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CONTRACTING ORGANIZATION: Boston University School of Medicine

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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 second project year, we analyzed the second time point MRI scans from the veterans and finished processing 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 which eventually lead to alteration or loss of consciousness (LOC). Mild TBI (mTBI) is the most common traumatic brain injury affecting military personnel. Previous reports showed that more than 15 percent of returning service members experienced mTBI and the rate is even higher (~30%) in the large, longitudinally followed Ft. Devens cohort and the Boston Gulf War Illness Consortium (GWIC) of Gulf War (GW) veterans [Hoge et al., 2008; Yee et al., 2016]. In fact, a recent survey found that even mTBI without LOC was associated with more than 2-fold increase in the risk of dementia in veteran populations in their later life compared to those who did not have history of mTBI [Yee et al., 2017]. This suggests that mTBI might have long-term neurodegenerative consequences. 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 the lack of standardized imaging and analysis methods. This also limits our understandings of commonalities in underlying neuropathobiological progression in 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 planned to 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 has been continuously collected from a recently funded GW longitudinal MRI project with the same veterans (Dr. Sullivan in PI of these GW studies). To examine the association between mTBI without LOC and AD risk, this project is also utilizing Alzheimer's Disease Neuroimaging Initiative (ADNI) data collection to combine those recently developed neuroimaging features to establish novel feature testing criteria. 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 3, 4, 5 and 6 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 3: Analysis on 2nd time point data - initial			
Subtask 1: Morphometry data processing – Freesurfer (default processing and hippocampal subfield processing will be performed), individual morphological network processing. / Diffusion data processing – Tracula processing, Noddi, GQI processing from in-house developed pipeline	13-18	Dr. Koo (up to 60 subjects of 2nd time point imaging data expected), Dr.Sullivan – managing data transfer from GWIC	Delay in second time point data acquisition: 1st scan started early August 2021. As of May 2022, total 38 subject's 2nd time point data was transferred from GW longitudinal study and processed in PI's laboratory.
Subtask 2 : Longitudinal analysis: morphometrical and individual network measures. Longitudinal pattern in diffusion markers will be also assessed.	18-20	Dr. Koo	Longitudinal pattern analysis: Initial analysis on 38 subjects' morphometry data is done. Work will be continued to the project year 3.
Subtask 3: Comparison between diffusion imaging marker and longitudinal patterns / Comparison between diffusion imaging marker and morpho/network markers in the 1st time point	20-22	Dr. Koo	Preliminary Analysis on part of data.
Milestone(s) Achieved: 1. high quality post-processed data for 2nd time point / 2. Longitudinal changing pattern in the brain (impact of mTBI) / 3. Relationship between baseline microstructural change in longitudinal pattern / 4. Alternative markers	13-22	Dr. Koo (Dr.Au, Qiu and Sullivan – discussions)	*Team discussions on the longitudinal data will be initiated in the project year 3.*
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 2: Morphometry data processing – Freesurfer (default processings and hippocampal subfield processing will be performed), individual morphological network processing.	3-22	Dr. Koo	All ADNI data processing is finished. A new ADNI classifier was built.
Milestone(s) Achieved: 1. high quality post-processed data for ADNI data	1-22	Dr. Koo	
Major Task 5 : GWIC and ADNI data analysis	Months		
Subtask 1: Multivariate pattern proximity assessments between GWIC and ADNI data.	23-25	Dr.Koo	On-going.
Subtask 2: Random forest-based similarity assessments.	24-26	Dr. Koo and Sullivan	On-going.
Specific Aim 3: Test the diagnostic and prognostic value of the selected biomarkers based on a supervised machine learning framework			
Major Task 6 : Analysis on 2nd time point data - final	Months		
Subtask 1: Morhometry and diffusion data processing on rest of 2nd time point dataset (additional 40 subjects processing)	23~28	Dr.Koo	*Work will be continued to the project year 3.*

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

1) Major activities:

Major activities in this project year include followings:

- Processing of 2nd time point data using the pipelines built in the previous year: In the project year 1, we built multimodal neuroimage processing pipeline. Newly added time point 2 data in Boston Biorepository, Recruitment & Integrated Network for GWI (BBRAIN) was transferred to the secured parallel computing server located in Boston University's scientific computing cluster network and processed. 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.

- Finalize the processing of ADNI data: In this project year, we continued to process ADNI data and finalized the processing work. Although we originally planned 697 subject data processing from ADNI go and 2, we added ADNI 3 subject data to this pool to increase the analytic power. Total sample size used here is now 1,023 (control:336, MCInc:121, MCIc:263, AD:303). Combining ADNI go and 2 data with ADNI 3 and GWIC required data harmonization because merging neuroimaging data from different sites can introduce unwanted heterogeneity from non-biological sources, typically related to scanner hardware, image acquisition settings, and image processing pipelines (Buchanan et al., 2021, Bhagwat et al., 2020). Such variations can hinder the detection of key imaging profiles associated with clinical covariates of interest and cause spurious findings. Ideally, regulations on calibration protocols in different scanners, building and use of standard acquisition protocol would decrease inter-scanner variability. More practical solutions, especially for the already collected data problem, reside in using standardized image processing pipeline and statistical/mathematical harmonization approaches to reduce unwanted site variability while preserving the biological variability (Fortin et al., 2017, 2018, Rauda et al., 2020, Pinto et al., 2020). We used ComBat harmonization method (Johnson et al., 2007). The combat harmonization method assumes site-specific scaling factors and uses empirical Bayes method to estimate the site parameters.

2) Specific objectives:

In the second project year, the main goal was to process all ADNI data and more than half of the GWIC 2nd time point data. Initial analyses on the collected/processed longitudinal data with ADNI data were also planned in this project year.

3) Significant results and Key outcomes:

   a. Relationships between baseline tissue microstructural patterns (from diffusion MRI) and morphometrical analysis (from baseline T1-weighted MRI):

      • From the baseline diffusion MRI data, we previously reported following patterns in GWI with mTBI (case_TBI+) group compared other groups:
      - Significantly lowered neurite density (ND) in the anterior callosal tract.
      - Significantly lower ND in various gray matter (GM) regions (figure 1A), including bilateral anterior cingulate cortex, bilateral lateral occipital cortex, bilateral inferior temporal lobe, bilateral medial orbitofrontal cortex, bilateral postcentral gyrus, bilateral middle frontal gyrus, left pars orbitalis, left triangularis. These regions were not significantly different between in GWI without mTBI (case_TBI-) and controls.

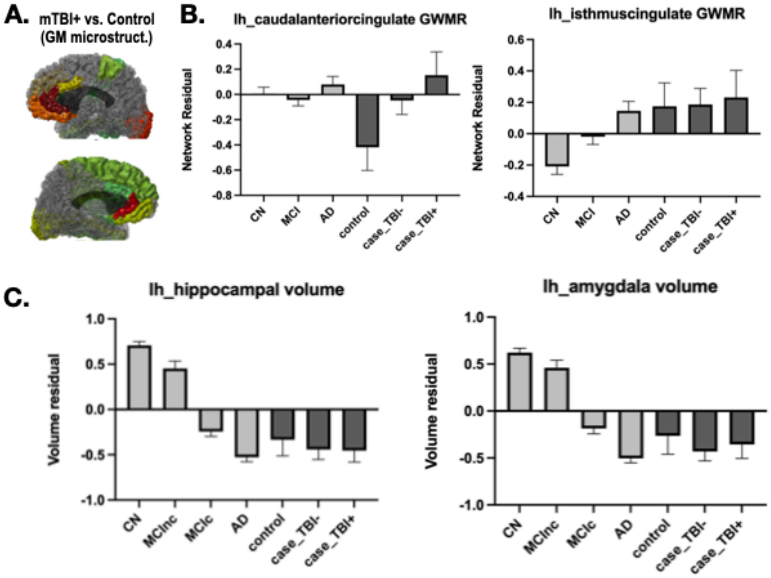

Figure 1. Diffusion vs. Morphometric mapping in GWI with mTBI. A: ND mapping in case_mTBI+ vs. Controls. Bilateral anterior cingulate cortices and lateral occipital cortices showed lowered ND in mTBI+. B: (left) GWMR in case_TBI+ showed clearly distinct profile compared to controls and case_TBI-. (right) GWMR in isthmuscingulate in all GW veterans could be compared to GWMR in AD. C: Subcortical volumetry in all GW veterans showed similar patterns with MCI-to-AD converters and AD in ADNI.

      • In morphometrical analysis, intensity network profile in the GM and white matter (WM) tissue boundary (GWMR) was also significantly different in anterior cingulate region in case_TBI+ vs. controls (figure 1B, left), which overlaps to the findings from diffusion MRI (figure 1A). This may indicate that intensity profile mapping from T1-weighted MRI measures also reflect the tissue microstructural damages in this region. However, not all the regions highlighted from diffusion MRI showed the similar patterns in group comparison results, which may indicate that there are some sensitivity differences on detecting abnormal profiles between different scan measures.

   b. Comparison between GWIC baseline and ADNI data:

      • Subcortical volumetry in GW veterans different than ADNI control cohorts: GW veteran's subcortical volumetry in their baseline data was slightly lower than MCI converters and higher than AD subjects in ADNI. Hippocampus and Amygdala volumetry in case_TBI+ and case_TBI- groups were not significantly different when they were compared each other (figure 1C).

      • GWMR in GW veterans: case_TBI+ group's GWMR in caudal anterior cingulate region showed more degenerative pattern (i.e., higher GWMR means more abnormal pattern resides in the region) than ADNI AD subjects (figure 1B, left). GW controls showed lowest GWMR among all groups, which may indicate minimal microstructural changes in that region.

c. Longitudinal pattern analysis (preliminary): In this project year, only 38 subjects' 2nd time point data was collected from Dr.Sullivan's group and transferred to PI's team. We finished processing T1-weighted MRI on these subjects and currently working on diffusion data processing. Therefore, the results reported here are preliminary stage.

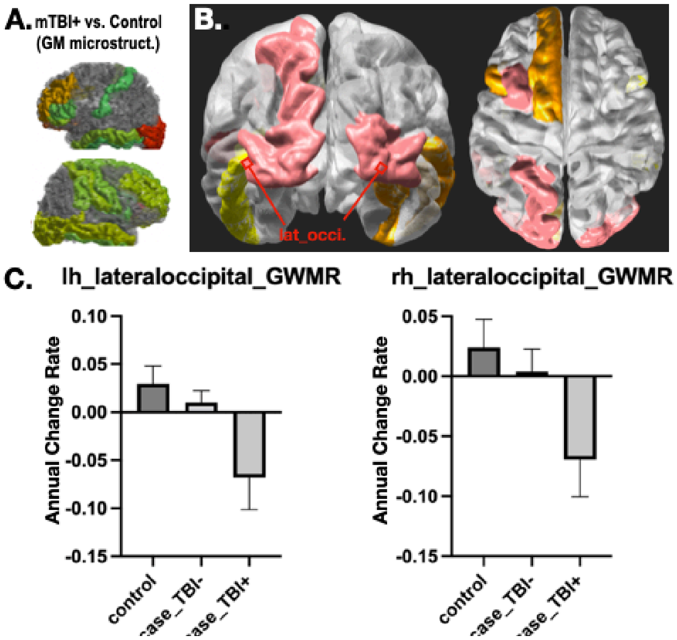

Figure 2. Longitudinal change in GWMR measures in GW veterans. A: ND mapping in case_mTBI+ vs. Controls (lateral view). B: Regions with the most changes in the follow-up measures. Bilateral lateral occipital cortices, left superior parietal cortex, left caudal middle frontal regions showed increase in GWMR in the follow-up data. C: Bar graph plots on the annual change rate of GWMR in lateral occipital cortex.

- Longitudinal change in GWMR in case_TBI+ group: We investigated the annual pattern change rate on GWMR measure and found clear differences in case_TBI+ group compared to others. GWMR in lateral occipital region, superior parietal, caudal middle frontal regions showed significantly high annual change rate compared to other two groups (figure 2B,C). This means that more degenerative GWMR pattern is shown in the follow up data in case_TBI+ group. Interestingly, some of those regions were also spatially overlaps to the regions highlighted in the baseline diffusion MRI analysis (figure 2A). There were other regions showing minor changes in the follow up data including inferior temporal gyrus, lateral frontal cortex, and medial temporal cortex.

- Machine learning (ML) assessments: We used the ML classification framework that we reported in the previous year to test whether the case_TBI+ group has different AD prediction results in their longitudinal data compared to other groups. The ML testing was applied to 38 subjects who has both baseline and follow up scans. Among these subjects, sample size in each group was 5 in controls, 27 in case_TBI-, 6 in case_TBI+. Case_TBI+ subjects showed highest AD probability among 3 groups (Figure 3). Both case_TBI- and control groups showed increased AD probability in the follow up data. Due to the imbalanced sampling in each group in this test samples, it is difficult to determine the group specific effect on AD related brain imaging patterns. However, prediction results in case_TBI+ in both timepoint may indicate that there is more consistent pattern related to AD in this group in their longitudinal observations. In the next project year, we will test ML to larger samples with more balanced test sampling scheme.

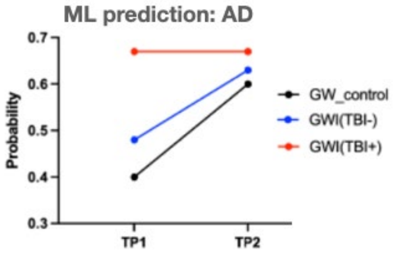

Figure 3. ML prediction in longitudinal data. TP1: baseline data, TP2: follow-up data. Probability: # of subjects predicted as AD in each group (%).

4) Other achievements:

a. ML classification: Development of efficient ML framework can provide better prediction of subsequent risk of AD and understanding of mTBI as a risk factor for AD. PI established a collaboration work with Dr. Jae-Hun Kim’s group last project year to discuss current machine learning and deep learning topics. We continued this discussion and started collaborative development work for a new ML classification framework in the project year 2. This framework utilizes morphometrical network features (e.g., GWMR) and allows multigroup classification (figure 4). Testing on this model was performed on ADNI data and the average accuracy on 4 groups (i.e., control, MCI converter, MCI stable, and AD) was 78.4%, while the performance on 2 group binary classification showed 84.7%. Compared to our previous model, this model provided 6.9% performance improve in classifying stable MCI vs. MCI to AD converters. The results were published in the journal Human Brain Mapping. We expect that this work will help define AD prognostic features and similarity measures between GW and ADNI data at individual level.

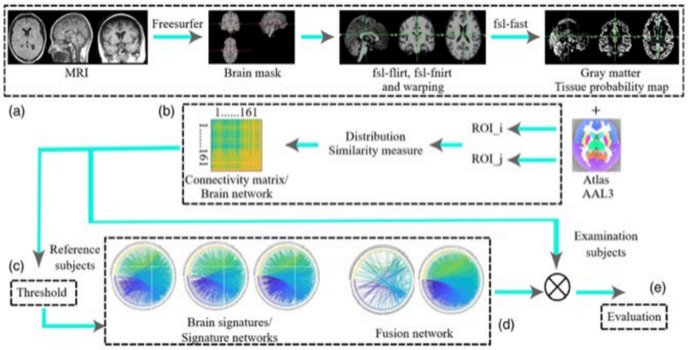

Figure 4. ML classification pipeline based on classical and novel network features.

a. Evaluation of diffusion MRI markers: To identify important features for differentiating GW veterans with progressive neurological change associated with mTBI, microstructural assessment based on high-dimensional diffusion MRI was suggested by the research team. There have been active discussions on what neurological changes are giving the differences in this microstructural diffusion imaging. In our initial investigation, we found that the microstructural diffusion imaging features reflect changes in active glial cells due to the toxic insults to the brain. However, this work was tested in the acute stage model of GWI. Since the microstructural imaging measures are used as a central measure to investigate the impact of microstructural damage responses to mTBI in this project, we had a consensus that understanding of which the neurological sources giving the contrast on the microstructural imaging is important. PI and the research team planned additional validation works to further investigate this topic.

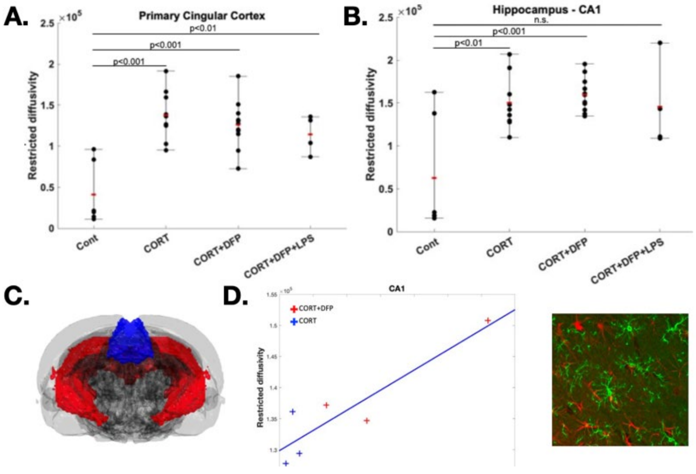

Figure 5. Microdiffusion mapping in the rat model of GWI. A: restricted diffusivity in the cingulate cortex. B: restricted diffusivity in the hippocampus (CA1). CORT+GFP group showed clear differences compared to controls. C: 3D map of cingulate (blue) and hippocampus (red) regions. D: Immuno-histochemical assessments in the tissue samples. Microstructural diffusivity was correlated with active glial cell counts (green: microglia, red: astrocytes)

- Animal model assessment: In continuation to our previous work (Koo et al., 2018), we also assessed high dimensional diffusion MRI in chronic model of

GWI (figure 5). In the chronic model, microstructural diffusion profiles in the hippocampus and the cingulate cortex both had significant alterations compared to controls. Consistent to the TSPO findings, we also confirmed that the active glial cells are the major component giving the imaging signal contrast.

• Glial PET comparison: In collaboration work with Dr.Marco Loggia at Martinos Center for Biomedical Imaging, we compared the Translocator protein (TSPO) positron emission tomographic imaging in GW veterans with diffusion MRI. We confirmed that glial activations in cingulate cortex correlated with microstructural diffusion measures (figure 6). This may indicate that active glial cells due to mTBI are the major source of the significantly lower GM microstructral measures shown in GWI_TBI+ group.

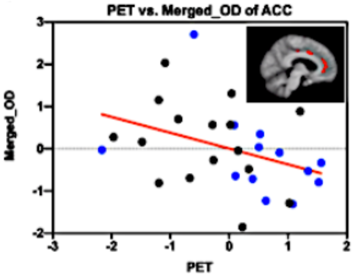

Figure 6. TSPO PET vs. microstructural diffusion in anterior cingulate cortex.

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

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 has been doing weekly virtual study meetings (every Thursday) with Dr. Jae-Hun Kim's group at Samsung Medical Center, Seoul, Republic of Korea, to discuss current machine learning and deep learning topics.

Research assistant, Ms. Chia-Hsin Cheng, gained most of cutting-edge image processing and data analysis from this project. Ms. Cheng was promoted to Professional Data Analyst II position at Boston University School of Medicine.

- **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 the 2nd time point GW dataset and building the different types of machine learning models to provide efficient computational framework for estimating mTBI and AD risks in GW veterans.

Impact

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

From the cross-population analysis, we confirmed that GW veterans have different morphometrical profiles than the elderly control subjects. Among the GW veterans, GWI_TBI+ group had more altered profiles in anterior cingulate cortex and other peripheral cortices. We found that some of new morphological measures from T1-weighted MRI can also reflect overlapping patterns captured from diffusion MRI measures. Some of those regions also showed clear changes in the follow up observation, which may indicate that the baseline microstructure patterns may also be correlated with further longitudinal changes. However, to make clearer conclusion, we still need to add more samples to the analysis. In the next project period, we will continue to process the second time point data and perform additional analyses.

- **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**

  PI has been doing discussions with BBRAIN for searching additional imaging data with mTBI information. The first phase work on collecting the imaging data and relevant subject information from other sites was recently done in BBRAIN. PI will continue to discuss with BBRAIN researchers for searching available data for exploring mTBI specific imaging markers and for building computational models for mTBI.

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

  Nothing to report.

Product

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

  Nothing to report

- **Journal publications**

Gonuguntla, V., Yang, E., Guan, Y., **Koo, B. B.**, & Kim, J. H. (2022). Brain signatures based on structural MRI: Classification for MCI, PMCI, and AD. *Human Brain Mapping*.

Chia-Hsin Cheng, Zeynab Alshelh, Yi Guan, Kimberly Sullivan, Marco L. Loggia, **Bang-Bon Koo**, Association of the tissue microstructural diffusivity and translocator protein PET in Gulf War Illness, Brain, Behavior, & Immunity – Health, 2021, 18, 100364,

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

Nothing to report

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

Steele L, Klimas N, Krengel M, Quinn E, Toomey R, Little D, Abreu M, Aenlle K, Killiany R, **Koo B-B**, Janulewicz P, Heeren T, Clark AN, Ajama J, Cirillo J, Buentello G, Lerma V, Coller JK, Sullivan K. Brain–Immune Interactions as the Basis of Gulf War Illness: Clinical Assessment and Deployment Profile of 1990–1991 Gulf War Veterans in the Gulf War Illness Consortium (GWIC) Multisite Case-Control Study. *Brain Sciences*. 2021; 11(9):1132.

D. Keating, C.G. Zundel, M. Abreu, M. Krengel, K. Aenlle, M.D. Nichols, R. Toomey, L.L. Chao, J. Golier, L. Abdullah, E. Quinn, T. Heeren, J.R. Groh, **B.B. Koo**, R. Killiany, M.L. Loggia, J. Younger, J. Baraniuk, K. Sullivan. Boston biorepository, recruitment and integrative network (BBRAIN): A resource for the Gulf War Illness scientific community. *Life Sciences* 2021 Nov.

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: 7
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?**

Dietary quality, cognitive decline, and brain (NIH-NIA)
Cal mos.: 0.5
No cost extension started May 2022.
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 ended September 2021.
role: PI

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

Nothing to report

Special Reporting Requirements

- **COLLABORATIVE AWARDS:**

Nothing to report

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

Nothing to report

Appendices

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Yee MK, Janulewicz PA, Seichepine DR, Sullivan KA, Proctor SP, Krengel MH. (2017) Multiple Mild Traumatic Brain Injuries Are Associated with Increased Rates of Health Symptoms and Gulf War Illness in a Cohort of 1990-1991 Gulf War Veterans. *Brain Sci.* Jul 9;7(7). pii: E79.