

Department of Defense Epilepsy Research Program

CUTTING EDGE RESEARCH



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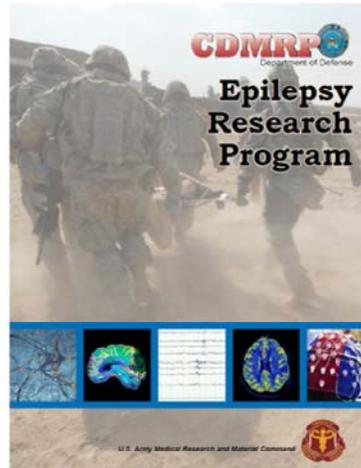
CDMRP

Department of Defense



Program Overview: Introduction

- ◆ **History:** Initiated in 2015 to develop an understanding of the magnitude of post-traumatic epilepsy (PTE) within the military and to expand research into the basic mechanisms by which traumatic brain injury (TBI) produces epilepsy
- ◆ **Vision:** The ERP envisions a time when the causative links between TBI and epilepsy are understood and PTE is both preventable and treatable
- ◆ **Mission:** The ERP's mission is to advance research to understand the mechanisms underlying the genesis and progression of PTE, especially in Service members and Veterans



Scope of the Problem

◆ Health Impact of Epilepsy

- ❖ Hirtz, et al. estimated 2.1 million (M) cases, with 142,000 new cases per year in 2005¹
- ❖ 4th most common neurological disorder¹
- ❖ Incidence (new cases) is highest in children and the aging²
- ❖ 2015 costs were estimated between \$9.6 billion (B) and \$12.5B (Institute of Medicine Report²)
- ❖ Surveillance report of active duty military (1998-2012) reported 11,295 incident cases of epilepsy among active component Service members (incidence rate: 52.8 per 100,000 person-years)³

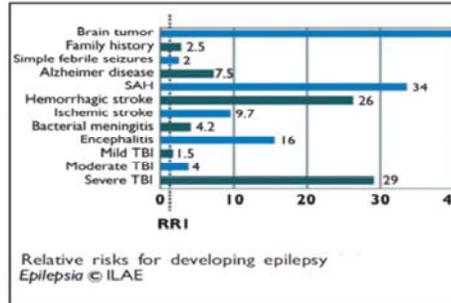


Figure 1: Adapted from Lowenstein, 2009⁴.

◆ Study also reported gender-based differences; concluded that TBI could not account for increased incidence of epilepsy during the surveillance period³

¹Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. 2007. How common are the "common" neurologic disorders? *Neurology*. 68(5):326-337.

²England MJ, Liverman CT, Schultz, AM, et al. 2012. *Epilepsy Across the Spectrum: Promoting Health and Understanding*. Institute of Medicine Report Brief.

³Medical Surveillance Monthly Report. 2013. Vol 20, Number 5, 19-23.

⁴Lowenstein. 2009. Epilepsy after head injury: An overview. *Epilepsia*. 50 (Suppl. 2):4-9.

Scope of the Problem (cont.)

◆ Health Impact of TBI

- ❖ Defense and Veterans Brain Injury Center (DVBIC) reported roughly 380K cases since 2000¹
- ❖ Centers for Disease Control and Prevention (CDC) reports 716 emergency department visits/92 hospitalizations per 100,000 US population (2010)²
- ❖ Number of civilian TBIs increased between 2001 and 2010²
- ❖ CDC reported cost estimate for domestic TBI medical costs in 2010 at \$76.3B³
- ❖ Study on Vietnam-era Veterans showed 53% had post-traumatic epilepsy after penetrating TBI (n=421) (Salazar, et al.)⁴

¹<http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>

²<http://www.cdc.gov/traumaticbraininjury/data/rates.html>

³<https://www.cdc.gov/cdcgrandrounds/pdf/grtbi20sep2011.pdf>

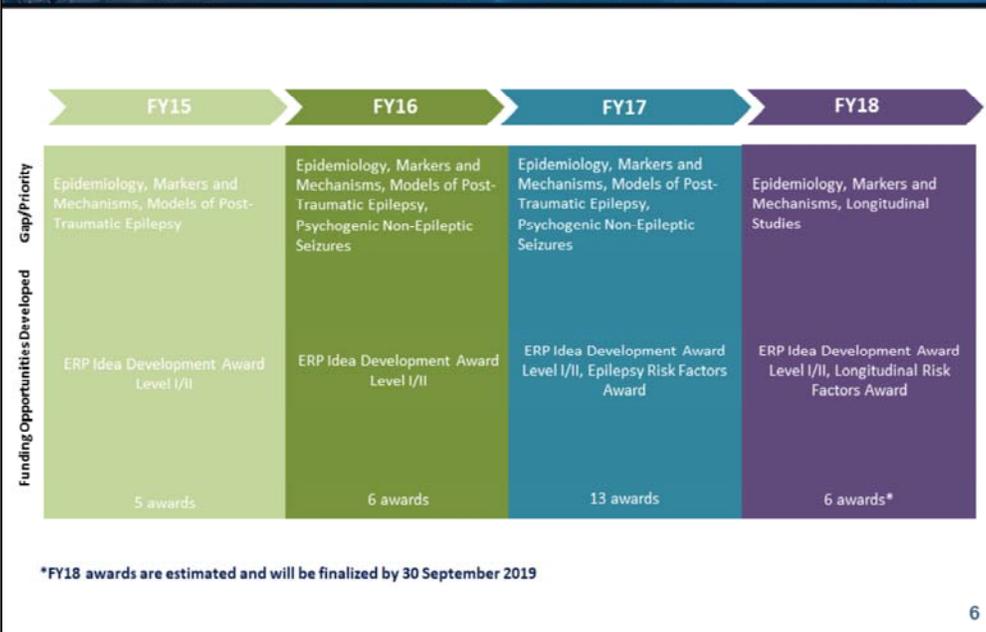
⁴Salazar AM, Jabbari B, Vance SC, et al. 1985. Epilepsy after penetrating head injury. I. Clinical correlates: A report of the Vietnam Head Injury Study. *Neurology*. Oct;35(10):1406-1414.

Strategic Guidance

- ◆ **Congressional language (FY15)*:** As current TBI longitudinal studies have not included epilepsy, the Committee encourages the Department to place greater priority and invest more funding in longitudinal epidemiological research, including epilepsy surveillance, to better understand the magnitude of the problem and improve patient care and outcomes. To assist in these efforts, the Committee recommends \$7,500,000 in support of epilepsy research. Additionally, the Committee urges the Department to expand research into the mechanisms by which brain injury produces epilepsy and research directed at the prevention of epilepsy and concomitant comorbidities in those known to be at high risk.

*Department of Defense (DoD) Appropriations Bill (2015) Report 113-211, pages 257-258

Epilepsy Research Program (ERP) Portfolio Strategy



FY18 ERP Focus Areas

Epidemiology: Epidemiological characterization of PTE following TBI, which may include the following:

- ◆ Risk factors such as demographics, genetic factors, organic head injury factors, or type of insult
- ◆ Differentiation of PTE and psychogenic non-epileptic seizures (PNES)
- ◆ Outcomes, including latency to epilepsy, morbidities and comorbidities, and mortality
- ◆ Pre-existing conditions including psychological and psychiatric risk factors
- ◆ Treatment

Markers and Mechanisms: Identifying markers or mechanisms (via clinical prospective or preclinical models) that address PTE, which may include the following:

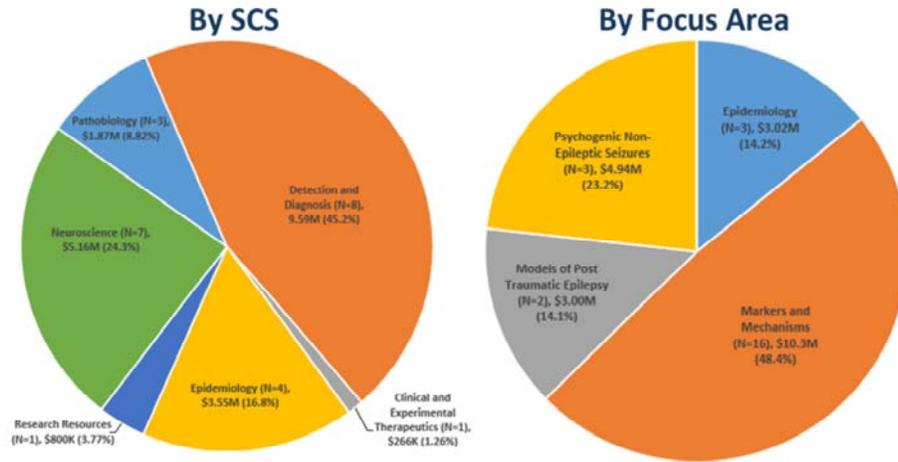
- ◆ Early detection
- ◆ Diagnosis
- ◆ Prognosis
- ◆ Morbidity
- ◆ Comorbidity
- ◆ Mortality
- ◆ Risk stratification

Longitudinal Studies: Studies of the natural evolution of PTE, which may include the following:

- ◆ Seizure frequency and severity
- ◆ Comorbidities (e.g., depression, functional deficits, sleep disorders, major illness)
- ◆ Latency between injury and PTE
- ◆ Mortality
- ◆ Treatment
- ◆ Quality of life of individuals with PTE

- Address technical “bottlenecks”
- Mechanism-specific
- All applications should address at least one bottleneck, unless a strong rationale is presented

ERP Research Investment FY15-FY17 By CDMRP Scientific Classification System (SCS) Code Series/Focus Area** (N=24;\$21.3M)



*Congressionally Directed Medical Research Programs
**Subject to final budget negotiations

Technology Readiness Levels (TRLs) for ERP Awards (FY15-FY17)

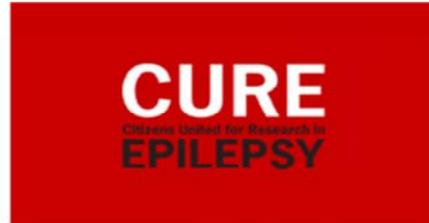
SCS Code Series	Basic and Applied Science/Technology				Phase I/II Studies		Phase II/III		Total Projects	Total Investment
	TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8		
Epidemiology				4					4	\$3.55M
Neuroscience			6	1					7	\$5.16M
Research Resources			1						1	\$800K
Pathobiology			3						3	\$1.87M
Detection and Diagnosis			3	5					8	\$9.59M
Clinical and Experimental Therapeutics			1						1	\$266K
Total Projects			14	10					24	
Total Investment			\$10.7M	\$10.6M						\$21.3M

TRL 3: Data and knowledge representation schema modeled.

TRL 4: Prototype produced. Hardware/Software pieces work together. Models use real data/knowledge.

Grant Partnerships: Team Approach to the Prevention and Treatment of PTE (PoP*: Sept. 2015 to Sept. 2020)

- ◆ Award made to Citizens United for Research in Epilepsy (CURE)
- ◆ Funded by the Psychological Health and Traumatic Brain Injury Research Program (\$10.1M), with the intent to compliment the ERP
- ◆ Coordinated at CURE (Grant PI: Laura Lubbers), Joint Program Committee 6/ Combat Casualty Care Research Program (JPC-6/CCCRP), and CDMRP
- ◆ Unique management/selection system based on successes in infantile spasms
- ◆ Research grants made as sub-awards to multiple institutions selected by EAB; Dr. Lubbers coordinates all research activities.



External Advisory Board:

- ◆ Patrick Bellgowan, NINDS
- ◆ Douglas Coulter, University of Pennsylvania
- ◆ Nsini Umoh (JPC-6), USAMRMC
- ◆ COL Sidney Hinds II, USAMRMC
- ◆ Stuart Hoffman, VA
- ◆ Jim McNamara, Duke University

*Period of Performance

**US Army Medical Research and Materiel Command 10

Partnerships: EpiBioS4Rx Public Engagement Core

- ◆ Funded by the National Institutes of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS)
- ◆ Public Engagement Core brings together stakeholders from across the post-traumatic epilepsy community, to include academicians, not-for-profits, DoD, and US Department of Veterans Affairs (VA)



<https://epibios.loni.usc.edu>

Data Sharing and the Federal Interagency Traumatic Brain Injury Registry (FITBIR)

- ◆ A robust data-sharing/research resource plan is required as part of the application process
 - ❖ FY18 Program Announcements contain revised criteria
- ◆ Applications that include human studies of TBI must consider the FITBIR and NINDS TBI and Epilepsy Common Data Elements as part of their data-sharing plan

What is FITBIR?

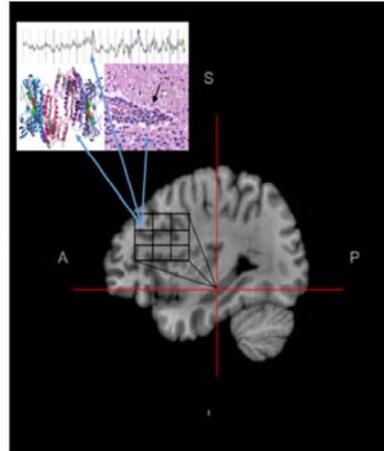
- ◆ Joint NIH/DoD partnership
- ◆ Central repository for phenotypic, genomic, and imaging data from TBI studies
- ◆ Free web-based application with a user-friendly interface for contributing and accessing data



<https://fitbir.nih.gov>

“Vertical Bioinformatics” (Working across multiple datasets as opposed to horizontally harmonizing a specific technique (e.g., a common MRI research protocol) for post-processing of large datasets:

- ◆ Potential for bringing together datasets produced by research funded in Post-Traumatic Epilepsy by the Epilepsy Research Program and other funding sources.
- ◆ Limited in this concept to animal models (brain slices), but high-quality MRI data could be used as an atlas in future projects.
- ◆ Some data (e.g., proteomic) may not be feasible in humans; but the animal work may serve as a platform for discovery. Will eventually need to modify this for a more in vivo approach, but could work for autopsy.
- ◆ Idea is to take proteomic and other analytical measurements and map them to specific brain regions.
- ◆ Major challenge will be coming up with a common denominator for spatial resolution across all integrated modalities.
- ◆ A follow-up challenge will be integrating the data and then designing the post-processing software for the analyses.



Long-Term Investment Strategy of the ERP Strategic Plan

- ◆ More Research into the Epidemiology of PTE
 - ❖ Reveal incidence/prevalence and risk factors
- ◆ Conduct Longitudinal Studies
- ◆ Translate findings into clinical trials to prevent/treat
- ◆ Launch Phase 0/I clinical trials

More Information on the ERP Strategic Plan: <https://cdmrp.army.mil/erp/default>

