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TITLE: Assessing Neuroinflammation in Gulf War Illness with Whole-Brain Magnetic Resonance Spectroscopy

PRINCIPAL INVESTIGATOR: Jarred Younger, PhD

CONTRACTING ORGANIZATION: University of Alabama, Birmingham, AL

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Currently, there are no targeted treatments for Gulf War Illness (GWI). In order to solve that problem, it is essential that researchers discover the cause of GWI. It is similarly important that an objective test be developed that can clearly show why individuals suffer from GWI. While many attempts at developing such a test have been made, none of them have yielded a clinically-useful tool. Our central hypothesis is that GWI involves chronic neuroinflammation. The symptoms of GWI (e.g. fatigue, musculoskeletal pain, sleep disturbances, and cognitive dysfunction) overlap heavily with classic cytokine-induced sickness responses. In the case of GWI, microglial cells in the brain can be pushed into a hypersensitized state by toxins or abnormal immune challenges, leading to chronic overproduction of pro-inflammatory factors that result in the primary symptoms of GWI. To test the central hypothesis, it is necessary to measure neuroinflammation in humans in vivo. However, most techniques are too invasive for using in living individuals. To address that problem, we use an MRSI scan which provides metabolite concentrations in 4,000 separate voxels, giving whole-brain coverage. The scan yields measurements for: myo-inositol (a marker of glial cell proliferation), lactate (a product of anaerobic metabolism), choline (a sign of cellular breakdown), and N-acetylaspartate (a marker of neuronal health). The scan also provides absolute brain temperature, which is elevated with severe neuroinflammation.

15. SUBJECT TERMS

Gulf War Illness

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1. INTRODUCTION:

The primary objective of this study is to determine if Gulf War Illness (GWI) likely involves neuroinflammation. By assessing the five neuroinflammatory outcomes across the brain, we can determine if there are focal or global signs of one or more neuroinflammatory markers in brains of individuals with GWI. The magnetic resonance spectroscopy imaging (MRSi) technique may allow our group and others to detect cases of GWI neuroinflammation, which would improve treatment decisions as well as the development of new targeted therapies. It is an ideal diagnostic tool because it has low patient risk, is noninvasive, can be used repeatedly in longitudinal studies, provides whole-brain coverage, yields multiple independent markers of inflammation, and can be employed at most hospital and research neuroimaging suites.

2. KEYWORDS:

Gulf War Illness, neuroinflammation, neuroimaging

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major goal of this work is to determine if GWI involves neuroinflammation. Our completed and anticipated milestones for study activities are as follows:

Milestone	Target Date	Actual or Anticipated Completion Date
Agreement on eligibility criteria, screening protocol, and procedures	July 2019	July 2019
Consent form and human subjects protocol finalized	July 2019	July 2019
All UAB, HRPO, and other approvals granted	August 2019	March 2020
Study protocol ready to begin	August 2019	October 2020
First participant enrolled	December 2019	December 2020
20 GWI participants enrolled	May 2022	September 2022
20 control participants enrolled	June 2022	December 2022
Results reports generated	August 2022	August 2023
Report full results from all analyses	August 2022	August 2023

What was accomplished under these goals?

34 participants (20 GWI; 14 controls) have been enrolled in the study and completed the protocol. We are currently at 85% of our target enrollment goal. Our recent progress has positioned us to accomplish our enrollment goal of 40 participants by February 2023. We were not able to recruit or enroll participants at the start of this study due to the COVID-19 pandemic, which pushed our enrollment milestone targets back. However, we have been steadily enrolling participants since then (including during the reporting period) and are close to completing our enrollment goal.

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

The study coordinator was trained in MRI/MRS acquisition and processing and presented at two conferences with preliminary project data. Three undergraduate research assistants received data management, MRI safety, and Research, Ethics, and Compliance training.

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?

We plan to continue recruitment efforts via radio and digital advertisement campaigns to enroll the remaining 6 healthy control participants. Once all participants have completed the study, we will assay all of the blood samples that were collected. Then we will conduct statistical analyses on the neuroimaging and blood sample data to prepare manuscripts as well as the final technical report for this study.

4. IMPACT:

What was the impact on the development of the principal discipline(s) 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:

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Recruitment is always an obstacle. However, utilizing radio advertisements increased our recruitment rates and we are now on track to finish recruitment of all participants within the next few months.

Changes that had a significant impact on expenditures

Nothing to report.

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

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Two poster presentations were given during the reporting period:

Jones, C., Maudsley, A., Sherriff, S., Wetzel, E., Robinson, J., Younger, J. (2021). Assessing neuroinflammation in Veterans with Gulf War Illness: A pilot study using whole-brain magnetic resonance spectroscopy. Presentation at the 50th Society for Neuroscience Annual Meeting, Chicago, IL.

Jones, C., Maudsley, A., Sherriff, S., Wetzel, E., Robinson, J., Younger, J. (2021). Assessing neuroinflammation in Veterans with Gulf War Illness: A pilot study using whole-brain magnetic resonance spectroscopy. Presentation at the Alabama Advanced Imaging Consortium, Birmingham, AL.

- **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.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Jarred Younger, PhD	Paige Palenski	Chloe Jones
Project Role	PI	Lab Manager	Study Coordinator
Researcher Identifier (ORCID)	0000-0003-3616-9919	0000-0001-5628-8013	0000-0002-7288-8235
Nearest person month worked	2	1	2
Contribution to project	Dr. Younger has developed protocol for execution of study and overseen study procedures.	Paige has handled the regulatory and financial aspects of this study.	Chloe has screened and completed data collection for all participants in this study.
Funding support	AFSA, ME Research UK, R01NS109529 (NIH/NINDS), GWI180071 (DOD), GW210009 (DoD)	R01NS109529 (NIH/NINDS)	GW180071 (DOD)

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

Yes, there has been a change in the active other support of the PI. The AFSA grant “Detecting neuroinflammation in fibromyalgia with the positron emission tomography (PET) radioligand DPA-714” ended on June 15, 2022. Dr. Younger has also received a new grant since the last reporting period, entitled “Curcumin, Resveratrol, and Stinging Nettle as Treatments of Gulf War Illness” (DoD award number W81XWH2210420) which started on August 1, 2022.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: