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Assessment of MRI-Based Marker of Dopaminergic Integrity as a Biological Indicator of Gulf War Illness

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14. ABSTRACT

Gulf War illness (GWI) is characterized symptomatically in veterans who served in the 1990-1991 Gulf War by a constellation of symptoms including headache, pain, fatigue, gastrointestinal problems and alterations in cognition. Diagnostic tests and effective treatments have not been identified. The proposed project leverages existing brain imaging data from a sample of 1990-91 Gulf War veterans and includes an in-depth, detailed analysis of the integrity of the corticostriatal circuit using high resolution diffusion imaging. While institutional human subjects approvals have been obtained during this period, there is no other progress to date under this award as the start of this project is pending initiation of the parent study which has been delayed due to DMDC regulation changes and delays in institutional contracting which are detailed in the annual reports for the parent grant. The revised timeline for the parent study has a data collection start date in the first quarter of 2016. Consistent with this delayed start, no funds have been used to date.

15. SUBJECT TERMS
Gulf war illness; magnetic resonance imaging; dopamine; diffusion tensor imaging

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1. Introduction

Gulf War illness (GWI) is characterized symptomatically in veterans who served in the 1990-1991 Gulf War by a constellation of health symptoms that typically include some combination of persistent headache, widespread pain, fatigue, gastrointestinal problems and alterations in cognitive function. Diagnostic tests and broadly effective treatments have not been identified for GWI. Although there are multiple indications of significant central nervous system differences between GWI cases and controls, there is still no comprehensive understanding of the spectrum of alterations in cerebral neurobiology/neurophysiology and how they result in GWI symptoms. One understudied area of research is the role of the corticostriatal circuit. Multiple studies have demonstrated preliminary indications of neuronal dysfunction in this circuit (1, 2) but these are limited in scope and in the characterization of the symptoms. This project will leverage existing brain imaging data from a well-characterized sample of 1990-91 Gulf War veterans to assess brain structures and processes of high interest for understanding GWI (CDMRP funded, PI: L. Steele), but not previously studied in ill Gulf War veterans. Our aims are to assess the integrity of the substantia nigra, basal ganglia and cortex as markers of integrity of the nigro-striatal dopaminergic pathway using high resolution diffusion tensor imaging (DTI) in 80 veterans with GWI and 50 healthy Gulf War veteran controls and to characterize the etiological and clinical correlates of alterations in brainstem and basal ganglia integrity. If successful, this study will form the foundation for novel approaches to clinical intervention to include specific targeting of the dopaminergic system.

2. Keywords

Gulf war illness; Corticostriatal circuit; Nigro-striatal circuit; Dopamine; Diffusion tensor imaging; Magnetic resonance imaging

3. Accomplishments

As administrative background, the grant described in this progress report supports the secondary analyses of data collected under the CDMRP funded grant "Assessment of diverse biological indicators in Gulf War Illness: Are they replicable? Are they related?" (W81XWH-11-1-0812; PI: Lea Steele). W81XWH-11-1-0812 "Assessment of diverse biological indicators in Gulf War Illness: Are they replicable? Are they related?" will be referred to as the "parent" grant (**parent**) throughout. The parent is a multi-site study with the responsible institution being Baylor College of Medicine following a transfer from Baylor University. The data collection site for the parent is now Baylor College of Medicine (was, Scott and White Memorial Hospital).

The parent study has not yet begun data collection due to a number of significant delays involving access to DMDC data as well as three changes in the secondary site for imaging data and a transfer to Baylor College of Medicine. As such, and as has been communicated to program staff, we have not begun this secondary analysis grant.

At present, all regulatory approvals are in place but no data is yet available to conduct the research proposed. We will work with program staff on an alternate plan to supplement the originally proposed data with other available data.

What were the major goals of the project?

Major goals of the project are identified as the major tasks as described in the approved statement of work. For this contract, there are 7 major goals which fall into the general categories of regulatory, quality assurance of data quality, quality assurance of staff for the required imaging analysis, and

development and validation of methods. These are outlined below as well as a statement of degree of completion.

Task 1. Human Subjects Initial Approval and Review (months 1-4):

Completed at both the initial site and at the transfer site as well as HRPO.

Action plan, Task 1.

Task 2. Quality assurance protocol and data collection (1-24):
No progress to date.

Task 3. Training of staff on image preprocessing (months 1-5)
No progress to date.

Task 4. Methods development and validation for Substantia Nigra characterization (training data analyst on region of interest placement) (Aim 1)
No progress to date.

Task 5. Methods development and validation for thalamic nuclei assessment (training data analyst on seed voxel placement) (Aim 2)
No progress to date.

Task 6. Methods development and validation for regions to be extracted via normalized masks (putamen, caudate, cortex) (Aim 3)
No progress to date.

Task 7. Data Analysis
No progress to date.

What was accomplished under these goals?

All approvals prior to HRPO were obtained at which point the parent grant PI notified the PI of this grant of a change in employment which will require additional IRB approvals prior to HRPO submission.

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

Using institutional support, the PI travelled to Boston to meet with a major Gulf War Illness consortium study staff. This meeting had the intention to ensure sufficient overlap in imaging methods to allow leveraging of imaging data to be collected for the consortium.

How were the results disseminated to communities of interest?

No data has been collected for the parent grant resulting in no data analysis for this project. As such, there are no results to disseminate.

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

1. Working with program staff to identify an alternate plan for data for the proposed research.

4. Impact

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

Data analysis has not yet begun. As such, there is nothing to report.

What was the impact on other disciplines?

Data analysis has not yet begun. As such, there is nothing to report.

What was the impact on technology transfer?

Data analysis has not yet begun. As such, there is nothing to report.

What was the impact on society beyond science and technology?

Data analysis has not yet begun. As such, there is nothing to report.

5. Changes/Problems

Changes in approach and reasons for change

Nothing to report.

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

The project is years behind due to challenges met by the parent grant. We will discuss with program staff alternative solutions for data for the proposed research.

Changes that had a significant impact on expenditures

No funds will be used until data collection for the parent grant has begun and revised timelines, budget period, and all other approvals from program staff are in place.

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

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Not applicable as no vertebrate animals are included in the scope of work.

Significant changes in use of biohazards and/or select agents

Not applicable as no biohazards and no select agents are included in the scope of work.

6. Products

Data analysis of imaging data collected in the parent grant have not begun. As such, there are no products to report.

7. Participants & Other Collaborating Organizations
What individuals have worked on the project?

No budgeted effort has been used for this project and will not until data collection for the parent grant has begun. As such, there is nothing to report.

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.

What other organizations were involved as partners?

The project is currently entirely at Baylor College of Medicine.

8. Special Reporting Requirements

Nothing to report.

9. Appendices

No appendices are included.

10. References Cited in this Report

1. Haley RW*, et al.* (2000) Effect of basal ganglia injury on central dopamine activity in Gulf War syndrome: correlation of proton magnetic resonance spectroscopy and plasma homovanillic acid levels. *Arch Neurol* 57(9):1280-1285.
2. Haley RW*, et al.* (2000) Brain abnormalities in Gulf War syndrome: evaluation with 1H MR spectroscopy. *Radiology* 215(3):807-817.