

AWARD NUMBER: W81XWH-19-1-0765

TITLE: Clarifying the Role Played by Microglia and Astrocyte Activation in Veterans with Gulf War Illness Using Positron Emission Tomography (PET)

PRINCIPAL INVESTIGATOR: Kimberly Sullivan, PhD

CONTRACTING ORGANIZATION: Boston University Medical Campus

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 SEPT 2022 - 29 SEPT 2023	
4. TITLE AND SUBTITLE Clarifying the Role Played by Microglia and Astrocyte Activation in Veterans with Gulf War Illness Using Positron Emission Tomography (PET)				5a. CONTRACT NUMBER W81XWH-19-1-0765	
				5b. GRANT NUMBER GRANT12744547	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Kimberly Sullivan, Ph.D. E-Mail: tty@bu.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Boston University Medical Campus 25 Buick Street, Suite 200 Boston, MA 02215- 1301				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 study objective is to assess whether veterans with GWI will show evidence of a chronic inflammatory process as measured by increased levels of astrocyte and microglial activation. We will determine the regionally specific pattern of astrocyte activation in 20 GW veterans. We will determine if there is regional independence of the astrocyte activation from microglial activation and we will assess the utility of using FDG PET as a marker for activated astrocytes. We have now obtained all appropriate IRB approvals and begun subject recruitment. This study is taking place at Mass General Brigham Hospital and Boston University School of Medicine. We have a subcontract in place between these institutions for this study. We have contacted 22 participants from the BBRAIN study to gage their interest in this call-back study. Seven veterans were found eligible and four participants have been consented and enrolled in the study. We will continue to contact BBRAIN study participants for recruitment efforts and will be collecting data from them once they are consented.					
15. SUBJECT TERMS Microglia, Astrocytes, PDG-PET, Positron Emission Tomography, chronic inflammatory process					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 8	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

Page

1. Introduction
2. Keywords
3. Accomplishments
4. Impact
5. Changes/Problems
6. Products
7. Participants & Other Collaborating Organizations
8. Special Reporting Requirements
9. Appendices

1. Introduction

The study objective is to assess whether veterans with Gulf War Illness will show evidence of a chronic inflammatory process as measured by increased levels of astrocyte and microglial activation. We will determine the regionally specific pattern of astrocyte activation in 20 GW veterans. We will determine if there is regional independence of the astrocyte activation from microglial activation and we will assess the utility of using FDG PET as a marker for activated astrocytes. We believe that information about astrocyte activation in veterans with GWI will help to clarify whether activation of astrocytes and microglia is regionally independent, representing separate processes or regionally related potentially representing a combined process. This is a multimodal PET imaging study that will be conducted in 20 GW veterans (10 GWI cases, 10 controls). GWI cases will be determined by Kansas GWI criteria. All participants will be recruited from the Boston Biorepository and Integrated Network (BBRAIN) for GWI which is conducting cognitive assessments and collecting blood, saliva, urine and other relevant biomarkers to share for GWI relevant studies. The veterans with GWI in this study will be asked to undergo an FDG PET scan at Boston Medical Center, [11C]-I-Deprenyl PET scan at Massachusetts General Hospital and a [11C]PBR28 PET scan at Massachusetts General Hospital. The healthy control veterans will only undergo the FDG PET scan at Boston Medical Center and [11C]-I-Deprenyl PET scan at Massachusetts General Hospital. This study will be a BBRAIN call-back study, and the PET imaging data will be included in the BBRAIN repository.

2. Keywords

Gulf War Illness

Microglia

Astrocytes

Positron Emission Tomography

Chronic Brain Inflammation Fluorodeoxyglucose

Kansas Gulf War Illness Criteria

Boston Biorepository and Integrated Network Deprenyl PET

PBR28 PET

3. Accomplishments – What were the major goals of the project?

Aim 1: To determine the regionally specific pattern of astrocyte activation using [11C]-l- Deprenyl PET ligand in combination with MRI based anatomical regions in 20 GW veterans (10 GWI cases, 10 controls). Aim 2: To determine if there is regional independence of the astrocyte activation from microglial activation using the [11C]PBR28 PET ligand in the same 10 veterans with GWI who were imaged under Aim 1. Aim 3: To assess the utility of using FDG PET as a marker for activated astrocytes we will image the same subjects scanned under aim 1 using FDG PET.

Accomplishments – What was accomplished under these goals?

In the current year of this project, we have completed all the regulatory requirements needed to start conducting research and have begun subject recruitment. The Boston University Institutional Review ceded review to the Mass General Brigham's IRB for this project, and we submitted it to the Human Research Protections Office (HRPO). HRPO approved it and we have begun conducting research. We found that we needed to amend the protocol to be better understand how COVID could impact the results of the study and change some of the surveys being given. The amendment was approved by the Mass General IRB. We have been contacting BBRAIN study participants who agreed to be re-contacted for future studies for recruitment. We have also posted recruitment flyers on research related websites. At this point, we have approached twenty-two BBRAIN participants who have expressed interest in in taking part in our study. Out of these individuals, 17 have completed the study screener. 5 individuals were ineligible upon screening. To date, 5 GWI participants have been eligible and 2 GW controls are eligible. Two participants from each group have been consented to participate for a total of 4 participants (Table 1). We are continuing to work with the radiology team at MGH as well as BUSM to conduct the PET scans. Scans acquired at Mass General Brigham will be transferred between Dr. Loggia's lab and Dr. Sullivan's lab via secure file transfer protocols. Scans acquired at BUSM will be transferred from the Department to Dr. Sullivan's lab on a CD and then shared with Dr. Loggia's lab via secure file transfer.

Table 1. Recruitment Report

	GWI	GW Healthy	Total
Eligible	5	2	7
Ineligible	4	0	4
Consented/Enrolled	2	2	4

Accomplishments – What opportunities for training and professional development has the project provided?

This project has provided unique and highly valuable hands-on training for one full-time graduate student Renee DeVivo and then Jenna Groh and one half-time graduate student Yashar Rahimpour in the process of working with Institutional Review Boards, the development of protocols for use with human subjects recruitment, methods for ensuring confidentiality and the use of radioligands in human studies. This project has also offered them the experience of working with the Department of Radiology at BUSM in setting up the protocol for scanning subjects on their clinical/research device. Finally, this project has provided for these two students in discussions with radiation safety officials and scientists using radioligands with human subjects. Currently, Dylan Keating is coordinating the study and gaining valuable professional development.

Accomplishments – How were the results disseminated to communities of interest?

Nothing to Report

Accomplishments – What do you plan to do during the next reporting period to accomplish the goals?

In the next reporting period, we expect to continue to recruit, consent, and acquire data from participants in this study. We will be processing the data as they are acquired to facilitate the statistical analyses and reporting of results of the PET imaging data.

4. Impact – What was the impact on the development of the principle discipline of the project? Nothing to Report

Impact – What was the impact on other disciplines?

Nothing to Report

Impact – What was the impact on technology transfer?

Nothing to Report

Impact – What was the impact on society beyond science and technology?

Nothing to Report

5. Changes/Problems – Changes in approach and reasons for change.

After the unfortunate passing of Dr. Killiany, Dr. Sullivan has become the study PI and will continue the study as planned with Dr. Loggia at MGH.

Changes/Problems – Actual or anticipated problems or delays and actions or plans to resolve them.

We now have full regulatory (IRB) approval in place for this study. As a call-back study to Dr. Sullivan's BBRAIN project we have been recruiting BBRAIN participants in taking part in this study. To

date, we have been in contact with twenty-two interested participants. Four participants have been consented while we continue to approach other BBRAIN participants to gauge their interest. We believe this process will allow us to identify the subjects we need and will help us to collect the data for this study.

Changes/Problems – Changes that had a significant impact on expenditures.

Nothing to Report

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

Nothing to Report

Changes/Problems – Significant changes in use or care of human subjects.

Nothing to Report

Changes/Problems – Significant changes in use or care of vertebrate animals.

Nothing to Report

Changes/Problems – Significant changes in use of biohazards and/or select agents.

Nothing to Report

6. Products – Publications, conference papers and presentations.

Nothing to Report

Products – Websites or other internet sites.

Nothing to Report

Products – Technologies or techniques.

Nothing to Report

Products – Inventions, patent applications and/or licenses

Nothing to Report

Products – Other products

Nothing to Report

7. Participants & Other Collaborating Organizations

What individuals have worked on this project?

Name: Ronald Killiany, Ph.D.

Project Role: Principal Investigator

Research Identifier: ORCID ID 0000-0003-4740-2181 *Nearest Person Month Worked:* 2

Contribution to the Project: Review/submission of Institutional Review Board applications, administration of MGH subcontract, coordination of return to research.

Name: Renee DeVivo

Project Role: Full time graduate student

Research Identifier: NA

Nearest Person Month Worked: 9 – Dr. DeVivo completed her doctoral work in May 2022.

Contribution to the Project: Drafting of Institutional Review Board protocol and amendments, interfacing and preliminary review with Massachusetts General Institutional Review Board application and response to comments raised.

Name: YASHAR RAHIMPOUR

Project Role: Half-time graduate student

Research Identifier: NA

Nearest Person Month Worked: 3 – Dr. Rahimpour completed his doctoral work in Dec 2021.

Contribution to the Project: Editing of Institutional Review Board protocols, discussion with Boston University Radiation Safety office concerning use of multiple PET ligands in the same subjects, responds to IRB preliminary review questions, development of study materials for recruitment.

Participants & Other Collaborating Organizations – has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

Participants & Other Collaborating Organization – What other organizations were involved as partners?

Organization Name: Mass General Brigham (formally Massachusetts General Hospital Location of

Organization: Boston, Massachusetts, USA

Partner's contribution to the project: Subcontracted performance site.

8. Special Reporting Requirements Nothing to Report

9. Appendices

Nothing to Report