

AWARD NUMBER: W81XWH-16-2-0046

TITLE: The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanism, and Outcomes

PRINCIPAL INVESTIGATOR: Mary Jo Pugh, PhD RN

CONTRACTING ORGANIZATION: Foundation for Advancing Veterans Health Research San Antonio, TX 78229

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<b>14. ABSTRACT</b> Our previous research has found that Post-9/11 Veterans with any kind of traumatic brain injury (TBI) were more likely to develop epilepsy than those without a prior TBI - however, its association with closed head injury such as mild TBI is as of yet unclear. To begin to rigorously evaluate this association, we have reviewed the 7238 cases of epilepsy identified using International Classification of Diseases Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes in Department of Veterans Affairs care, finding that 4664 (64.4%) were valid cases of epilepsy. We hope to use the results of this research to identify risk factors for post-traumatic epilepsy that will enable early identification for those at risk of its development.						
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## 1. INTRODUCTION

Studies of Veterans from World War II, the Korean War, and Vietnam provided groundbreaking information regarding the understanding of combat-related traumatic brain injury (TBI) and epilepsy. Because these studies focused on penetrating TBI (pTBI), our understanding of the association of closed head injuries including mild TBI (mTBI)—the majority of TBI exposures—with posttraumatic epilepsy (PTE) is unclear. By conducting an expansive evaluation of epilepsy epidemiology in Post-9/11 Veterans deployed in support of Wars in Iraq and Afghanistan using available data from the Departments of Defense (DoD) and Veterans Affairs (VA) and primary data collection allows us to go beyond a simple incidence/prevalence study to provide a targeted evaluation of the impact of epilepsy on Post-9/11 Veterans compared to controls, and to harness the power of cutting-edge neuroimaging (and eventually biomarker) data to answer immediate questions regarding etiology and provide the foundation for longitudinal study that will ultimately identify specific aspects of mTBI/other risk factors that will allow early identification of those at greatest risk of PTE.

### 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 for epilepsy (Aim 1)
- Major Task 3: Identify Sample for Aims 2-3
- Major Task 4: Conduct telephone interviews/surveys for Veterans with Epilepsy and Controls to conduct analyses for Aims 2 and 3
- Major Task 5: Identify TBI phenotypes
- Major Task 6: Conduct analyses comparing Veterans with epilepsy and controls on self-report measures (Aim 3)
- Major Task 7: Conduct analyses comparing Veterans with epilepsy and controls on neuroimaging and neuropsychological testing (Aim 4)

### What was accomplished under these goals?

#### ➤ Major Task 1: Complete Regulatory Requirements for Study

We have finalized consent forms, human subjects protocols, and the chart abstraction tool, survey, and interview needed to conduct all work outlined in this grant. Further, we have secured local regulatory (Department of Veterans Affairs (VA) Research and Development and Institution Review Board) approval at all sites (i.e., South Texas Veterans Healthcare System (Site 1), University of Missouri, St. Louis (UMSL; Site 2), Hunter Holmes McGuire VA Medical Center (Richmond, VA; Site 3), Tampa VA Research and Education Foundation (TVREF; Site 4); Baylor University (BU; Site 5), as well as at the additional Chronic Effects of Neurotrauma Consortium (CENC) Longitudinal Cohort Study (Study 1) sites of Portland, OR and Boston, MA. We received Human Rights Protection Office approval for Aims 1-3 (Research Activities local to the main site in San Antonio, TX) in 2016. Salt Lake City, UT was added and approved by IRB as a study site in March and 2018 for Aims 2 and 3. HRPO approved all study sites as of June 2018.

#### ➤ Major Task 2: Identify cohort who meet criteria for epilepsy (Aim 1)

We have secured all proposed VA data for Veterans who entered VA care FY02-12 and received care in FY04 through FY14. After removing deceased cases, a total of 824,698 Veteran records were available. We excluded 14,349 cases because they had diagnoses of convulsion or more severe TBI, which did not fit our research criteria. The final study population is N = 810,349. We completed medical chart reviews and have validated 7328 cases who met epilepsy criteria based on International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes. We then were able to group the overall population into four distinct sub populations to obtain our samples for Aims 2-3. (See Major Task 3.)

➤ **Major Task 3: Identify Sample for Aims 2-3**

After completing the chart reviews, our team divided the total N for analyses into sub populations from which samples were obtained as follows:

	Population	Sampled
No TBI: No Epilepsy	695,875	2,625
No TBI: Epilepsy	2,405	1,286
mTBI: No Epilepsy	109,801	2,746
mTBI: Epilepsy	2,268	610
Totals	810,349	7,267

➤ **Major Task 4: Conduct telephone interviews/surveys for Veterans with Epilepsy and Controls to conduct analyses for Aims 2 and 3**

**Surveys (SATX)** – Invitation letters were mailed out to the samples for each of the four groups. The letters included a paper survey with instructions of how to access and complete the survey online if preferred. As of September 30, 2018, we have received a total of 1,732 surveys (24% response rate). We are continuing to administer follow up invitation letters to potential participants and expect surveys to continue coming in through the end of 2018. Response rates by group are listed below.

	Sampled	Responded
No TBI: No Epilepsy	2,625	753
No TBI: Epilepsy	1,286	373
mTBI: No Epilepsy	2,746	680
mTBI: Epilepsy	610	163
Totals	7,267	1969

**Interviews (SLC)** – A total of 1,480 (75%) of our survey completers have agreed to participate in additional, related research. 1,159 (59%) have agreed to a follow up telephone interview. Preparation for the interviews is underway in Salt Lake City, Utah. We submitted an invitation

letter and the full telephone interview protocol as an amendment in the Utah IRB and are awaiting approval. Staff have been hired and are being trained in survey administration. Our team expects to begin interviews in early 2019.

➤ **Major Task 5: Identify TBI phenotypes**

Work on this task will begin in early 2019 once the survey has been fielded, a sufficient number of responses have been received, and data has been cleaned and prepared for analyses.

➤ **Major Task 6: Conduct analyses comparing Veterans with epilepsy and controls on self-report measures (Aim 3)**

Work on this task will begin in late calendar year 2019 once the survey has been fielded, a sufficient number of responses have been received, and data has been cleaned and prepared for analyses.

➤ **Major Task 7: Conduct analyses comparing Veterans with epilepsy and controls on neuroimaging and neuropsychological testing (Aim 4)**

As of September 30, 2018 a total of 1,480 (75%) of survey completers have agreed to participate in additional, related research. Of these, 123 have been referred and 27 have been enrolled at one of the six CENC Study 1 sites, which collect a variety of functional tests, including neuropsychological and neuroimaging measures which are integral to Aim 4 of this study.

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

Post-doctoral fellow Dr. Hari Krishna Raju Sagiraju, MD has received training on national survey administration through the San Antonio, TX team and recently moved to Salt Lake City, Utah where he will be assisting with research processes, interpretation of data and writing manuscripts. Senior SATX staff, will train and mentor all SLC staff in administration of the BTACT and OSU TBI assessment instruments in November 2018.

**How were the results disseminated to communities of interest?**

The Salt Lake City team has launched a TORCH team website to provide information on the study, including an FAQ page to answer frequently asked questions by survey recipients. We provide the link (<https://torchhub.com/tbi>) in survey invitation and follow up letters. The website has been viewed by 230 unique visitors to date, with over 1,419 page views. The majority of the page views are the “Home” page with information about Dr. Pugh’s research on TBI, and the specific pages provided for this study. Our team will continue to update this information as surveys are completed and analyzed. The SATX and SLC teams have begun drafting a paper related to this study to examine TBI severity and blast exposure risk factors in epilepsy. We anticipate producing multiple academic publications and other forms of research dissemination from this study.

Dr. Pugh presented an overview, “TBI and Epilepsy: What we know and we don’t know” to the Red Cross Caregiver Network. This lay presentation was well-received and provided an opportunity to present future findings to this important stakeholder group.

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

During the next year, we plan to continue to administer the survey and begin to interview participants who have indicated their interest in additional, related research (Major Task 4). We will clean all survey data in order to conduct the analyses for Major Tasks 5-6. We will continue to enroll willing participants that meet eligibility criteria for CENC Study 1 and begin the neuroimaging research (Major Task 7).

**3. IMPACT:**

The chart abstraction process revealed a significant number of individuals who died since meeting epilepsy criteria. Using this study as a foundation, we submitted a proposal to the Epilepsy Research Program Idea Development Award to further evaluate the cause of death and the impact of comorbidity phenotypes on mortality. This study was funded in FY18 and research will begin in 2019.

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

Through the epilepsy verification process we identified revisions to the algorithm that may make the epilepsy algorithm even more useful for surveillance purposes in both VA and DoD data.

**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.

**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**

Delayed subaward to Utah: Dr. Pugh, PI for this project, transferred to the SLC VA and University of Utah (UU) in fall 2017. Due to the complexity of transferring elements of work associated with this project, the subaward was delayed, which prevented hiring staff and completing related regulatory tasks. The UU IRB was approved in March 2018, and staff were hired in June 2018.

Delayed HRPO IRB Approval: Because of the complexity of this project, the numerous sites involved in this interdisciplinary work, and a change in the assigned HRPO Specialist assigned to this project, we were delayed in securing HRPO IRB approval for Aim 4 and the sites involved in that work. We received HRPO approval June 2018.

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

Delays in administrative data access, in part due to administrative delays with the transfer of the study PI to the SLC VA, reduced the amount of time that the data analyst and SLC research staff worked this Fiscal Year. Thus, increased research staff costs will be required in upcoming fiscal years as this work is accomplished.

**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 to answer frequently asked questions by survey recipients (<https://torchhub.com/tbi>). 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:	<i>Mary Jo Pugh</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	0000-0003-4196-7763
Nearest person month worked:	3
Contribution to Project:	<i>Dr. Pugh has overseen project staffing, management, and execution</i>
Funding Support:	

Name:	<i>Alicia Swan</i>
Project Role:	<i>Research Scientist</i>
Researcher Identifier (e.g. ORCID ID):	<i>orcid.org/0000-0003-2412-0499</i>
Nearest person month worked:	6
Contribution to Project:	<i>Dr. Swan has completed regulatory requirements, project management, planning and execution.</i>
Funding Support:	

Name:	<i>Andrea Kalvesmaki</i>
Project Role:	<i>Senior Research Analyst</i>
Researcher Identifier (e.g. ORCID ID):	<i>orcid.org/0000-0002-4282-0619</i>
Nearest person month worked:	4
Contribution to Project:	<i>Ms. Kalvesmaki leads the SLC team with scientific project management, supervision of staff, planning and execution</i>
Funding Support:	

Name:	<i>Brice Terpstra</i>
Project Role:	<i>Senior Research Analyst</i>

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	<i>Mr. Terpstra works on Aims 2 and 3</i>
Funding Support:	

Name:	<i>Charlene Humpherys</i>
Project Role:	<i>Research Analyst</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	<i>Ms. Humpherys works on Aims 2 and 3</i>
Funding Support:	

Name:	<i>Adriana Reyes Miranda</i>
Project Role:	<i>Research Analyst</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	<i>Ms. Reyes Miranda works on Aims 2 and 3</i>
Funding Support:	

Name:	<i>Silvia Padilla</i>
Project Role:	<i>Research Analyst</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	<i>Ms. Padilla works on Aims 2 and 3</i>
Funding Support:	

Name:	<i>Bronson Nye</i>
Project Role:	<i>Program Manager</i>

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	<i>Mr. Nye manages the regulatory processes and program management tasks for this project.</i>
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?**

Nothing to Report.

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

Nothing to Report.

## 7. SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS:** Not Applicable.

**QUAD CHART:** Attached.

8. **APPENDICES:** None.

The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanisms, and Outcomes  
 ERMS/EP150013  
 W81XWH-16-2-0046



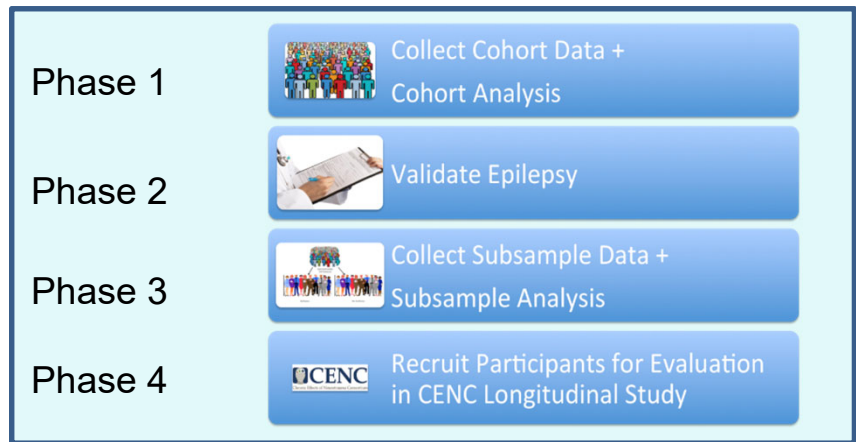
**PI:** Mary Jo Pugh PhD, RN **Org:** Foundation for Advancing Veterans Health Research **Award Amount:** \$2,199,189

**Study Aims**

- Aim 1: Identify a cohort of Post-9/11 Veterans who received VA care during at least two years (2002-2015), calculate the prevalence of epilepsy in 2015 and identify the association between mTBI and epilepsy
- Aim 2: Among a subsample of surveyed Veterans, examine the association between lifetime history of mTBI and epilepsy.
- Aim 3: Among the surveyed subsample, compare those with and without epilepsy on functional outcome measures (e.g., employment status, mental, physical and social functional status, community reintegration).
- Aim 4: Enroll 200 survey respondents in the Chronic Effects of Neurotrauma Consortium (CENC) Longitudinal study to obtain advanced clinical, cognitive, and MRI data.

**Approach**

This study utilizes data from existing VA and DoD data repositories, patient self-reports from surveys/interviews and data collected through the CENC longitudinal study. These unique data sources will allow us to examine population prevalence of epilepsy, identify its association of mTBI, assess outcomes associated with epilepsy, and reveal neuroimaging and biomarker correlates of mTBI and epilepsy. The longitudinal nature of the CENC longitudinal study provides an opportunity to follow this cohort beyond the course of this study to better understand the long-term impact of mTBI exposures and epilepsy among the Veterans of the Afghanistan and Iraq wars.



**Accomplishments:** Our team has completed Aim 1, validating 7,328 cases meeting epilepsy criteria out of a total population of 810,349. Aims 2-4 are in progress. For Aims 2-3, we have received 1,969 surveys, of which 1,159 (59%) have agreed to participate in telephone interviews, which will commence in 2019. A total of 123 respondents have been referred for CENC Study 1 (Aim 4), and 27 have been enrolled at one of the six CENC study sites.

**Timeline and Cost**

Activities	CY	17	18	19	20
Identify Cohort and estimate prevalence of epilepsy		█			
Examine association between lifetime mTBI and epilepsy			██████████		
Compare surveyed Veterans with and without epilepsy on outcomes			██████████		
Obtain clinical, cognitive, and MRI data on the select CENC subsample			██████████		
<b>Estimated Budget (\$K)</b>		<b>\$508</b>	<b>\$558</b>	<b>\$568</b>	<b>\$566</b>

Updated: October 19, 2018

**Goals/Milestones**

- CY17 Goal** – Regulatory approval, data acquisition, survey design
  - Gain regulatory approval and logistical readiness to execute aims
- CY18 Goals** – Survey administration, data compiling, aim 1 analysis
  - Calculate epilepsy prevalence and its association with mTBI
  - Begin compiling survey data
- CY19 Goal** – Finalize survey data, chart abstractions, and commence referral to and enrollment in CENC study 1
  - Execute analyses of outcomes among the surveyed Veterans with and without epilepsy and a history of mTBI
- CY20 Goal** – Complete enrollment and testing 150-200 of the surveyed subsample in the CENC Longitudinal Cohort study
  - Analyze advanced clinical, cognitive and MRI data among those referred to CENC study 1

**Comments/Challenges/Issues/Concerns**

- No challenges, roadblocks or concerns to date

**Budget Expenditure to Date**

Projected Expenditure: \$1,066,000  
 Actual Expenditure: \$460,585.73