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TITLE: Connectome Biomarkers for Predicting Alzheimer's Risk in Traumatic Brain Injury

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6. AUTHOR(S)

Jane Joseph, PhD; Olga Brawman-Mintzer, MD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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(MUSC) - 171 Ashley Avenue,
Charleston, SC 29425

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109 Bee St., Charleston, SC 29401

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8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Development Command
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14. ABSTRACT

Many Veterans have suffered a traumatic brain injury (TBI), and recent studies have shown that head injury is a risk factor for the development of dementia or Alzheimer's Disease (AD). Although there is strong emerging evidence that TBI and AD show similarities in neuropathology, measuring cellular and molecular changes following TBI is difficult in clinical populations. However, network analysis of resting state fMRI data is a non-invasive approach that can be used to characterize alterations in network communication in the brain in AD. The overall goal of this project is to characterize brain network alterations in AD as potential biomarkers, then determine whether these biomarkers are already present in the TBI brain, even prior to the onset of cognitive impairment or AD.

15. SUBJECT TERMS

Traumatic Brain Injury, Alzheimer's Disease, resting state fMRI, diffusional kurtosis imaging, network analysis, graph theory, positron emission tomography, amyloid beta, cognitive testing

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1. INTRODUCTION:

Traumatic brain injury (TBI) is a risk factor for Alzheimer's Disease (AD). The goal of this study is to examine whether neuroimaging and brain network analysis can be used to identify features of AD-like network disruption in Veterans with TBI who do not yet show clinical signs of AD. The long-term goal is to establish neuroimaging markers of risk for AD. Existing resting state and diffusional kurtosis MRI data from AD patients (n=30) and matched controls (n=30) will be used to build models of AD network disruption. AD models with then be applied to military Veterans and civilians with TBI (TBI+, n=30) and without TBI (TBI-, n=30). PET scanning will also be conducted in the TBI+ group to determine beta-amyloid status. Participants will also return for a 6-month follow-up visit for cognitive testing.

2. KEYWORDS:

Traumatic Brain Injury, Alzheimer's Disease, resting state fMRI, diffusional kurtosis imaging, network analysis, graph theory, positron emission tomography, amyloid beta, cognitive testing

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Milestone 1 (by month 4): Establish experimental procedures
Milestone 2 (by month 30): Select MRI and DTI images to use from ADNI and ADNI/DOD repository.
Milestone 3 (by month 36): Conduct machine learning analyses to build models of AD network pathology for Aim 1. Submit papers for publication.
Milestone 4 (by month 36): Screen, enroll and test TBI+ and TBI- subjects.
Milestone 5 (by month 36): Preprocess rsfMRI and DTI data in 30 TBI+ and 30 TBI- subjects and conduct machine learning analyses proposed for Aim 2. Submit papers for publication.
Milestone 6 (by month 36): Analyze PET images and correlate SUVR with functional and structural network properties. Submit manuscripts for publication.

What was accomplished under these goals?

1) Major activities:
    a. Establish procedures (Milestone 1)
    b. Select data for AD+ and HC subjects from existing repositories / studies (Milestone 2)
    c. Collect data in TBI+ and TBI- subjects (Milestone 4).

2) Specific Objectives:
    a. Establish Procedures (Milestone 1):
        i. Obtain MUSC IRB approval
        ii. Obtain VA IRB approval
        iii. Obtain USAMRMC and HRPO approvals
        iv. Set up and test fMRI and DTI scanning protocols, train research coordinator for MRI data collection
        v. Train research coordinator for cognitive testing
        vi. Establish data sharing procedures with FITBIR
    b. Select data for AD and HC subjects from existing repositories / studies (Milestone 2)
        i. Query ADNI repository for AD and HC rsfMRI and DTI data
        ii. Select AD and HC DTI data from prior funded grant (Helpern R01AG027852).
        iii. Select rsfMRI and DTI/DKI data from ongoing separately funded grant (Joseph R01AG055132).
        iv. Query HCP repositories for AD and HC rsfMRI and DTI data when data are released (Two funded HCP grants: 1UF1AG051216, 3UF1AG051197).

v. rsfMRI data processing in 30 AD subjects and 30 HC subjects: Download and convert images, perform quality checks on images, preprocess data, GTB analysis
vi. DTI data processing in 30 AD subjects and 30 HC subjects: Download and convert images, perform quality checks on images, preprocess data, GTB analysis.

c. Collect data in TBI+ and TBI- subjects (Milestone 4).
   i. Screen and test TBI+ and TBI- subjects (Target = 24 total).
   ii. MRI scanning in TBI+ and TBI- subjects (Target = 24 total).
   iii. PET scanning in TBI+ subjects (Target = 24 total).

3) Significant Results:
   a. Establish Procedures (Milestone 1): Completed
   b. Select data for AD and HC subjects from existing repositories / studies (Milestone 2)
      i. We have identified a total of 18 fMRI (18 AD and 18 HC subjects) and 8 DKI (8 AD and 8 HC subjects) case-control matched datasets from ADNI, our prior pilot study and ongoing study using inclusion criteria of sex=male, age range=55-85, magnetic field strength=3 Tesla, MMSE=20-26 for AD, MMSE=28-30 for HC. Our goal will be to match the AD and HC groups on study site / magnet manufacturer as closely as possible; that is, if we cannot get enough data from the same study site and manufacturer, we will make sure the two groups have the same representation from different study sites and scanners. Of the 18 matched rsfMRI datasets identified thus far, 13 are matched on scanner. As more data become available from various sources identified in Section 2a-d above, we will match rsfMRI cases by scanner as well, if possible. All the identified DKI datasets are from Siemens scanners. We will also ensure that the rsfMRI scans are matched on length across subjects (which means truncating some of the scans for some subjects). We will include the following aspects of acquisition as covariates: manufacturer, sequence type, data collection site, truncated rsfMRI scan (yes/no).
      ii. We have not yet begun identifying potential DKI datasets from Helpern R01AG027852.
      iii. We have 8 fMRI and 3 DKI datasets that meet inclusion criteria for the present study from Joseph R01AG055132.
      iv. Alzheimer Connectome data has not yet been released
      v. fMRI and DKI data from ADNI have been downloaded and rsfMRI data preprocessing has begun in the case-control matched datasets identified thus far.
      vi. Dr. Jensen's data analysis pipeline for DKI data is ready to be used. A graduate student in the lab (Duncan Nowling) plans on relating functional to structural connectivity in preclinical Alzheimer's Disease; he and the new data manager Nico Bustos are starting to receive training in DKI analysis using this pipeline.
   c. Collect data in TBI+ and TBI- subjects (Milestone 4).
      i. Screen and test TBI+ and TBI- subjects: We have enrolled 13 TBI+ subjects (as of 9/30/20).
      ii. MRI scanning in TBI+ and TBI- subjects: Of the 13 TBI+ subjects enrolled, 4 have completed MRI scanning.
      iii. PET scanning in TBI+ subjects: Of the 13 TBI+ subjects enrolled, 4 have completed PET scanning.

4) Other achievements: Nothing to report
5) Stated Goals Not Met: We have not met our original targeted recruitment goal for 9/30/20, which was to enroll 48 of the 60 total subjects by the end of the second year. COVID-19 caused a significant delay because the Ralph H. Johnson VAMC suspended all non-essential research studies for about 7 months. There have also been delays due to our institution not allowing PET scanning to proceed until billing issues were resolved.

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

Research coordinators are receiving training in neuropsychological testing

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?

During the next reporting period we will continue to recruit and test both TBI+ and TBI- subjects. We will also continue to identify existing AD and matched-control fMRI and DKI datasets and conduct preprocessing of that data.

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:

Changes in approach and reasons for change

Due to COVID-19 delays, we have extended the time period for follow-up cognitive testing in TBI+ participants from 6 months to a year.

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

One major delay in the second year of the award was the Ralph H. Johnson VA Medical center hold on research participation due to COVID-19, which resulted in delayed recruitment and enrollment by approximately 7 months. We will focus our efforts on recruitment and enrollment in the next award period. Another delay has been issues of billing for PET charges at our institution. Dr. Joseph had a meeting with MUSC's Assistant Provost for Research Compliance and Regulatory Affairs on October 24, 2019 to discuss the issue. Although PET scanning is now happening at MUSC, the issue of PET imaging costs has re-surfaced (see below). Finally, there have been delays due to personnel turnover. Laura Lohnes and Brandon Vaughan are no longer in the lab, but their replacements have been hired as of end of July (Nico Bustos to replace Brandon Vaughan as Data Manager) and mid-September (Katie Barlis to replace Laura Lohnes).

Changes that had a significant impact on expenditures

Billing for PET charges at our institution is not consistent with the amount we were told to budget for PET scanning. We are being billed for an amount that is twice the amount budgeted. Since PET scanning is already costly, doubling this amount would have a significant impact on our budget. Dr. Joseph is working to resolve this difficult issue, but there may be significant budget impacts if not fully resolved.

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

Amendment 8: submitted 11/19/2019, approved 11/26/2019; specificity of non-penetrating traumatic brain injuries.

Amendment 9: submitted 4/3/2020, approved 4/6/2020; Visit timeline has been adjusted to account for the potentially lengthier delays between study visits due to COVID-19. This change has been made in the ICFs and protocol document.

Amendment 10: submitted 8/2/2020, approved: 8/10/2020; modifying protocol, ICF, HIPPA to allow for telehealth and consent due to COVID-19 as approved by MUSC.

Amendment 11; submitted 8/27/2020, approved 9/18/2020; modifying protocol to reflect the use of REDcap survey(s) as a means of recruitment at MUSC for civilians and non-VA veterans within the protocol.

Significant changes in use or care of vertebrate animals

Not Applicable

Significant changes in use of biohazards and/or select agents

Not applicable

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.

Nothing to Report

- **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: Jane Joseph, PhD
Project Role: PI
Researcher Identifier: ORCID: 0000-0002-8180-7206 / eRA Commons: JANEJOSEPH
Nearest person month worked: 1
Contribution to Project: Dr. Joseph has served as the MUSC site PI. She has overseen the establishment of MRI scanning procedures as well as querying of the ADNI database and preliminary analyses.

Name: Olga Brawman-Mintzer, MD
Project Role: PI
Research Identifier: eRA Commons: MINTZERO
Nearest person month worked: 1
Contribution to Project: Dr. Brawman-Mintzer has served as the VAMC site PI. She has conducted all chart reviews, neurological and physical exams, and TBI assessments.
Funding Support: 2% VA support

Name: Katy Donovan
Project Role: Study Coordinator
Research Identifier:
Nearest person month worked: 1
Contribution to Project: Ms. Donovan has worked as the VA site study coordinator. She has recruited, screened, and consented all study participants to date.

Name: Laura Lohnes
Project Role: Study Coordinator
Research Identifier:
Nearest person month worked: 1
Contribution to Project: Ms. Lohnes has worked as the MUSC site study coordinator. She has performed at the neuropsychological testing to date. She has also assisted with all regulatory submissions for the project.
Funding Support: R01AG05513

Name: Shaquanda Ross-Simmons
Project Role: Study Coordinator
Research Identifier:
Nearest person month worked: 1
Contribution to Project: Ms. Ross-Simmons has worked as the MUSC site study coordinator. She has performed at the imaging visits to date. She has also assisted with all regulatory submissions for the project.
Funding Support: R01AG05513

Name: Brandon Vaughan
Project Role: Data Manager
Research Identifier:
Nearest person month worked: 1
Contribution to Project: Mr. Vaughan has queried the ADNI database for AD+ subjects to be used in analyses. He has also attended FITBIR Deep Dives.

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

Jane Joseph, PhD Support changes:
NIH/NIAAA R01-AA028811 (co-I) now active.
DOD/VA 1I01CX001288 (co-I) now closed.

Olga Brawman-Mintzer, MD:
AgeneBio, Inc. AGB101 MCD (PI)
Aisen U19AG042904 (PI)
DOD W81XWH1810816 (PI)

Jens Jensen, PhD:
NIH/NINDS R01NS110347 (co-I) now active.
NIH/NIDCD P50DC000422 (co-I) now active

Brian Dean, PhD (Co-I):
No changes to report.

What other organizations were involved as partners?

Organization Name: Medical University of South Carolina
Location of Organization: Charleston, SC
Partner's contribution to the project: In-kind support, facilities, collaboration, personnel exchanges

Organization Name: Ralph H. Johnson VAMC
Location of Organization: Charleston, SC
Partner's contribution to the project: In-kind support, facilities, collaboration, personnel exchanges

Organization Name: Clemson University
Location of Organization: Clemson, SC
Partner's contribution to the project: Collaboration, personnel exchanges

8. SPECIAL REPORTING REQUIREMENTS COLLABORATIVE AWARDS:

QUAD CHARTS: Attached.

9. APPENDICES: None.