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14. ABSTRACT

Magnetic resonance imaging (MRI) has been successfully applied to identify neurological changes prior to the AD onset. The central objective in this project is to investigate the utility of the novel MRI markers in predicting progressive neurological damage in veterans with mild traumatic brain injury (mTBI), estimate the probability of AD progression based on the neuroimaging proximity measures between mTBI and AD prognostic imaging markers, and build a computational model to provide accurate classification of mTBI and prediction of subsequent risk of AD. In the first project year, we analyzed baseline MRI scans from the veterans and also processed ADNI data. We also tested new machine learning framework to define better imaging biomarkers and enhance the prognostic power on AD risks.

15. SUBJECT TERMS
Gulf War Illness, Mild Traumatic Brain Injury, AD, Neuroimaging, Immune markers, Cognitive markers, Machine learning

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Introduction

Traumatic brain injury (TBI) is defined as an injury sustained from external forces to the head, leading to alteration or loss of consciousness (LOC). The severity of TBI is classified into mild, moderate, or severe based on the presence and duration of LOC, alteration of consciousness, and post-traumatic amnesia. Among different stages of TBI, mild TBI (mTBI) is the most common type of TBI affecting military personnel. The Defense and Veterans Brain Injury Center estimated that 10%-20% of those returning home after combat exposure might have sustained mTBI. The rate is even higher (~30%) in the large, longitudinally-followed Ft. Devens cohort and in the Boston Gulf War Illness Consortium cohort of Gulf War (GW) veterans [Hoge et al., 2008; Yee et al., 2016]. Recent survey data found that even mTBI without LOC was associated with more than a 2-fold increase in the risk of dementia in veteran populations. This may suggest that mTBI might have long-term neurodegenerative consequences.

Almost 200,000 veterans returning from the 1991 Gulf War presented with multiple illness symptoms, such as fatigue, cognitive dysfunction, chronic pain, gastrointestinal issues, and other symptoms. These symptoms are thought to have developed due to an innate immune response to various types of risk factors, such as toxicant insults [Chao et al., 2010]. Recently, it has been demonstrated that there is a correlation between GW illness symptom severity and the occurrence of mTBI among veterans suffering from multiple illness symptoms [Yee et al., 2017]. It is also possible that layering a mTBI incident over other GW-related or AD risk factors (e.g., genetic or other health risks) may increase detrimental effects to the brain and result in AD progression. However, detecting and evaluating ongoing pathology in mTBI has been challenging due to lack of standardized imaging and analytical methods and the right population with a history of mTBI and the age range to begin to see AD development. This also limits our understanding of the underlying neuropathobiological progression between mTBI and AD. The central objective in this project is to investigate the utility of the novel MRI markers in predicting progressive neurological damage in veterans with mTBI, estimate the probability of AD progression based on the neuroimaging proximity measures between mTBI and AD prognostic imaging markers, and build a computational model to provide accurate classification of mTBI and prediction of subsequent risk of AD.

In this project, we will utilize the abundant amount of biomarker data which has already been collected from the large, multi-site CDMRP funded Boston Gulf War Illness Consortium (GWIC) and the follow-up data, which will be collected from a recently funded GW longitudinal MRI project with the same veterans (Dr. Sullivan in PI of these GW studies). From the ADNI database, baseline MRI scans on more than 200 subjects who converted to AD in their later time point observations will be combined with traditional prodromal AD classifications for building reference information for machine learning analyses. These 2 different ground-breaking cohort study datasets (ADNI, GWIC) will be combined in computer algorithms (jointly embedded) to provide time and cost-efficient data to answer the question of who is likely to develop AD after mTBI.

Keywords

Mild TBI
Gulf War Illness
White matter integrity
Gray matter microstructure
Connectivity
Morphometry
Neuroinflammation
MRI marker
Machine Learning
Brain mapping

Accomplishments

- **What were the major goals of the project?**

Major tasks 1, 2, and 4 are relevant to the first project year and summarized below. The primary goals of each task are highlighted in the 'Milestone(s) Achieved' cells in the table below.

Specific Aim 1: Identify the impact of microstructural damage responses to mTBI in 3~8 years follow up data on neurological, cognitive and symptom profiles.	**Timeline**	**Site 1**	**Outcomes and Reactions**
Major Task 1 : Obtain IRB approval	Months		
Subtask 1: Obtain local IRB approval	1-3	Drs. Koo and Sullivan	Both Approved.
Subtask 2: Obtain HRPO approval	3-4	Dr. Koo and Sullivan	
Milestone(s) Achieved: Obtained local IRB and HRPO approvals	1-4		
Major Task 2: Analysis on Baseline 1st time point data.			
Subtask 1: Morphometry data processing – Freesurfer (default processings will be done before the project start / additional process step for hippocampal subfield) processing on 250 subjects. Individual morphological network processing will be also performed.	4-9	Dr. Koo (total 250 human subjects), Dr.Sullivan – managing data transfer from GWIC	Setting up computational environment. Additional subject data was transferred to PI's lab.
Subtask 2: Diffusion data processing – Tracula processing, Noddi, GQI processing from in-house developed pipeline.	4-9	Dr. Koo (total 175 human subjects)	New processing pipeline developed.
Subtask 3 : Statistical processing- comparison between mTBI and noTBI group on the imaging measures.	10-13	Dr. Koo (Dr.Au, Qiu and Sullivan – discussions)	On-going.
Milestone(s) Achieved: 1. high quality post-processed data / 2. Microscale diffusion feature for mTBI / 3. Other feature (DTI, cognitive, and symptom) for mTBI	4-12		
Specific Aim 2: Validate biomarker profiles common to the selected neuroimaging markers and novel MRI measures for AD prognosis.			
Major Task 4 : ADNI data processing	Months		
Subtask 1: DATA transfer from ADNI	1-2	Dr.Koo	Data transferred from ADNI database.
Subtask 2: Morphometry data processing – Freesurfer (default processings and hippocampal subfield processing will be performed), individual morphological network processing.	3-22	Dr. Koo (total 697 subject data for 6 groupings)	On-going.
Milestone(s) Achieved: 1. high quality post-processed data for ADNI data	1-22	Dr. Koo	On-going

- **What was accomplished under these goals?**

1) Major activities:

Major activities in this project year include followings:

- Computing environment set up: the research team did parallel computing environment set up. We created the project space in Boston University's scientific computing cluster network. The UNIX cluster computing system dedicated to this project allows up to 180 cpu cores with 1 gpu box, which allows faster processing speed than desktop computing. In the system, the following computer languages and software packages were installed: MATLAB, python, pytorch, skit-learn, Tensor-flow, JAVA, FMRIB software library, AFNI (NIH), Freesurfer pipeline, SPM, DSI studio, Conn toolbox, Connectome workbench, MRIcron, and in-house built software library.

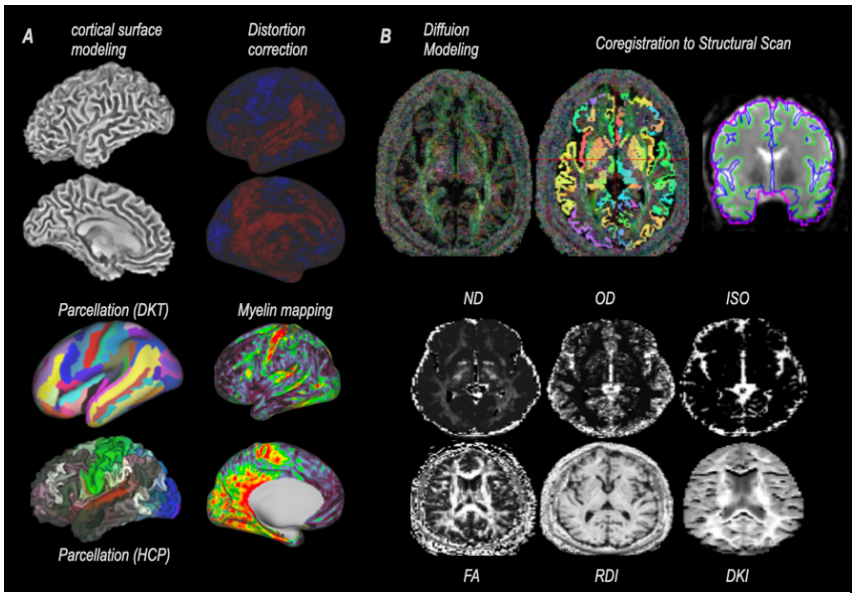

Figure 1. Image processing pipeline (applied to a GWIC data). A. Processing of structural MRI including cortical surface modeling, bias correction, brain region defining, and surface mapping. B. Complex diffusion MRI processing pipeline including diffusion modeling, co-registration of diffusion MRI into anatomical space, generation of different diffusion measures (ND: neurite density, OD: orientation dispersion, ISO: isotropic diffusion, FA: fractional anisotropy, RDI: restricted diffusivity, DKI: diffusion kurtosis map).

- Building processing pipelines for neuroimaging data: The research team built multimodal neuroimage processing pipeline. Compared to the old version of pipeline we had before, this new pipeline can offer more detailed parcellations of cortical region, multi-scale white matter (WM) connectivity measures, cortical myelination mapping, cortical surface-based analysis, and also offers different diffusion modeling scheme.

- Processing of neuroimaging data:

The processing includes,

- Cortical surface modeling and defining regional cortical structures
- Co-registration between structural and diffusion MRI
- Diffusion data preprocessing for correcting motion and eddy current distortions
- Diffusion modeling on following diffusion indices NODDI and generalized q-space imaging (GQI) maps.
- Structural connectivity matrix reconstructions and network measures (based on graph-theory).
- Cortical diffusivity mapping
- Diffusion sampling along WM major fiber pathway
- Global Morphometry (i.e., volume, gyrification, etc.)
- Regional Morphometry (i.e., regional volume, thickness, etc.)
- Myelination mapping
- Cortical intensity profile mapping
- Hippocampal subfield volume

- Quality assurance work on the processed results. We performed repeated quality assurance works (i.e., detailed visual inspection, checking modeling errors, distributions and outliers in the quantification values) on the processed results.

2) Specific objectives:

In the first project year, the main goal was to process all 1st time point data from GWIC and the half of ADNI data to have high quality post-processed data.

3) Significant results and Key outcomes

From GWIC, we received 169 subject image files. Twenty subject data had some issues (e.g., movement, low signal-to-noise, quit scanning, etc.) during the diffusion MRI scan. We processed 148 subject images has been processed without any issues for multiple diffusion encoding processing (b=1000, 2000, and 3000). We also performed diffusion processing using the scans in the highest diffusion encoding shell (b=3000). In this additional processing, six subjects were added, and a total of 155 subject data was generated. Diffusion imaging was based on 124 directions with multiple b encodings and reconstructed by NODDI and GQI. We performed statistical analyses on this dataset and have confirmed the following patterns:

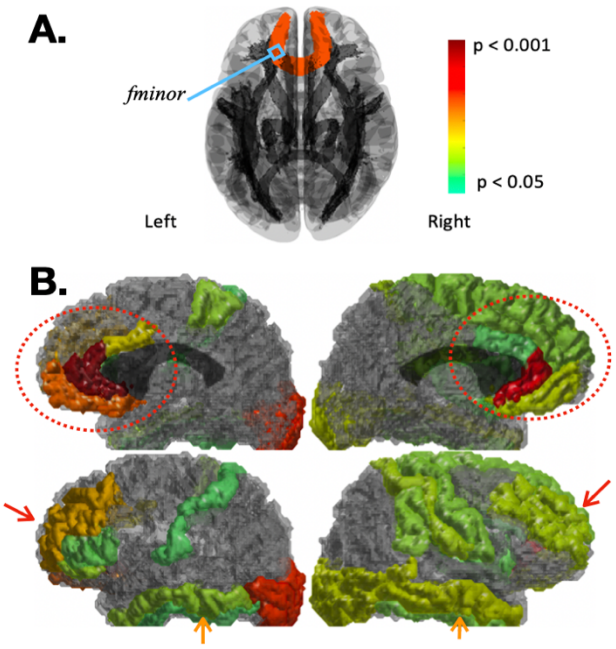

Figure 2. Group differences in Neurite density (ND) between GWI+mTBI vs. GW veterans withour illness. A. ND differences in the white matter. fminor: anterior callosal tract. B. ND differences in the gray matter. dotted circles: anterior cingulate and medial prefrontal regions. red arrows: Dorso-lateral frontal regions. Orange arrows: inferior temporal regions.

- GWI+mTBI group also showed lowered neurite density (ND) in the anterior callosal tract (Figure 2A. fminor) compared to controls, while no significant patterns were found in GWI-mTBI. In isotropic volume fraction (ISO) and orientation dispersion (OD) measures, bilateral cortical spinal tract, left cingulum bundle and right uncinate fasciculus showed lowered diffusivity in GWI-mTBI.

- Compared to GW healthy controls, GWI cases who reported mTBI during the war (GWI+mTBI) revealed significantly lower ND in various GM regions, including bilateral anterior cingulate cortex, bilateral lateral occipital cortex, bilateral inferior temporal lobe, bilateral medial orbitofrontal lobe, bilateral postcentral gyrus, bilateral middle frontal gyrus, left pars orbitalis, left triangularis (Figure 2B). These regions were not significantly different between in GWI cases without mTBI (GWI-mTBI) and controls. OD and ISO mapping also highlighted additional regions (e.g., the posterior cingulate) with lowered diffusivity in GWI+mTBI, indicating minor microstructural changes in those regions.

- GWI+mTBI groups showed higher pain (Mcgill pain score), fatigue (MFI), sleep deprivation (PSQI) than controls. These differences were more significant than the comparison results between GWI-mTBI and controls. There were correlations between GM diffusivity measures and these symptom scores. Lowered GM ND in the caudal anterior cingulate cortex was associated with higher MFI (rho: -0.39, $p<0.05$) and Kansas pain domain score (rho: -0.47, $p<0.01$) in GWI+mTBI. Most of the GM ND measures highlighted in GWI+mTBI group analysis were correlated with PSQI scores.

For structural MRI processing, we processed 122 subjects from BU site and 47 subjects from Baylor site. Global and regional morphometry was performed. Regional GM volumetry did not reveal significant patterns in GWI+mTBI. Statistical analysis on other measures (e.g., myelination map and intensity profile analysis) are on-going.

For ADNI, the data was transferred from the database to our server. We processed 448 subjects up to now (64% from the targeted samples).

4) Other achievements: In this project, we planned to use ADNI data as reference information on estimating the risks of Alzheimer's disease. As we previously stated, image processing work has still yet to reached the planned sample size. We have been working on testing two different machine learning (ML) concepts, which will help define AD prognostic features and similarity measures between GW and ADNI data at individual level.

ML classification: The research team has started testing a multivariate ML classifier framework based on a canonical correlation forest (Rainforth and Wood, 2017). The framework initially search imaging features statistically different between groups and defines features pool in other measurement domains (e.g., volume, intensity profile measures) (Figure 3A). Then, the framework iteratively searches the best feature combinations to build the classification trees and define the classification forest. This framework was tested for binary classification on ADNI control, mild cognitive impairment converters (MCIc, MCI subjects who converted to AD during 5 years of follow-up), mild cognitive impairment nonconverters, and AD. The first trial revealed 77% accuracy in MCIc vs MCInc, 82% accuracy in MCI vs control, and 86% in AD vs controls (Figure 3B). Many of the top features selected by this model were novel imaging measures, such as periventricular intensity and hippocampal subfield measures. Compared to the well-known Mini-Mental State Examination (MMSE), the combined imaging markers revealed prognostic value for predicting conversion. This result is comparable to many earlier studies which defined converter and non-converter groups based on a much shorter time frame (0-3 years), and achieved an accuracy ranging from 70-76% by only using conventional structural MRI measures (Moradi et al., 2015, Tong et al., 2017, Spasov et al., 2019). Our result supports the potential of proposed novel imaging features for predicting the conversion of MCI to AD at an early stage. Although we initially planned to use a single time point data in ADNI, we are now planning to assess longitudinal change information in ADNI to test whether the combining of ADNI follow-up data can enhance prognosis and classification accuracy.

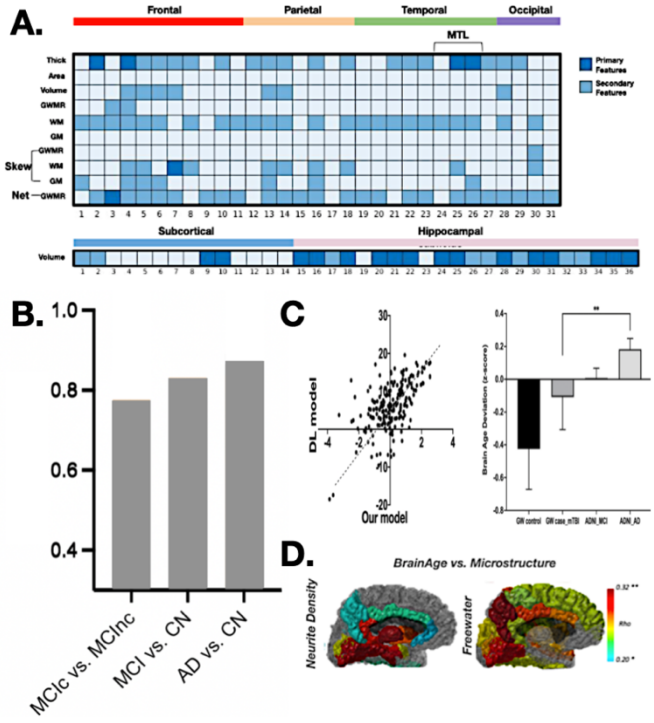

Figure 3. New computational framework tested in the project year 1. A: candidate imaging features defined from the ML framework. B: Performances of ML classifiers (Accuracy measures on MCIc vs. MCInc, MCI vs. control, AD vs. control). C. Brain age modeling (left: comparison of 2 models, right: brain age deviation in different groups, GW control, GWI+mTBI, ADNI MCI, and ADNI AD respectively). D. association between regional diffusion markers and estimated brain age.

Brain age modeling: The concept of brain age modeling, which is a single measure derived from neuroimaging data using ML, has recently been used as a holistic representation of global neurological changes associated with disease or aging. The deviation between imaging-derived brain age and chronological age was related to multiple mental and physical fitness aspects. Accelerated brain aging (i.e., more significant positive deviation) was observed in Major Depression and Parkinson's disease subjects. It is also associated with decreased cognitive capacity (Jonsson et al., 2019, Kaufmann et al., 2019). Regional-specific brain age measures derived from individual brain lobules also demonstrated disease-specific patterns: for example, the cerebellar-subcortical structures showed more aging deviation than other brain regions among subjects with dementia, while subjects with schizophrenia showed more aging in the insular cortex (Kaufmann et al., 2019). We built the first version of brain age modeling using morphometry features from T1-weighted structural scan in this preliminary work. Brain age predicted by our model was highly correlated (r=0.596, p=1.34e-20) with the model suggested by Kaufman et al. (2019) (Figure 3C left). In our initial work, brain age deviation in GWI+mTBI was placed between GW controls and ADNI MCI. Compare to ADNI MCI, GWI+mTBI brain age deviation was not significantly different. However, the brain age deviation of GWI+mTBI was markedly lower than the ADNI AD (Figure 3C right). Since the brain age modeling provided an abstract measure on brain structure, we will use this measure to assess how this measure changes in the follow-up data. Interestingly, the estimated brain age was also associated with some regional diffusion markers (Figure 3D), supporting potential linkages between microstructural and brain age estimation based on the morphometric markers.

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

  PI attended a virtual meeting at VA-DoD Gulf War Illness SOTS Conference on August 18, 2020. PI shared the imaging works and preliminary findings with the research community.

  One-on-one research mentoring was offered to 2 research assistants from the PI. Research assistants learned basic concept of MRI, brain mapping and statistics processing and had hands-on trainings using the data from open sources.

  PI has been attending group meetings in BBRAIN (PI: Kimberly Sullivan, co-I in this project) to discuss new ideas and findings.

  PI's group had weekly virtual study meetings (every Thursday) with Dr. Jae-Hun Kim's group at Samsung Medical Center, Seoul, Republic of Korea, from June to December 2020 to discuss current machine learning and deep learning topics. The idea on using brain age modeling was generated from this meeting.

- **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?**

  For the next reporting period, we will continuously work on processing GW dataset and building the different types of machine learning models to provide efficient computational framework for estimating AD risks in GW veterans. Important imaging and non-imaging features used in the classifiers will be defined throughout of the works. We will also continue to work on processing the newly acquired data to produce a quality dataset.

Impact

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

  In the baseline dataset, we confirmed that GWI+mTBI have more significant GM and WM microstructural alterations than GWI-mTBI. We also found that those microstructural changes might be associated with different brain aging patterns. This may indicate that 'in theater' exposure condition is an important neurological risk factor to describe and understand the current condition of veterans. In the next project period, we will extend this work to see how these regions change after several years and whether those patterns are associated with an increased risk of AD.

- **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.

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**

  Although our original plan was to use 150 subject data from the Boston GWIC, 120 subject data was available from Boston GWIC. We have included 49 subjects from other site data (Baylor site) for the first-time point data assessments. Among these, diffusion MRI was available on 148 subjects, as we described earlier. From Boston GWIC data, 59 subjects reported mTBI, and 33 subjects reported mTBI during the war. Those 33 subjects have multimodal MRI data and will be included in our follow-up analysis. Since we anticipated 50 subjects with mTBI during the war, this reached 66 percent level. In Baylor site, 13 subjects reported mTBI during war, and 11 among those had multimodal MRI.

  PI is also discussing with BBRAIN for searching additional imaging data with mTBI information. Adding more single-time point data may help to define more reliable markers for mTBI in veterans. In our new imaging protocol, we added myelination mapping and novel intensity markers. This can be acquired from structural MRI and has been shown some overlapped information (Fukutomi et al., 2018) with microstructural mapping using complex diffusion MRI. This allows combining other site data which does not have complex diffusion MRI scans. Defining refined markers from the single time point data can provide reference information for studying longitudinal patterns. Discussion is still on-going and we will update this to next report.

  We will also continuously add efficient computational models to study the impact of mTBI in AD risks with finer resolution. Adding new models such as brain age estimation can provide good estimations on aging patterns even from a single time point data.

- **Changes that had a significant impact on expenditures**

  - Grant account was created in June 2020.

  - Delay in the recruiting process: Due to the pandemic, there was a delay in recruiting process in the first quarter. There was difficulty in recruiting process because most of the applicants went back to their homes. Research Technician (Ms.Cheng) in PI's laboratory joined this project to support PI and handle this problem.

  - PI recruited an undergraduate-level research assistant from the computer engineering and neuroscience department to help out ADNI data processing. We will continue to recruit graduate student-level research assistants.

Product

- **Publications, conference papers, and presentations**

  - Nothing to report

- **Journal publications**

  - Nothing to report

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

- Nothing to report

- **Other publications, conference papers, and presentations.**

- Presentation on Gulf War Illness Imaging works at the virtual meeting, VA-DoD Gulf War Illness SOTS Conference.
- PI provided a virtual lecture introducing multimodal neuroimaging for studying neurodegeneration on Oct 26th, 2020: Undergraduate program at Biomedical Engineering, Hanyang University, Seoul, Korea.

Participants & Other Collaborating Organizations

- **What individuals have worked on the project?**

Name: *Bang-Bon Koo*
Project Role: *Principal Investigator*

Name: *Kimberley Sullivan*
Project Role: *co-Investigator*

Name: *Rhoda Au*
Project Role: *unpaid consultant*

Name: *Wendy Qiu*
Project Role: *unpaid consultant*

Name: *Michael Alosco*
Project Role: *unpaid consultant*

Name: *Jasmine Cheng*
Project Role: *research technician*
Nearest person month worked: *3*
Contribution to Project: *Support on developing the computational resources.*

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

National Emerging Infectious Diseases Laboratories Operations (Y1 Core 5 ISS-SAL 9500305795)
role: co-I
Cal mos.: 6.0 Cal Mos. changed to 3.0 in June 2020. This support will be ended May 2021.

Dietary quality, cognitive decline and brain (NIH-NIA)
Cal mos.: 1.8 Cal Mos. changed to 0.6 in June 2020.
role: co-I

Neural substrates of exosome-mediated enhancement of recovery after cortical injury in non-human primates. (NINDS)
Cal mos.: 0.6 Cal Mos. started Oct 2020.
role: co-I

Extracellular Vesicle treatment and age-related neuropathology in non-human primates (NIA)
Cal mos.: 0.6 Cal Mos. started Oct 2020.
role: co-I

Computer aided decoding of brain-immune interactions in Gulf War illness: a joint embedding on brain connectomic and immunogenetic markers (DOD)
No cost extension started September 2020.
role: PI

- **What other organizations were involved as partners?**

  Nothing to report

Special Reporting Requirements

- **COLLABORATIVE AWARDS:**
  Nothing to report

- **QUAD CHARTS:**

Appendices

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