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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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RECIPIENT: Baylor College of Medicine

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14. ABSTRACT

At least one in four 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, these pathways have 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, institutional changes, and extended administrative procedures, several project changes were approved during the reporting period to support study progress and increase sample size, including addition of two study sites. The additional period needed to finalize agreements and regulatory approvals in connection with these changes necessitated a requested timeline extension to complete analyses for the study. In anticipation of approval, research staff training was underway in key procedures for MRI data processing and consolidation in order to accelerate analytic progress. Primary analyses will systematically evaluate GWI-related 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 and deployment exposures.

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 condition 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) institutional transfers of key personnel, (2) delays in recruitment and data collection for the parent project providing data to be analyzed for the current study, (3) second institutional change of previous PI leading to request for change to a new Baylor College of Medicine (BCM) PI, addition of two study sites, and additional delays in obtaining administrative and regulatory approvals for the requested changes. At the end of the period covered by the current report (March 5, 2020), subaward agreements/funding approval for the new study sites had recently been finalized and an extension without funds (EWOF) had been requested to allow subaward sites to move forward with data transfer, processing, and analyses as specified in project objectives. The EWOF approval was still pending at the time of the report date (April 5, 2020). Also at that time, human subjects research had been put on hold at all 3 project sites, in connection with the SARS-CoV-2 pandemic.

In conjunction with the requested EWOF, a revised performance plan and timeline were developed. The extension and revised performance plan were subsequently approved by DOD on May 18, 2020, after the reporting date for the present report. We therefore provide below a summary of the major projects goals/tasks in the revised performance plan, along with the accomplishments/status of each during the current project period (3/6/2019 – 3/5/2020). Due to the open status of approvals and activities at the completion of the current project period, we also provide, as an Appendix to the current report, an updated summary of the status of study objectives and tasks as of August 31, 2020.

Major Project Goals/Tasks and Accomplishments (3/6/2019 – 3/5/2020)

Task 1. Obtain approvals for award amendments and funding for change in PI, addition of study sites.
Sponsor approvals for the change in PI, additional study sites at the University of Texas Health Science Center-Houston (UTHSC-H) and Boston University (BU), and project extension were provided 5/28/19. Invoicing and USAMRAA processing of study funds prior to expiration were completed 8/15/19.

Task 2. Finalize subaward agreements and regulatory approvals: all sites.
Subaward agreements for both UTHSC-H and BU, reflecting approved project changes and funding were both finalized the last week of January, 2020. Regulatory/Human Subjects: Initial human subjects protocols were approved by BCM IRB per the original study timeline and maintained throughout the project period, with the most recent BCM continuing review (CR) approved 1/16/20. The amendment for the change in PI was approved by BCM IRB on 12/26/19, and the amendment to add the two new study sites was approved 2/18/20, after completion of subaward agreements. All BCM IRB CRs and amendments were submitted to HRPO and approved April 3, 2020. HRPO was also notified that the BU IRB determined that BU activities on the project did not constitute human subjects research. Additional regulatory approvals were obtained after the current project period (see Appendix A).

Task 3. Data transfer
Final data transfer from the BU site was not completed during the project period, pending finalization of regulatory approvals.

Task 4. Analysis of Quality Assurance (QA) data and staff training
Finalization of regulatory approvals and amended subawards for project revisions did not occur until after the current report period, disallowing data transfer and processing prior to 3/5/2020. However, a preliminary de-identified GWIC dataset was available to investigators, allowing Dr. Little to organize and conduct an initial QA assessment process (see updates in Appendix A).

Task 5. Scanning/rescanning of Gulf War Veterans for reliability-repeatability assessment
Nothing to report. No MRI data were transferred or collected for the project during current reporting period.

Task 6. Assess alterations in substantia nigra
Nothing to report. Data not available for regional analyses or validation until after current reporting period.

Task 7. Assess alterations in thalamic nuclei
Nothing to report. Data not available for regional analyses or validation until after current reporting period.

Task 8. Assess alterations in putamen, caudate, cortex
Nothing to report. Data not available for regional analyses or validation until after current reporting period.

Task 9. Integration of clinical data, data analyses, finalize manuscripts, data sharing
Nothing to report. Data not available for analyses until after current reporting period.

Summary: What was accomplished under the project goals during the current period?
As detailed above, our activities during much of the current period focused on securing sponsor, institutional, and regulatory approvals associated with requested changes in the project PI, expansion to two additional study sites, and securing project funding prior to expiration. Once approved and funded, we proceeded with finalizing subaward agreements and regulatory approvals resulting from these changes. As of the report date (4/5/20), all subaward agreements and BCM IRB and HRPO human subjects approvals were in place. But, as originally suggested by our contract officer, the extended period needed to address administrative, regulatory, and fiscal requirements stemming from the project changes also required that we request an extension of the performance period, to allow us to accomplish the major scientific goals of the project, that is, use of MRI scans to conduct detailed analyses of the brain's dopaminergic pathways to characterize changes associated with GWI. So, although administrative, fiscal, and human subjects' approvals were in place at the end of the current project period, data analyses had not yet been conducted.

What opportunities for training and professional development has the project provided?
Nothing to report in current period.

How were the results disseminated to communities of interest?
No data analyses have yet been conducted, so there are not yet results to disseminate.

What do you plan to do during the next reporting period to accomplish the goals?
Under the revised timeline and plan for the project, we anticipate finalizing remaining subaward amendments and regulatory approvals in the first quarter. This will be followed by full MRI data transfers, staff training, and multi-observer analyses of specified brain regions of interest. After baseline case/control comparisons for regions of interest are completed and validated, further analyses will evaluate alteration in dopaminergic pathways in GW veteran subgroups and in relation to GW deployment exposures. In addition, additional scans will be conducted on a subset of veterans to determine reliability and/or progression of our findings, once pandemic restrictions allow us to bring in human subjects for in-person evaluation. Study findings will be compiled and reported in manuscripts submitted for publication.

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?

Study results are not yet available; nothing to report in current period.

What was the impact on other disciplines?

Nothing to report in current period.

What was the impact on technology transfer?

Nothing to report in current period.

What was the impact on society beyond science and technology?

Nothing to report in current period.

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:

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.

Key changes were proposed and reviewed in the previous project period, with final approvals secured during the current period. Although a requested timeline extension is pending, no additional changes are proposed, as of the current reporting date. Problems encountered during this reporting period related primarily to time delays due to extended periods required for administrative approvals and activities for finalizing subaward agreements and amendments.

A problem anticipated in the next period relates to the hold put in place for in-person human subjects research beginning in March 2020, and continuing into the next project period. Although we fully support the need for this hold in the interest of safety for our study subjects and staff, this will no doubt delay our ability to re-scan GW veterans to evaluate reliability-repeatability of MRI findings in the study.

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.

Project delays have resulted in reduced spending for all aspects of the project. As detailed in the revised budget, only minimal expenditures have been billed to this project thus far, with all subaward payments to be billed in Year 2. As a result, available funds are sufficient to complete all study objectives.

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

During the current period, there have been no changes in relation to contact with or use of data from human subjects. The primary focus of the study is secondary analyses of de-identified MRI data, and does not involve direct contact with human subjects or personal identifying information for the large majority of subjects whose data are analyzed. In the coming year, however, we will work with our collaborators to contact a limited number of subjects whose data were previously evaluated for the study in order to invite them to have a second MRI scan to evaluate any changes and assess reliability and reproducibility of our findings concerning dopaminergic pathways in veterans with GWI.

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

Veterans or other interested parties may also contact the program about the study or raise questions and comments for discussion 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. After approval of PI change in the current period, Dr. Little remained as Key Personnel, as Co-Investigator and lead investigator at the UTHSC-H site.)
Owing to delays in finalizing initial subaward agreements and later revising them for the project extension, no budgeted/paid effort for Dr. Little has been allocated during this period. However, we estimate that Dr. Little worked approximately 1 PM on the project during the reporting year. Her activities included working with BCM and BU on details and requirements for data transfer, working with the UTHSC grants office and Dr. Steele to finalize subaward budget and agreement, preparing/submitting human subjects' documentation, and initial hiring of staff to be assigned to the project.

Dr. Lea Steele (originally Co-I, became project PI in the current year after approval of PI change.)
Throughout the reporting year, we estimate that Dr. Steele has worked approximately 2.4 PM (20% effort) on this project. Once the change in PI and amended project budget were approved and funds secured, BCM billed 20% of Dr. Steele's effort to the project from July 2019 through early March, 2020. Dr. Steele's project work involved extended effort to submit and follow-up on BCM submissions and requests to USAMRAA concerning requested personnel, institutional, design, budgetary, and timeline changes for the project through August 2020, followed by collaborative efforts with UTHSC-H and BU investigators concerning data needs and transfer, as well as active efforts to finalize subaward agreements and regulatory approvals.

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 in other active support during current reporting period.

Dr. Lea Steele: Changes in "Other Support" during current reporting period (March 2019 – March 2020)

1. Subaward completed 9/29/19 for CDMRP project: "Brain-Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC)." Consortium grant to Boston University Medical Campus; PI: Kim Sullivan, PhD. Steele role: Co-I, Texas Site PI (25% effort).

2. Change from Co-I to PI for the current project beginning July, 2019 (20% effort).

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 we obtained sponsor approvals for adding two additional study sites, and finalized subaward agreements for both the University of Texas Health Science Center at Houston (UTHSC-H) and Boston University (BU).

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: August 2020 Update, Progress Since April 5, 2020 Annual Report Date" is attached at the end of the current report.

10. REFERENCES CITED IN THIS REPORT:

None cited/Nothing to Report.

Appendix A.

Award W81XWH-14-1-0622:
August 2020 Update on Project Activities following April 5, 2020 Annual Report

As noted in the current report, this project has encountered a number of significant delays over its course, most recently in relation to an institutional change by the original PI and a request for a change in PI, addition of 2 study sites, revised budget, and timeline extension by Baylor College of Medicine (BCM) in order to complete project objectives. Implementation of major research tasks could not be undertaken until all sponsor approvals, institutional subaward agreements and extensions, and all required regulatory approvals were in place. Following initial federal approval of requested project changes, the subsequent securing of federal funds and finalizing of subaward agreements and regulatory submissions required most of the remaining project period. Active research activities, therefore, were not in place until after the reporting date. We summarize below specific actions undertaken to advance study progress in the months following the annual report date.

A.1 Update on approval of extended timeline, and finalizing amended subawards and regulatory approvals

Our requested project extension was approved on 5/18/2020, after the reporting period covered by the current report. In connection with the approved extension, we finalized modified subaward agreements with BU on 6/9/2020 and with UTHSC-H on 6/30/2020. Regulatory: In addition to Army HRPO approval of BCM IRB submissions on 4/3/2020, UTHSC-H IRB-approved addition of UTHSC-H as a project site was reviewed by HRPO and approved 6/5/2020. HRPO was also provided with documentation that the Boston University (BU) IRB had determined that BU activities on the project did not constitute human subjects research.

A.2.Update on project research activities after approved extension, subaward agreements, and human subjects reviews

Once administrative and regulatory processes were in place, UTHSC-H implemented our plan to accelerate data consolidation and processing and acquisition and training of staff. By the end of June, UTHSC-H had hired 1 FTE and .5 FTE research staff and initiated training on data preprocessing (DTI Studio) and analyses. The preliminary de-identified GWIC MRI dataset was organized and initial quality assurance checks had been performed. Staff were trained on extraction of substantia nigra data and extraction had been initiated.

Status as of August 31, 2020. Due to pandemic restrictions, UTHSC-H research staff were allowed to work on site in our imaging lab only on a very limited basis through August. Therefore, nearly all training, data acquisition and processing were conducted remotely, using UT's secure network and data storage and processing resources. During this time, the lead technician continued data pipeline analyses to allow initiation of DTI region of interest (ROI) analyses of fibers associated with cortex, substantia nigra, and thalamus. Three additional research staff were added and cross trained to allow a minimum of 2 trained technicians to conduct ROI analyses on each measure, trained to a minimum standard of 0.9 inter-rater reliability for each measure. It is anticipated that all of the Houston site GWIC data will be extracted and quantified by mid-October, with all data fully extracted and validated by December, 2020.