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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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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 now obtained all appropriate IRB approvals. 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 contacted ten participants from the BBRAIN study to gage their interest in this call-back study. One has expressed interest in participating and we are working on getting this individual consented. We will be continuing to contact BBRAINS study participants to gage their interest and will be collecting data from them once they are consented.

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 third year of this project, we have completed all the regulatory requirements needed to start actively conducting research. The Boston University Institutional Review Board (IRB) ceded review to the Mass General Brigham's IRB. Mass General Brigham's IRB approved of the project, and we submitted it to the Human Research Protections Office (HRPO). HRPO approved it and we prepared to get started 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 Brigham's IRB and HRPO ruled that the changes were not substantive. We began to contact Boston Biorepository and Integrated Network (BBRAIN) study participants to gage their interest in taking part in this study. At this point, we have approached ten BBRRAIN participants and one has expressed on interest in taking part in our study. Our colleagues in Dr. Loggia's lab will be following up with this individual to get them through the consent process. We have all the proper protocols in place at Mass General Brigham and we have been working with the Department of Radiology at Boston University School of Medicine to ensure that the proper procedures are in place to acquiring research slots on the BUSM Positron Emission Topographer (PET). Scans acquired at Mass General Brigham will be transferred between Dr. Loggia's lab and Dr. Killiany's lab via secure file transfer protocols. Scans acquired at BUSM will be transferred from the Radiology Department to Dr. Killiany's lab on a CD and then shared with Dr. Loggia's lab via secure file transfer.

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 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, strategies for recruitment, methods for ensuring confidentiality and the use of radioligands in human experiments. 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 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 recruit, consent, and acquire data from all the research participants in this study. We will be processing the data as they are acquired to facilitate the statistical analyses and reporting of results.

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 now have full regulatory (IRB) approval in place for this study. As a call-back study to Dr. Sullivan's BBRAIN project we have begun to gage interest by the BBRAIN participants in taking part in this study. To

date, we have been in contact with ten of them. One has expressed an interest and we will be working to get this participant consented while we continue to approach other BBRAIN participants to gage 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