AWARD NUMBER: W81XWH-18-1-0247

TITLE: Phenotypes of Comorbidity in Epilepsy: Variation by TBI Severity and Deployment Status

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6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The proposed study will leverage data from an existing Department of Defense (DoD) funded Post-traumatic epilepsy study(W81XWH-16-2-0046) that is examining the relationship between mild traumatic brain injury (mTBI) and epilepsy in deployed Post-9/11 Veterans. We will add to that study by identifying patterns of comorbidity in Post-9/11 deployed Veterans with epilepsy using latent class analysis, and by adding a cohort of non-deployed Post-9/11 Veterans who are also in VA care for the same analysis. As a result, with a small investment we will be able to identify specific phenotypes of comorbidity in Veterans with epilepsy and be able to determine if those patterns are different for individuals who 1) were deployed, where the likelihood of blast exposure is higher, and 2) have TBI exposure compared to those who do not. Finally, we will examine the extent to which these comorbidity phenotypes help explain premature death, and the specific cause of death in these individuals with epilepsy. These findings will have enormous implications for health care delivery for Veterans and Active Duty Service Members with epilepsy. For instance, the data may suggest that chronic disease is an important cause of death. This finding would suggest the importance of care coordination between primary care providers and neurologists/epileptologists providing subspecialty care for patients with epilepsy. In addition, data from this study can be used as a foundation to identify genetic markers that are associated with distinct epilepsy comorbidity phenotypes.

15. SUBJECT TERMS
Epilepsy, comorbidity, deployment

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	09	**19b. TELEPHONE NUMBER** *(include area code)*

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1. **INTRODUCTION**

The literature indicates that epilepsy is a chronic condition that, in combination with its comorbidities, has a profound impact on patients, their families, society, and health care systems. Moreover, data suggests a bi-directional relationship between epilepsy and a number of mental health comorbidities, and emerging data suggests bidirectional relationships with other conditions (i.e.,neuro-immunological conditions, dementia, obstructive sleep apnea). Recommendations for longitudinal research including epilepsy and comorbidity by the IOM are particularly salient for the current cohort of combat service members and veterans, due the high rates of mental health and other comorbidities thought to have a bidirectional relationship with epilepsy. Understanding the natural history of comorbidity in a military/veteran cohort in conjunction with advanced statistical models provide a unique opportunity to determine if 1) there are clinically meaningful comorbidity phenotypes in people with epilepsy 2) comorbidity phenotypes in epilepsy vary by deployment and TBI status, and 3) comorbidity phenotypes reliably predict mortality/SUDEP or disease-specific mortality.

KEYWORDS:

Epilepsy, mild traumatic brain injury, epidemiology

2. **ACCOMPLISHMENTS:**

What were the major goals of the project?

- Major Task 1: Complete regulatory requirements for study
- Major Task 2: Identify cohort who meet criteria
- Major Task 3: Create comorbidity phenotypes using latent class analysis
- Major Task 4: Conduct survey to assess lifetime TBI exposure
- Major Task 5: Identify adverse outcomes and conduct analysis by phenotype
- Major Task 6: Complete manuscripts

What was accomplished under these goals?

- **Major Task 1: Complete Regulatory Requirements for Study**

  All regulatory requirements have been completed.

- **Major Task 2: Identify cohort who meet criteria**

  All VA and DoD data has been requested and approved for use for this study. The team is currently waiting for access to all of the DoD data. Once data is accessed, it will be cleaned and merged with VA data to create out cohort.

- **Major Task 3: Create comorbidity phenotypes using latent class analysis**

  The team has begun to develop the list of conditions we will include in models one data is fully received. Similarly, the code for identifying all comorbid conditions for DoD and VA data are already developed which will facilitate rapid transition to data analysis once data are received.

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

We have one post-doctoral fellow who is working on this study, learning project management and gaining experience with publications.

How were the results disseminated to communities of interest?

The SLC team has begun drafting a paper related to this study conducting a social network analysis on Neurobehavioral Symptom Inventory (NSI) data for phenotypes while waiting for DoD data to be acquired. We anticipate producing multiple academic publications and other forms of research dissemination from this study.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, the team plans to finish the DoD data acquisition and to fulfill Major task 1. During this time the team will clean data received and identify cohort who meet the criteria laid out in the protocol working towards completing Major task 2. Similarly, the team will strive to works on Major task 3 and will do so by continuing to meet and discuss the preparation for the Latent Class Analysis. The team will also continue drafting the NSI social networking paper in preparation of publication.

3. **IMPACT:**

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

None to date. Our social network analysis will provide insights into symptom clusters in Veterans with and without epilepsy.

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?

Our stakeholder outreach will continue, providing community education opportunities. We have developed a relationship with the TBI Warrior Foundation and the EpiBiosRx community engagement team. We are working to expand our stakeholder engagement beyond these groups.

4. **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

There was a delay in the approval process of HRPO that took longer than expected. HRPO has since been approved and work on the project has resumed. We are now waiting for DoD data acquisitions and during this waiting period we have continued our regular team meetings, working on developing the list of conditions we will include in models and are anticipating issues we may encounter with data with mitigation strategies. We currently have code for identifying all comorbid conditions for DoD and VA data developed which will facilitate rapid transition to data analysis once data are received.

Changes that had a significant impact on expenditures

We have underspent on the project this year as we were delayed in approvals. We have hired staff and are making progress on data acquisition and will be able to rapidly curate data once obtained.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

5. **PRODUCTS:**

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.

Nothing to Report.

Website(s) or other Internet site(s)

We have launched a TORCH team website to provide information on the study, including an FAQ page (https://torchhub.com). We are currently developing a new website format in conjunction with the University of Utah in order to reach a wider audience and develop a more user-friendly

interface. We update this website quarterly and are adding information about related research studies we are working on.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Mary Jo Pugh*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	orcid.org/0000-0003-4196-7763
Nearest person month worked:	1
Contribution to Project:	*Dr. Pugh has completed project startup planning, site coordination, revision of protocol, and supervising study staff*
Funding Support:	

Name:	*Brice Terpstra*
Project Role:	*Research Scientist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Day to day management of project requirements
Funding Support:	

Funding Support:	

Name:	Hari Raju Sagiraju MD, PhD
Project Role:	Post-Doctoral Fellow
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Sagiraju has provided scientific support in the development of data requests and IRB application, preliminary scientific development
Funding Support:	

Name:	Chen-Pin Wang
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Dr. Wang has worked on development of code and logistics of conducting Latent Class Analysis*
Funding Support:	

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

09/28/2018 - 09/27/2022

Personal Biology & Comorbidity Impact on Post-TBI Cognitive Dysfunction & Neurodegenerative Disease
Principal Investigator(s): Amy Wagner
Direct Costs: $697,445 Total Costs: $816,011
Department of Defense Congressionally Directed Medical Research Programs

Role: Co-Principal Investigator (5% effort)

09/28/2018 - 09/25/2020

Epidemiological Characterization and Prognostic Models for PTE: A Collaborative TBI-MS and VHA Study
Principal Investigator(s): Mary Jo Pugh; Amy Wagner
Direct Costs: $121,154 Total Costs: $131,419
Department of Defense Congressionally Directed Medical Research Programs

Role: Co-Principal Investigator (5% effort)

09/28/2018 - 03/31/2020 **The UCD-DGMC TBI Neural Network- Precision Medicine Paradigm for Complex Trauma**
Principal Investigator(s): Mary Jo Pugh; Tina Palmieri
Direct Costs: $120,591 Total Costs: $149,591
Department of Defense Congressionally Directed Medical Research Programs
Role: Co-Investigator (10 % effort)

Studies that accounted for 35% effort were completed in FY19

What other organizations were involved as partners?

VA Epilepsy Centers of Excellence

7. **SPECIAL REPORTING REQUIREMENTS**

COLLABORATIVE AWARDS: Not Applicable.

QUAD CHART: Attached.

8. **APPENDICES:** None.

Phenotypes of comorbidity in epilepsy: Variation by TBI severity and deployment status

W81XWH-17-ERP-IDA

PI: Pugh M.J. **Org:** Western Institute for Biomedical Research **Award Amount: $567,672**

Study/Product Aim(s)

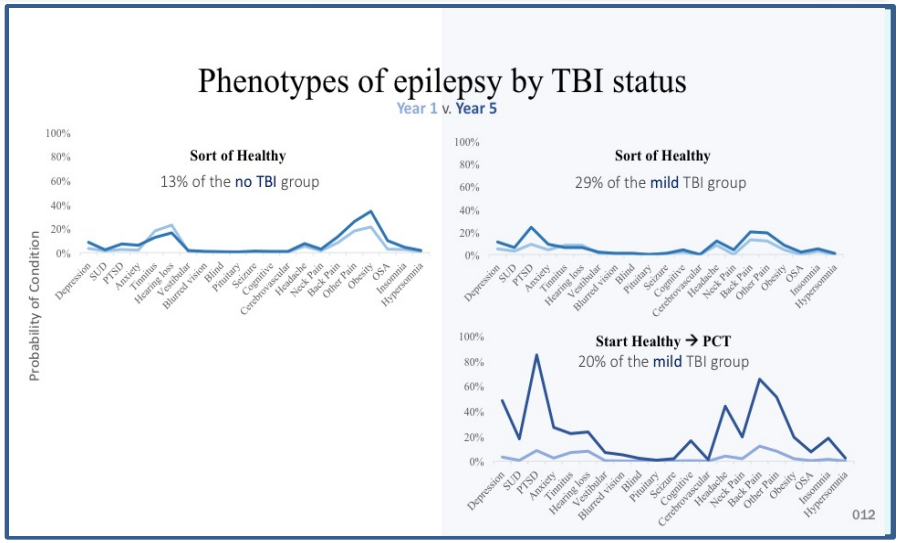
Aim 1: Identify neurological, psychological, and chronic disease comorbidity for a cohort of Post-9/11 Era Veterans with epilepsy who received VA care during at least two years (2002-2017) and determine if there are significant differences in comorbidity before and after identified epilepsy by TBI status (yes/no), TBI severity, Post-9/11 deployment status (previously deployed/not deployed).

Aim 2: Describe longitudinal phenotypes of comorbidity for Veterans with epilepsy and determine if phenotypes vary by TBI and deployment status.

Aim 3: Identify variation in adverse outcomes by comorbidity phenotypes adjusting for socio-/military demographic characteristics.

Approach

This observational cohort study will use VA and DoD data to identify comorbidity phenotypes among deployed and non-deployed Veterans with epilepsy using latent class analysis. It will also identify variation in phenotypes by TBI status and examine variation in adverse outcomes by phenotype.



Timeline and Cost

Activities / CY	19	20	21
Phase I: Regulatory and Administrative data compilation			
Phase 2: ID comorbidity phenotypes by deployment status (Aims 1-2)			
Phase 3: Outcomes analysis by phenotype (Aim 3)			
Estimated Budget (500K)	**$166**	**$194**	**$208**

Updated: 10/23/2019

Goals/Milestones

CY19 Goal –

☒Regulatory approvals

☐data acquisition (90% complete)

☐Identify non-deployed cohort and prevalence of comorbidity. (Aim 1)

CY20 Goal –

☐Identify phenotypes of comorbidity by deployment status

☐Determine if trajectories are significantly different by deployment and TBI status (Aim 2)

CY21 Goal –

☐Conduct analyses of adverse outcomes by phenotype (Aim 3)

Comments/Challenges/Issues/Concerns

- Regulatory (data access) taking longer than anticipated. Team has began social network analysis on NSI data while awaiting DoD data

Budget Expenditure to Date

Projected Expenditure: $166,123

Actual Expenditure: $53,132