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

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CONTRACTING ORGANIZATION: Trustees of Boston University, BUMC

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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 regionally 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 continued to focus on obtaining appropriate approvals while working with institutions which are trying to re-open their in person research programs. This study will take place a Mass General Brigham Hospital and Boston University School of Medicine. We have a subcontract in place between these institutions for this study. We have worked with the IRB at Boston University and they are in the process of ceding review of this study to Mass General Brigham Hospital's IRB. We have IRB approval from Mass General Brigham Hospital's IRB. The BBRAIN study from which we will be recruiting is up and running with in person visits.

15. SUBJECT TERMS
Microglia, Astrocytes, PDG-PET, Positron Emission Tomography, chronic inflammatory process

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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]-l-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]-l-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 second year of this project we have continued to focuse on completing the vital tasks that will make the collection of data and analyses possible in this project. We set up a subcontract with Mass General Brigham Hospital (formally known as Massachusetts General Hospital) in the first year of the project. We have continued our discussions with our colleague Marco Loggia Ph.D. about the proper Positron Emission Tomography to be using in the project and the logistics surrounding the recruitment of participants at Boston University Medical School with consent for both the Boston University and Mass General Brigham Institutional Review Boards (IRB). Our initial plan was to submit separate IRB applications to both Boston University and Mass General Brigham, however upon discussion with both IRBs and amongst ourselves it became clear that this study should have one IRB approval and that it should come from Mass General Brigham as that is where the experimental PET ligands would be produced and administered. We entered into discussions with the Boston University IRB on this and they agreed to cede review to Mass General Brigham's IRB. We have obtained approval from Mass General Brigham's IRB and are in the final process of responding to questions from Boston University's IRB before they will fully cede review. Once we have final approval at the local level we will submit to HARPO. We have had discussions with the Boston Medical Center Radiology department about the logistics that will be involved in this project and have made them aware of our needs for research slots on the PET scanner. We have also set up a mechanism through the BBRAIN project for the secure transfer of medical images such as those we will be generating in this project between Dr. Loggia's lab and Dr. Killiany's lab.

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

This project has provided unique and highly valuable hands-on training for our full-time graduate student Renee DeVivo and our half-time graduate student Yashar Rahimpour in the process of working with Institutional Review Boards, the development of protocols for use with human subjects, strategies for recruitment, methods for ensuring confidentiality and the use of radioligands in human experiments. This experience was enhanced at first by working with two separate IRBs each with a common mission but unique approaches and then in the process of working with an IRB to cede review. Further, this project has provided training for these two students in discussions with radiation safety officials and scientists using radioligands with human subjects.

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 have full IRB approval at the local level and will submit to HARPO. Dr. Sullivan's BBRAIN project has returned to in person research visits/assessments (permission required by BU COVID policy). As a call-back study to the BBRAIN project we will gage the BBRAIN participants interest in taking part in a studies like this one at the time of their on-site visit (no recruitment until all approvals are in place). This will allow us to fast track the recruitment process once we have all IRB approvals in place (including HARPO) and start collecting data sooner.

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.

Nothing to Report

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

We have continued to face delays in the past year with this project due to the COVID 19 virus.
The initial response by both Boston University Medical School and Mass General Brigham Hospital to the COVID 19 crisis was to fast-track research into the virus and how to care for those afflicted with it. Administrative and IRB/IACCUC resources were prioritized to this effort. As we began to "return" to research, the priority was placed on ongoing, approved research which had been suspended and on clinical trials in which treatments had been postponed or delayed. Studies such as this one which were still needing administrative approvals were given the least attention.

We are now at a point where both institutes (Mass General Brigham and Boston University) are fully open for research and most laboratories/departments have returned to fully in person activities. During the first year of this project, we were able to put in place a subcontract with Mass General Brigham Hospital for this award and began the process of having the procedures for this project reviewed by the two IRBs. Initially we thought that we would be obtaining independent approval from each IRB but as the IRB applications matured, it became more and more apparent that we would only be able to get one IRB approval and the second IRB was going to need to cede review. We elected to work with the Boston University IRB to discuss the process of ceding review as the experimental PET ligands in this project are being produced and administered at Mass General Brigham. Boston University's IRB agreed to cede review once we responded to the questions that they had raised on initial review. Mass General Brigham's IRB agreed to be the IRB of record and approved the protocol. We are awaiting our responses to Boston University's IRB for them to notify us that they have ceded review.

Towards the later part of this year, Dr. Sullivan's BBRAIN project was given permission from Boston University to return to in person research visits/assessments (permission required by BU COVID policy). The BBRAIN project is actively completing research visits. As an call- back study to the BBRAIN project we will gage the

BBRAIN participants interest in taking part in call-back studies like this one at the time of their on-site visit (no recruitment until all approvals are in place). This will allow us to fast track the recruitment process once we have all IRB approvals in place (including HARPO) and start collecting data sooner.

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 of Institutional Review Board applications, administration of MGH subcontract, coordination of return to research for BBRAIN project

Name: Renee DeVivo

Project Role: Full time graduate student

Research Identifier: NA

Nearest Person Month Worked: 12

Contribution to the Project: Drafting of Boston University Medical Center Institutional Review Board protocol, interfacing and preliminary review with Boston University Medical Center Institutional Review Board, consultation on 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: 6

Contribution to the Project: Editing of Boston University Medical Center Institutional Review Board protocol, 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