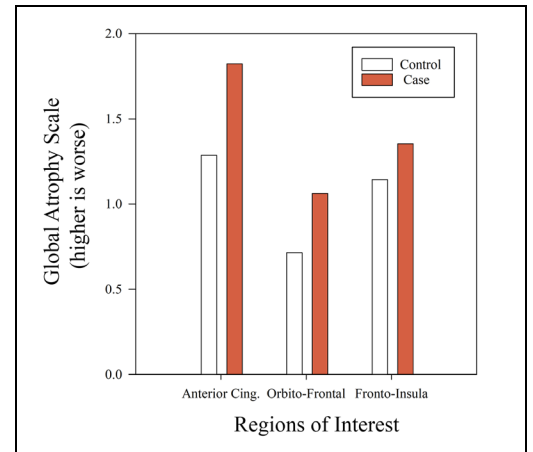


Figure 3. Global atrophy scale results for GW controls and GW cases.

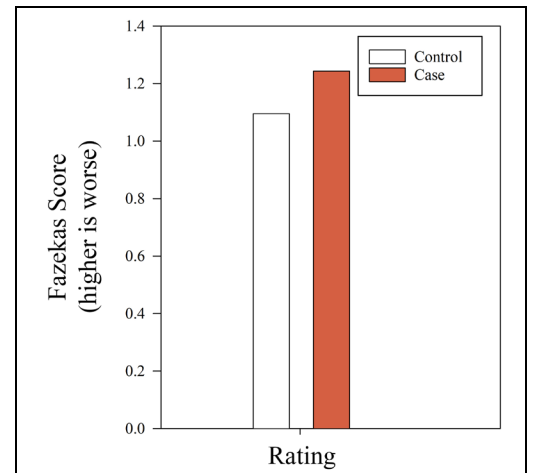


Figure 4. Fazekas Scale for GW Controls and GW Cases. Higher scores represent more white matter damage.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

9. 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

None.

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.

10. 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.

11. 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?

*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):

*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):

*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:

*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:

*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:

*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

12. Special Reporting Requirements

NA

13. Appendices

Quad Chart (separate file uploaded)