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

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14. ABSTRACT

Up to one third of military veterans who served in the 1990-1991 Persian Gulf War continue to suffer from Gulf War illness (GWI), a complex of chronic symptoms that includes persistent headaches, memory and cognitive difficulties, widespread pain, unexplained fatigue, gastrointestinal problems, and other difficulties. Multiple findings of significant central nervous system (CNS) involvement have been reported in veterans with GWI. But despite preliminary indicators of neuronal dysfunction in the corticostriatal circuit in veterans with GWI, it has not been well-studied. The current study leverages existing brain imaging data from well-characterized samples of 1991 Gulf War veterans to provide in-depth assessment 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). Due to project delays and institutional changes over the previous year, several project changes have been approved in order to accelerate study progress, including addition of two additional study sites. This will allow more rapid consolidation of data for the targeted sample in order to evaluate alterations in brainstem and basal ganglia integrity. Additional analyses will characterize etiologic and clinical correlates of dopaminergic pathway alterations, including associations with GWI symptom presentation.

15. SUBJECT TERMS
Gulf war illness; neuroimaging, magnetic resonance imaging, corticostriatal circuit; nigro-striatal circuit; dopamine; diffusion tensor imaging

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

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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

At least one in four military veterans who served in the 1990-1991 Persian Gulf War continue to suffer from a serious, often debilitating illness known as Gulf War illness (GWI). GWI is characterized by a complex of chronic symptoms that typically includes persistent headaches, memory and cognitive difficulties, widespread pain, unexplained fatigue, gastrointestinal problems, and other difficulties. Although multiple indicators of significant central nervous system (CNS) alterations and functional decrements have been reported in veterans with GWI, there is still no comprehensive understanding of GWI cerebral neurobiology/neurophysiology and how observed CNS changes underlie, or are associated with, GWI symptoms. In particular, the role of the corticostriatal circuit in GWI has not been well-studied, despite multiple preliminary indications of neuronal dysfunction in this circuit. The current study leverages existing brain imaging data from well-characterized samples of 1990-91 Gulf War veterans to assess brain structures and processes of high interest for understanding GWI. It provides in-depth assessment 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. Detailed analyses will characterize the etiologic and clinical correlates of alterations in brainstem and basal ganglia integrity, including associations of dopaminergic pathway alterations with GWI symptom presentation. If successful, this study will form the foundation for improved approaches to clinical intervention that include specific targeting of the dopaminergic system.

2. KEYWORDS

Gulf War illness, neuroimaging, magnetic resonance imaging, corticostriatal circuit; nigro-striatal circuit; dopamine; diffusion tensor imaging

3. ACCOMPLISHMENTS: What were the major goals of the project?

Administrative note: Prior to and during the current reporting period, this project has encountered a number of significant delays associated with (1) multiple institutional transfers of key personnel and (2) delays in recruitment and data collection for the original parent project that is providing data to be analyzed for the current study. During the current reporting period, the original study PI (Dr. Deborah Little) left Baylor College of Medicine (BCM) to accept a new position at the University of Texas Health Science Center (UT) and initiated the process of requesting DOD approvals for a change in PI to Dr. Lea Steele at BCM. As of the reporting date for this annual report (April 5, 2019), that process was underway but not yet finalized. As a result, there was a temporary lapse (Jan 2019 – May 2019) in clarity related to project reporting in the absence of an approved PI at the award institution. This was further complicated by technical and administrative difficulties at BCM in delivering project documents and requests to DOD in relation to these changes.

In conjunction with the request for the change in PI described, a revised performance plan and timeline were also developed. The proposed changes provide additional sources of MRI data for analysis in order to accelerate study progress to successfully address study objectives. Both the change in PI and revised performance plan were subsequently approved by DOD, and finalized after the reporting date for the present report.

We therefore provide below a summary of the approved study goals and tasks that were in place during the March 2018-March 2019 reporting period for this annual report. But we will also provide, as an Appendix to the current report, an updated summary of the status of study objectives and tasks as of January 31, 2020. Full details of the status of approved project changes that occurred March 2019-March 2020 will then be provided in the April, 2020 annual report.

Major Project Tasks, as Itemized in Approved SOW for March 2018 – March 2019:

Task 1. Human Subjects Initial Approval and Continuing Review:
Status: All human subjects protocols were successfully submitted and approved according to the designated timeline for the original study site IRB, the transfer site IRB, and Army HRPO. Continuing reviews and limited amendments have also been maintained and approved in a timely fashion, consistent with target/required dates.

Task 2. Quality assurance protocol and data collection.
Nothing to report. Data not available for QA or analyses; Data collection for the parent project not initiated as of March, 2019.

Task 3. Training of staff on image preprocessing.
Nothing to report. Data not available for training or image preprocessing as of March, 2019.

Task 4. Methods development and validation for Substantia Nigra characterization (training data analyst on region of interest placement)
Nothing to report. Data not available for regional analyses or validation as of March, 2019.

Task 5. Methods development and validation for thalamic nuclei assessment (training data analyst on seed voxel placement)
Nothing to report. Data not available for regional analyses or validation as of March, 2019.

Task 6. Methods development and validation for regions to be extracted via normalized masks (putamen, caudate, cortex)
Nothing to report. Data not available for regional analyses or validation as of March, 2019.

What was accomplished under these goals?
All human subjects and regulatory approvals were put in place for all IRBs associated for initial and subsequent institutions and Army HRPO. However, data analyses have not been conducted as of March, 2019, and a number of project changes have been proposed and initiated.

What opportunities for training and professional development has the project provided?
Using institutional support, the original project PI (Dr. Little) travelled to Boston to meet with investigators for a major Gulf War Illness consortium study (GWIC) and data repository. This meeting included evaluations to determine whether there was sufficient overlap in imaging methods and study populations to consider collaboration and inclusion of repository data in the current protocol.

How were the results disseminated to communities of interest?
No data analyses have yet been conducted for the current project. As such, there are no results to disseminate.

What do you plan to do during the next reporting period to accomplish the goals?
As of March, 2019, the original and proposed new project PIs were working with colleagues at Boston University to identify an alternate plan for obtaining additional MRI data for the proposed research, developing a plan and methods for conducting study analyses jointly at BCM and UT, and seeking institutional and DOD approvals for the proposed changes.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

As of the date of this annual report (April 5, 2019) the most prominent changes during the reporting period had been proposed, but not yet finalized. At that time, the original study PI (Dr. Little) was in the process of working with Baylor College of Medicine (BCM), the University of Texas Health Science Center (UT) and our CDMRP Project Officer and Contract Office to obtain all required approvals and meet administrative requirements for a change in the study PI, as well as adding an additional data source and revising the project performance timeline. These changes were necessary because the original study PI left BCM during the reporting period for a new position at UT and also because of continued delays in data collection on the parent study. In their original January 2019 letter to DOD, the original PI and BCM requested that Dr. Lea Steele at BCM be assigned as the new project PI, and also requested approval of specified changes to the performance plan and timeline. This would include approval of a subaward to UT to allow Dr. Little to continue to serve as senior neuroscientist on the project to oversee analyses of neuroimaging data in collaboration with BCM investigators. Close collaboration remained possible because the original PI's new location is less than a mile from Dr. Steele's location at BCM in Houston. The other major project change requested was the addition of a new data source to provide additional MRI data for the secondary analyses to be conducted for the study. Under this proposed change, neuroimaging data from 1990-91 Gulf War veterans would be provided by Boston University (BU), specifically, MRI data previously collected for the DOD-funded Gulf War Illness Consortium (GWIC). Addition of these data would allow investigators to accelerate progress to more quickly reach their target sample size for the current study.

Note that no changes have been made or proposed during this period with respect to the scientific approach of the project, specific aims, or individual protocol activities. The primary changes during this project year, as described above, relate to institutional changes and project delays that have pushed back milestone dates for completing major tasks.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

As previously described, the core problems and delays have occurred in relation to lack of data available from the original parent study for secondary analyses by the current project, as well as institutional and administrative delays associated with the change in PI request and addition of two additional study sites. We anticipate that utilization of data from the additional study site at BU, as well as availability of additional analytic and administrative support at the new UT site will accelerate progress in meeting study objectives.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

As of the date for this report (April 5, 2019) no expenditures have been billed to the project. Therefore, all funds awarded for the project were still available to complete the study. Both the original and proposed PIs for the project determined that expenditures would not be incurred until there was a clear plan for access to collected imaging data for secondary analyses, and proposed revisions in the project's timeline, budget, and scope of work were approved and in place.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects.

Significant changes in use or care of human subjects

There were no changes during the current reporting year that affect use or care of human subjects. As of the date of this annual report (April 5, 2019), the focus of this study was limited to secondary analyses of de-identified data. This did not involve direct contact with human subjects or personal identifying information of individual study participants.

We do anticipate relevant human subject changes in the next project year, however. Proposed project changes include recruitment of a limited number of subjects from the parent study for a second, longitudinal re-evaluation. No human subjects will be contacted or evaluated in relation to the proposed changes until required human subjects' approvals are in place in the coming year.

Significant changes in use or care of vertebrate animals

Not applicable/nothing to report.

Significant changes in use of biohazards and/or select agents

Not applicable/nothing to report.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

Publications, conference papers, and presentations

Report only the major publication(s) resulting from the work under this award.

Journal publications.

Nothing to Report.

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

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

Website(s) or other Internet site(s)

A summary description of the project is currently posted on Dr. Steele's BCM Veterans Health Research Program Website: www.bcm.edu/vethealth The project is also open for discussion and addressing comments and questions from veterans and other interested parties on the BCM Veterans Health Research Program Facebook page: https://www.facebook.com/bcmveteranshealth/

Technologies or techniques

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products
Identify any other reportable outcomes that were developed under this project.

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

Dr. Deborah Little (original project PI, will remain Key Personnel in the coming year under proposed changes). Although no budgeted/paid effort has been used for this project, we estimate that Dr. Little has worked approximately 1.5 PM on this project during the reporting year. Activities include travel to Boston University to evaluate potential for adding a second data source for the project, as well as regulatory submissions and extensive effort to develop and submit proposed changes to the project associated with her institutional move.

Dr. Lea Steele (Co-I/Key Personnel, will become project PI in the coming year under proposed changes). Although no budgeted/paid effort has been used for this project, we estimate that Dr. Steele has worked approximately 1 PM on this project during the reporting year. Activities include working with Dr. Little and Boston investigators to evaluate adding a second data source for the project, as well as regulatory submissions and extensive effort to develop, submit, and finalize other proposed changes to the project.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? *If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been.*

Dr. Deborah Little: no changes to report for current reporting period

Dr. Lea Steele: Changes in "Other Support" during current reporting period (March 2018 – March 2019)

Pending support from 2 newly-funded projects
1. Title: Gulf Coast Center for Precision Environmental Health (GC-CPEH). Funded by NIH/National Institute of Environmental Health Sciences. Award to Baylor College of Medicine, PI: Cheryl Walker. Steele role: Co-I, Effort: 5%.

2. Title: Defining and Characterizing GWI Pathobiology using Longitudinal Brain Imaging Biomarkers of White Matter Integrity and Hemodynamic Response. Funded by Department of Defense/CDMRP. Primary award to Boston University; PI: Kim Sullivan. Steele Role: Co-I, Effort: 5%

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

During the reporting year and on the current report date (April 5, 2019), the project has been entirely at Baylor College of Medicine (BCM) If the proposed changes are approved, both the University of Texas Health Science Center at Houston (UT) and Boston University (BU) will become project sites in the coming year.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

Not Applicable/Nothing to Report.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Appendix A. "Award W81XWH-14-1-0622: January 2020 Update on Proposed Project Changes that were Referenced in April 5, 2019 Annual Report" is attached at the end of the current report.

10. REFERENCES CITED IN THIS REPORT:

Nothing to Report.

Appendix A.

Award W81XWH-14-1-0622: January 2020 Update on Proposed Project Changes that were Referenced in April 5, 2019 Annual Report

As noted in Item 3 of the current report, prior to and during the current reporting period (March 5, 2018 – March 4, 2019) this project encountered a number of significant delays associated with (1) multiple institutional transfers of key personnel and (2) delays in recruitment and data collection for the original parent project that was the source of data to be analyzed for the current study. Our project team developed a plan to address these institutional and programmatic delays and facilitate completion of project aims under a revised performance plan. At the time the present annual report was due (April 5, 2019), project investigators were working with their respective institutions and with CDMRP Program Officers and the USAMRAA Contract Office to request/obtain approvals for the administrative, budgetary, and regulatory changes required. The proposed changes most prominently included (1) request to approve a change in PI. The original PI (Dr. Little) left Baylor College of Medicine (BCM) in early 2019 to accept a new position at the University of Texas Health Sciences Center-Houston (UT). The requested new PI was Dr. Lea Steele at BCM. This request also included a revised performance plan and timeline; (2) Addition of UT as a second study site to allow Dr. Little to continue as senior neuroscientist on the project for conducting secondary analyses of neuroimaging data; (3) Addition of Boston University as a third study site in order to utilize previously-collected MRI and related data from BU's GWIC study/data repository to accelerate progress in accomplishing the analytic objectives of the current project. This Appendix provides an updated summary of the status of the proposed changes as of January 31, 2020. Full details of the approved project changes that occurred March 2019-March 2020 will be provided in the April, 2020 annual report.

A.1 Requested Change in PI and Associated Timeline Extension.

The change in PI was approved by BCM and UT Departmental and Institutional offices and the letter requesting USAMRAA approval was initially submitted by the BCM Sponsored Programs Office (SPO) Feb. 12, 2019. However, DOD's receipt of this letter and later documents associated with requested project changes and approvals were delayed by unexpected DOD IT blocks to BCM emails. The IT issue blocked delivery of BCM emails/attachments sent to DOD but did not alert us that the emails/attachments had not been delivered. This problem continued through the Fall of 2019. As a result, despite all best efforts by BCM and our DOD Contract and Program Offices, the process for submitting documents and obtaining approvals for the change in PI and related project changes was protracted, and extended past the original study end date of March 5, 2019. Our Contract Specialist, Ms. Andou, therefore directed us to request an extension without funds (EWOF) to keep the project open through the process of obtaining approvals for and putting in place the requested changes. She also suggested that we request a second EWOF once the requested changes and administrative requirements are in place, in order to allow time for completing analytic activities in parallel with data collection from the parent project data sources. We received the award modification May 28, 2019, which included the EWOF, PI change, and approval for the proposed project changes. We then worked with Ms. Andou to complete additional steps required for USAMRAA to issue awarded funds to BCM prior to their expiration. These steps were completed and funds were received by BCM August 15, 2019.

A.2. Addition of UT as a project site.
The approved project revisions allowed BCM to add UT, Dr. Little's new institution, as a second project site so that she could continue as Co-Investigator and the project's senior neuroscientist in overseeing MRI data analyses. Once DOD approvals were obtained and funds transferred, BCM worked to establish a subaward with UT. After administrative delays at both institutions, the subaward agreement was finalized Jan. 29, 2020, allowing accounts to be established for project expenditures. At this time, UT human subject's approvals for the project have been obtained, although analyses have been initiated only with MRI Quality Assurance data. Transfer and analyses of de-identified human subjects data will begin in February 2020, once BCM human subjects approvals are in place for the new UT site.

A.3. Addition of Boston University as a project site and source for additional MRI data for secondary analyses.
The approved project revisions also allowed BCM to add Boston University (BU) as a third project site under the direction of Dr. Kim Sullivan as site PI. BU will provide MRI and associated GWI data from BU's previous CDMRP-funded GWI consortium study and BBRAIN data repository. After DOD approvals were obtained and funds transferred, BCM initiated the process of establishing a subaward with BU for this purpose. Similar administrative delays at both institutions resulted in the subaward agreement not being finalized until Jan.30, 2020. After reviewing the project submission, BU's IRB determined that BU's activities for the project do not constitute human subjects' research, in that BU activities do not involve contact with human subjects or collection, access, use, or distribution of PHI under 45 CFR 164.514. Transfer and analyses of de-identified human subjects data from BU will therefore begin in February 2020, once BCM human subjects approvals are in place for the new site.

A.4. Next Steps: Plans for Completing the Project
The revised project plan calls for secondary analyses of MRI and associated data provided by the parent project at BCM (GW100086) and previously collected data provided from BU GWI studies and data repository. This will include additional MRI scans from GWI cases and controls, allowing us to meet or exceed our original target sample size for the project.

It is anticipated that GWIC data for approximately 100 GWI cases/controls will be provided to BCM through secure data transfer from the BU Data Coordinating Center, as approved by BCM IRB, by late February. Data consolidation and analyses will begin soon after, conducted by research staff in place at both BCM and UT and overseen by Drs. Little and Steele. Data from veterans participating in the BCM parent project (GW100086) will be added to the project dataset in blocks, as data are collected.

In May 2020, we will recontact veterans who had previously received MRI scans for either the BCM parent project (GW100086) or the GWIC project to invite them to undergo a second MRI scan. This will provide an initial longitudinal evaluation to assess whether alterations observed in dopamine pathways are sustained and/or progressive. Recruitment for the longitudinal data collection will continue until 6 veterans are enrolled, a minimum of 6 months after their initial MRI scans.

As of January 31, 2020, we have continued to experience slow progress in completing milestones outlined in the revised SOW for the project. This began with the extended initial period required to successfully submit and obtain approvals for project changes and funds transfer. For example, although our revised timeline allowed up to 6 months to finalize subcontracts for the 2 new project sites, the subaward process for both sites did not begin until nearly 6 months into the initial EWOF period. As noted, we intend to request an additional EWOF in February 2020, as suggested by our Contract Specialist, now that all subawards and administrative requirements for the revised project are in place. This will allow us to complete secondary analyses of data being collected for the BCM parent project (GW100086), in conjunction with data soon to be provided by the BU site, by the end of 2020. The revised project budget provides 1 year of funding for all sites, and will be sufficient to complete all study objectives.