AWARD NUMBER: W81XWH-19-1-0381

TITLE: Autonomic Dysfunction, Brain Blood Flow, and Cognitive Decline in Veterans with Gulf War Illness

PRINCIPAL INVESTIGATOR: Jill N. Barnes, PhD

CONTRACTING ORGANIZATION: University of Wisconsin-Madison
Madison, WI 53715

REPORT DATE: JULY 2023

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
JULY 2023	Annual Report	1 July 2022 – 30 June 2023

4. TITLE AND SUBTITLE

Autonomic Dysfunction, Brain Blood Flow, and Cognitive Decline in Veterans with Gulf War Illness

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-19-1-0381

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Jill N. Barnes

E-Mail: jnbarnes@wisc.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Wisconsin-Madison
Madison, WI 53715

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

The incidence of multi-symptom illness or Gulf War Illness (GWI) in the Veterans deployed during the Gulf War is estimated to be 25-32%. The primary goal of this project is to examine cerebral blood flow responses to chemical and metabolic stress in Veterans with GWI compared with age and deployment-matched Veterans. We hypothesize that GWI is associated with both vascular dysfunction in the cerebral circulation and autonomic dysfunction. Participants will take part in a laboratory visit for autonomic function testing, and a magnetic resonance imaging scan (MRI) visit to determine brain structure and intracranial blood flow measurements at rest and in response to physiological stress. These experiments represent a novel and comprehensive approach and address fundamental and significant unresolved physiological questions in how GWI affects the human brain, with relevance to GWI symptoms.

15. SUBJECT TERMS
Gulf War Illness; Middle Aged; Neuroimaging; Autonomic; Cerebral Blood Flow

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	8	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. Introduction

The incidence of multi-symptom illness or Gulf War Illness (GWI) in the Veterans deployed during the Gulf War is estimated to be 25-32%. As Veterans from the Gulf War grow older, they may develop age-related conditions earlier and have a premature onset of disability. Importantly, many of the pathophysiological changes associated with GWI may increase the risk of developing Alzheimer's disease (AD) or other dementias. Altered regulation of cerebral blood flow is likely a key mechanism underlying the cognitive complaints in Veterans with GWI. In addition, autonomic dysfunction has been associated with GWI and this may be functionally linked to the impairment in cerebral blood flow regulation. Cerebral blood flow responses to chemical and metabolic stress will be measured in Veterans with GWI compared with age and deployment-matched Veterans. This project will be the first step in providing critical information and establishing a proof-of-concept regarding the pathophysiology of GWI.

2. Keywords

Gulf War Illness; Middle Aged; Neuroimaging; Autonomic; Cerebral Blood Flow

3. Accomplishments

What were the major goals of the project?
The major goals of this project include: 1) to determine if Veterans with GWI demonstrate vascular dysfunction in the cerebral circulation and impaired neurovascular coupling of blood flow with metabolic demand, compared with controls (n=30); 2) to determine if Veterans with GWI (n=30) demonstrate autonomic dysregulation compared with controls (n=30); 3) to determine if impaired cerebrovascular and autonomic variables in Veterans with GWI are associated with neuroimaging biomarkers of cognitive decline.

What was accomplished under these goals?
Our first major task on the Statement of Work for this project was to obtain the necessary human subject approvals. This project has obtained local IRB approval, HRPO approval along with ClinicalTrials.gov registration. This first major task is 100% complete. Our next major task was training trainees and students. Research staff have been trained on study specific protocols and on physiological measurements and radiology technicians have been trained on scanning protocols. This task is 100% complete. Our third major task was to initiate participant recruitment, which is ongoing. The study completed data collection for the first participant. Five additional participants have been enrolled at the time of this report. Recruitment flyers and documents have been prepared and distributed throughout the Madison, WI community. Newspaper ads have been scheduled to assist in recruitment. A list of Veteran organizations to contact for recruitment has been developed and communication has occurred. Social media announcements have also occurred. This task is 90% complete. In the next few months, we will look to hire a Veteran coordinator to assist with our recruitment. Our fourth major task is data collection. We have completed our pilot data collection studies, we have completed data collection on one participant. We are continuing to conduct phone screenings and data collection visits to enroll an additional 54 Veterans and collect data across three laboratory visits. This major task is ongoing, is approximately 10% complete, and will continue throughout 2023 and 2024.

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?
Recruitment is ongoing. Recruitment of Veterans and completing data collection will continue during the next reporting period.

4. Impact

This study received local IRB approval and HRPO approval in late February 2020. The University of Wisconsin-Madison shut down research laboratories and suspended all face-to-face human subject research in early March 2020. We received approval to restart human subjects research protocols on March 25, 2021. The space limitations (i.e. how many personnel allowed in the laboratory at one time) within research laboratories were lifted in Fall 2021 allowing the laboratory to return to data collection. At this time, we underwent considerable equipment issues due to non-use. This meant major equipment had to be tested, calibrated, and updated by the manufacturers. Once equipment returned, we performed re-training of the study protocol, began our pilot testing, and initiated recruitment. We had another delay in Fall 2022 and had to halt these activities while we waited for the MRI scanners to be upgraded and retraining performed by the Department of Radiology. We re-initiated recruitment, enrolled, and completed data collection for the first participant. The MRI scanner went down during Summer 2023, which resulted in rescheduling of our participants. At the time of this report, 5 additional participants have been enrolled. We are continuing to perform phone screenings for other potential participants. We have scheduled several more experimental study days through November.

We were able to publish the preliminary data that supports the use of our innovative cerebral blood flow measurements in middle-aged adults (https://pubmed.ncbi.nlm.nih.gov/37304825/). Importantly, this strategy of utilizing 4D flow MRI to determine intracranial blood flow responses will be used in this project for the first time.

What was the impact on the development of the principal disciplines 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 action or plans to resolve them.
Our MRI facility experienced has experienced significant delays in scheduling MRI studies due to MRI scanner upgrades and staffing shortages during late 2022 and early 2023. This resulted in

the halting of recruitment for all studies that involved MRI scans. This has significantly limited our ability to enroll participants and schedule MRI visits. Additional MRI technicians have been hired at the time of this report submission and we are now able to pre-schedule MRI visits. The MRI scanner went down again in Summer 2023, which resulted in rescheduling of our participants MRI scan visits. We are continuing to enroll and schedule participants for this study.

Changes that had a significant impact on expenditures.
Nothing to Report.

Significant changes in use or care of human subjects.
Nothing to Report.

6. Products

Nothing to Report.

7. Participants & Other Collaborating Organizations

Name:	Jill Barnes, PhD
Project Role:	PI
Researcher Identifier:	0000-0001-6317-4153
Nearest person month worked:	Effort: 3 months Funding: 1 month
Contribution to Project:	Dr. Barnes has performed work in the area of obtaining local IRB approval, HRPO approval, equipment calibration, training of trainees and students, MRI protocol testing, pilot testing, initiating participant recruitment, data collection, and handling of administrative duties.
Funding Support:	Funding for protected research time provided by the University of Wisconsin-Madison

Name:	Dane Cook, PhD
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	Effort: 1 months Funding: 0 months
Contribution to Project:	Dr. Cook has performed work as an advisor to the project, assisting with obtaining local IRB approval, revising research protocols, assisting with training of staff, and assisting with initiating recruitment and guidance for data collection.
Funding Support:	Funding for protected research time provided by the University of Wisconsin-Madison

Name:	Anna Howery, MS
Project Role:	Research Associate
Researcher Identifier:	
Nearest person month worked:	Effort: 3 months Funding: 3 months
Contribution to Project:	Ms. Howery has performed work in the area of obtaining local IRB approval, HRPO approval, revising study-specific protocols to comply with COVID-19-related regulations, performing equipment calibration and maintenance, ordering supplies and equipment, training of study staff, collaborating with radiology, MRI protocol testing, assembling recruitment materials, initiating recruitment and advertisements, performing phone screenings, and data collection.
Funding Support:	University of Wisconsin-Madison

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

The PI had a pending grant administrative supplement (NIH/NIA R03AG070469-S1) during the last reporting period. This was awarded in late August 2022 and the PI has effort of 20% from 9/2022 through 6/2024.

What other organizations were involved as partners?

Nothing to Report.

8. Special Reporting Requirements

None.

9. Appendices

None.