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

PRINCIPAL INVESTIGATOR: Jane Joseph, PhD

CONTRACTING ORGANIZATION: Medical University of South Carolina (MUSC), Charleston, SC

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Jane Joseph, PhD; Olga Brawman-Mintzer, MD

5d. PROJECT NUMBER

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

Medical University of South Carolina
(MUSC) - 171 Ashley Avenue,
Charleston, SC 29425

Ralph H. Johnson VA Medical Center -
109 Bee St., Charleston, SC 29401

Clemson University - 230 Kappa St.
Suite 200, Box 345702
Clemson, SC 29634

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13. SUPPLEMENTARY NOTES

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, 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). 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, cognitive testing

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Milestone 1 (by month 4): Establish experimental procedures
Milestone 2 (by month 42): Select MRI and DTI images to use from ADNI and ADNI/DOD repository.
Milestone 3 (by month 48): Conduct machine learning analyses to build models of AD network pathology for Aim 1. Submit papers for publication.
Milestone 4 (by month 47): Screen, enroll and test TBI+ and TBI- subjects.
Milestone 5 (by month 48): 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.

What was accomplished under these goals?

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

2) Specific Objectives:
    a. 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.
    b. Collect data in TBI+ and TBI- subjects (Milestone 4).
        i. Screen and test TBI+ and TBI- subjects (Target = 60 total).
        ii. MRI scanning in TBI+ and TBI- subjects (Target = 60 total).
        iii. 6-month follow-up cognitive testing in TBI+ and TBI- subjects.

3) Significant Results:
    a. Select data for AD and HC subjects from existing repositories / studies (Milestone 2)
        i. We have identified 40 fMRI (40 AD and 40 HC subjects) and 14 DKI (14 AD and 14 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 40 matched rsfMRI datasets identified thus far, 21 are matched on scanner. As more data become available from various sources identified in Section 2a above, we will match rsfMRI cases by scanner as much as possible. All the identified DKI datasets are from Siemens scanners. We will also ensure that the rsfMRI scans are matched on length and TR 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. We will only use this source of data if we cannot identify enough datasets from other sources.
        iii. We have 20 fMRI and 20 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 been completed in 80% of the case-control matched datasets identified thus far (34 AD and 34 HC subjects).
        vi. DKI preprocessing is approximately 75% completed for all datasets identified thus far.
    b. Collect data in TBI+ and TBI- subjects (Milestone 4).
        i. Screen and test TBI+ and TBI- subjects: In total, we have enrolled 53 subjects, including 30 TBI+ subjects and 23 TBI- subjects (as of 9/30/22). All enrolled subjects have completed baseline cognitive testing.
        ii. MRI scanning in TBI+ and TBI- subjects: By the end of this reporting period, 28 out of 30 TBI+ subjects and 22 out of 23 TBI- subjects completed MRI scanning
        iii. In total, 21 subjects, including 13 TBI+ subjects and 8 TBI- subjects have completed follow-up cognitive testing (as of 9/30/22).

4) Other achievements: We have begun to establish the machine learning analysis pipeline for the fMRI connectome data with Dr. Brian Dean. This preliminary analysis used 30 AD and 30 HC datasets from ADNI and computed eigenvector centrality (one of the graph theory measures we proposed to use in this project) in each of 280 brain nodes. The goal of this analysis was to be able to classify AD and HC subjects based on the graph-theory information in this whole-brain network. A number of different machine learning classification models were tested, including support vector machine (SVM) classification as proposed for this project. With elastic net regularization selection of 65 nodes, and a radial basis SVM with its parameters properly tuned, accuracy reached 100% accuracy in predicting AD vs HC, using leave-one-out validation – every one of the 60 subjects is predicted correctly on a model trained on the other 59. Accuracy slowly declines if we start using significantly more or fewer nodes. While the AD and HC groups are matched on age, sex, TR, and scan length, and all three scanner manufacturers are represented in each group, we are exploring whether other variables that are not matched across the groups might be accounting for this very high accuracy. We are also further exploring whether this result may be due to overfitting. Although this analysis is very preliminary and we are still tuning the matching of AD and HC groups, these initial steps are critical for establishing the machine learning analysis pipeline to be used for the final analysis.

5) Stated Goals Not Met: We have not met our original targeted recruitment goal for 9/30/22, which was to enroll 60 of the 60 total subjects by the end of this reporting period. However, we have reached our target recruitment goal for the TBI+ subjects, enrolling 30 out 30 TBI+ subjects, and we have recruited 77% (23 out of 30) of the TBI- subjects.

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

The research assistant has received training in administration of study procedures, including assisting with MRI scan administration. The data manager / analyst for the project has received continued training in preprocessing analysis of DKI data.

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 TBI- subjects to achieve our goal of 30 TBI- subjects. Chart review of potential participants will continue to be conducted by Dr. Brawman-Mintzer. During this reporting period, Jory Crull (research assistant) received a Without Compensation (WOC) appointment at the VAMC in order to assist with recruitment and consenting of VA-affiliated participants. We have established connections with the PTSD Clinic at the VAMC and will continue to utilize this collaboration to identify Veterans who may be eligible to serve as TBI- control subjects. We will continue to collaborate with other research teams to facilitate referrals of participants who completed other studies. Additionally, we have added MUSC patient outreach as a method of recruitment which we can utilize to recruit TBI- controls.

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

Nothing to Report

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

The interruption to research activities due to COVID-19 has resulted in delayed recruitment, enrollment, and scheduling of participants. We have reached out to clinicians at MUSC and the Ralph H. Johnson VAMC to determine how best to facilitate patient recruitment. Specifically, we worked with the PTSD Clinic at the VAMC, which has allowed us to rapidly increase our enrollment numbers of both TBI+ and TBI- subjects. Additionally, we received IRB approval to add MUSC patient outreach as a recruitment method for our study, so we can utilize this avenue for identifying potential TBI- control subjects to reach our recruitment goals.

We also experienced delays in receiving Without Compensation (WOC) appointments at the VA. Our most recent research assistant, Jory Crull, applied for WOC appointment in August 2021, but the approval process took approximately 4 months. Jory Crull received the WOC appointment during this reporting period and has since been able to assist in recruitment and enrollment for Veteran participants.

To reach our total enrollment goal and to allow time to analyze data once all data have been collected, a second Extension Without Funds was requested for the project for 1-year.

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 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
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 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
Project Role: PI
Researcher Identifier: eRA Commons: MINTZERO
Nearest person month worked: 1
Contribution to project: Dr. Brawman-Mintzer has served as the VA PI and point of contact and has overseen all regulatory submissions and personnel.

Name: Nicholas Bustos
Project Role: Data Manager
Research Identifier:
Nearest person month worked: 1
Contribution to project: Mr. Bustos has worked on data management and analysis as well as the uploading and sharing of data to FITBIR.

Name: Katherine Barlis
Project Role: Research Coordinator
Research Identifier:
Nearest person month worked: 1
Contribution to project: Ms. Barlis has administered neuropsychological testing and run imaging for study visits.

Name: Jory Crull
Project Role: Research Assistant
Research Identifier:
Nearest person month worked: 1
Contribution to project: Mr. Crull has assisted in study recruitment, screening, and imaging visits.

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/NIDA R01 DA037968 (co-PI) now closed.
NIH/NIAAA R01 AA025086 (co-I) now closed.
AARP "To Support a Randomized Experiment Testing Music's Impact on the Brains of Older Adults with Moderate-to-Severe Alzheimer's Disease" (co-I) now active

Olga Brawman-Mintzer, MD:
NIH/NIA R01AG068324 (co-I) now active.
NIH/NIA R01AG046543 (co-I) now closed.

Jens Jensen, PhD:
NIH/NINDS R01NS097775 now closed.
NIH/NIDA R21DA050085-02 (MPI) now active.
NIH/NCI R01CA161664 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.