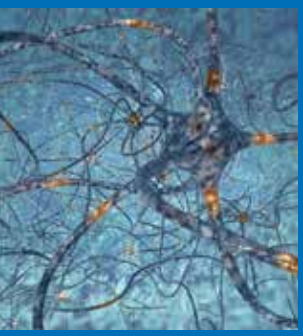
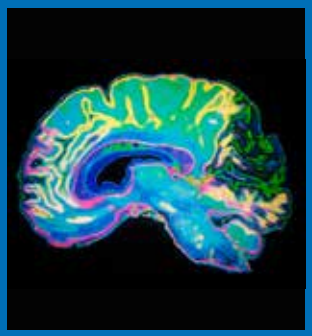
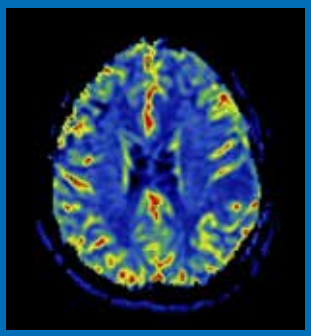
CDMRP

Department of Defense

Epilepsy Research Program




U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

HISTORY

The Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 by a powerful grassroots effort led by the breast cancer advocacy community. This initiated a unique partnership between the public, Congress, and the military. Since then, the number of national and military health programs has grown. Over the course of its history, the CDMRP has managed over $11.9 billion in congressional appropriations for both military and domestic health research programs. The research spectrum supported by the CDMRP extends from basic science to large, multi-institutional consortia. The spectrum for each program is tailored to meet the specific research priorities envisioned by its stakeholders. Funds for the CDMRP are added annually to the Department of Defense (DoD) budget in order to support individual programs, such as the Epilepsy Research Program (ERP), and are allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation. Both tiers involve dynamic interaction between scientists and consumers. Examples of consumers can be disease survivors or those responsible for the care of someone living with a disease. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the research program's stakeholders. The stakeholders, collectively referred to as the ERP Programmatic Panel, are composed of leading scientists, clinicians, and consumer advocates. The Programmatic Panel members make recommendations for funding based on a number of programmatic review criteria. These criteria include not only scientific merit, but also potential for innovation, potential impact of the research, and portfolio composition. The programmatic review allows the stakeholders to select the particular science that will best satisfy the mission and vision of the program.

Epilepsy Research Program

VISION: The ERP envisions a time when the causative links between Traumatic Brain Injury and epilepsy are understood and Post-Traumatic Epilepsy (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.

ABOUT THE PROGRAM

Service members suffering from PTE face a number of complex challenges in everyday life. These difficulties may include seizures, cognitive and social challenges, and depression. The ERP is focused on understanding who is affected by PTE in the military in order to understand who may be most vulnerable and how it affects the individual's prognosis and risk factors. The program is searching for prospective markers, models, and mechanisms of PTE in order to improve detection at the earliest stages, which will minimize related health risk factors for the individuals and the community affected.

The ERP was established in fiscal year 2015 (FY15) to develop an understanding of the magnitude of PTE within the military and to expand research into the basic mechanisms by which traumatic brain injury (TBI) produces PTE. Epilepsy is the fourth most common neurological disorder[1] and can be found in the active duty military population.[2] Mild, moderate, and severe TBI are all linked to epilepsy,[3] but the nature of the connection is not well understood. Mechanisms and markers of pathology and population-based research are needed to understand the connection between TBI and epilepsy. These gaps are reflected in the FY18 ERP's Focus Areas, which change as the direction of the ERP evolves and are summarized below.

Epidemiology: Epidemiological characterization of PTE following TBI, which may include studies of risk factors, differentiation of PTE and psychogenic non-epileptic seizures (PNES), outcomes/morbidity, pre-existing conditions, and treatment.

Markers and Mechanisms: Identifying markers or mechanisms that address PTE in terms of early detection, diagnosis, prognosis, morbidity, comorbidity, mortality, and risk stratification.

Longitudinal Studies: Studies of the natural evolution of PTE, which may include seizure frequency and severity, comorbidities, latency between injury and PTE, mortality, treatment, and the quality of life of individuals with PTE.

References

[1] Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. 2007. "How Common Are the 'Common' Neurological Disorders?" *Neurology.* 68(5):326–337.

[2] Armed Forces Health Surveillance Branch. 2013. "Epilepsy in Active Component Service Members, 1998–2012." *Medical Surveillance Monthly Report.* 20(5):19–22.

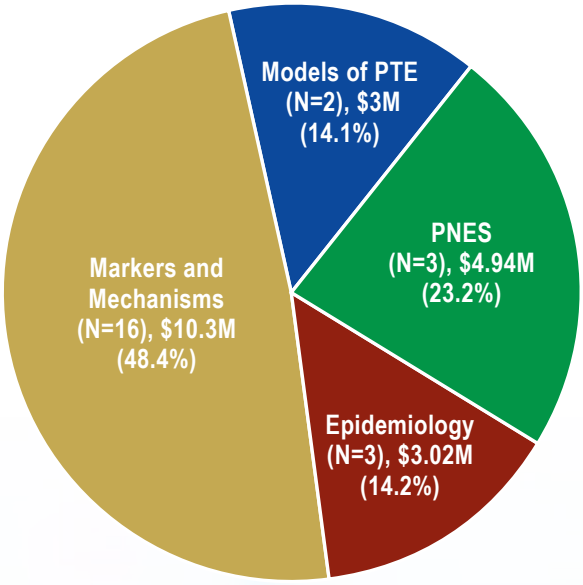
[3] Lowenstein DH. 2009. "Epilepsy After Head Injury: An Overview." *Epilepsia.* 50(Suppl. 2): 4–9.

Applications submitted to the ERP must address one or more of these Focus Areas, which are revisited each year at the annual ERP Vision Setting meeting. The ERP Focus Areas are used as the basis for Program Announcements of funding opportunities. Through Program Announcements, applicants can help move the ERP toward realizing its vision and mission.

ERP RESEARCH INVESTMENT

Between FY15 and FY17, the ERP has received $22.5 million (M) to fund research in PTE. The funding has resulted in 24 awards. Across the portfolio, ERP-funded research is examining (1) new and innovative animal models for evaluating the connection between TBI and PTE, (2) the differences between PTE and PNES, and (3) connectomics approaches to look at functional brain changes associated with PTE subsequent to TBI. This is in addition to epidemiological studies of Service members. Research into PNES is necessary in order to characterize the similarities and differences between PNES and PTE. This will provide a better understanding of both. For FY18, the ERP continues to fund needed and innovative research. FY18 is the first year that the ERP will emphasize the need for longitudinal, population-based research studies. These studies may help the ERP understand how issues such as comorbidities figure into patient care and quality of life.

FY15-FY17 ERP Investment by Focus Area



ERP PARTNERSHIPS

Research initiatives that will have an impact on populations affected by PTE require strong research funding partners. In 2015, the DoD provided funding to Citizens United for Research in Epilepsy (CURE) to examine PTE. Research funded by CURE is often multidisciplinary by nature, and the CURE DoD PTE initiative allows grantees to regularly learn from each other. The DoD also closely partners with the National Institute of Neurological Disorders and Stroke, which has a significant grant portfolio on PTE, through a number of workshops and other meetings regarding PTE. These partnerships are key, as they allow public and private entities to use their differing scientific models to accelerate PTE research.

ERP STRATEGIC PLAN

At the start of FY18, the ERP developed a strategic plan in order to define the goals and direction of the program. The ERP strategic plan was developed in partnership with the ERP Programmatic Panel and outlines the near-term and medium- to long-term goals of the ERP. In addition, the strategic plan reviewed the progress and investment that the ERP has made through to the start of FY18 and provides an emphasis on ERP Focus Areas.

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

Mary Jo Pugh, Ph.D., R.N., South Texas Veterans Health Care System

While the link between severe TBI and epilepsy is well known, the long-term consequences of mild TBI (mTBI), the most common brain injury among Post-9/11 Veterans, remain unclear with regard to PTE. To address this, Dr. Mary Jo Pugh was awarded an FY15 ERP Idea Development Award (IDA) to examine the association between TBI and PTE in Veterans who were deployed in Post-9/11 conflicts. By comparing the medical records of Post-9/11 Veterans, Dr. Pugh and her team found that Veterans with mTBI were twice as likely to have epilepsy as Veterans without TBI. In addition, Dr. Pugh's group is conducting a national survey to examine the unique effects of mTBI and epilepsy on the social, emotional, and physical functioning of our Veterans. Dr. Pugh and her team will also collect advanced clinical, cognitive, and neuroimaging data from a subset of participants. Importantly, this study seeks to identify populations at highest risk for developing PTE after mTBI, which may lead to earlier identification and treatment. Additional outcomes may include identifying individuals who may benefit from non-pharmacological therapy, such as cognitive or lifestyle interventions. These types of interventions may benefit patients with PTE by improving their ability to manage their epilepsy, leading to better health outcomes for both patients and their families.

"The Epilepsy Research Program will play a critical role in elucidating and understanding post-traumatic epilepsy and the role of trauma in non-epileptic seizures. Post-traumatic epilepsy is a consequence of traumatic brain injury, and post-traumatic epilepsy is the most common cause of new-onset epilepsy in young adults. The panel's work will have a direct impact on Service men and women, as well as civilians who have sustained traumatic brain injury."

CPT Karen Parko, M.D.,
US Public Health Service, Ret.,
Inaugural National Director,
VA Epilepsy Centers of Excellence

Neuroimaging Biomarker for Seizures

William Curt LaFrance, Jr., M.D., M.P.H., Ocean State Research Institute

Soldiers are exposed to a number of physical and psychological stressors in combat that can have long-term consequences. TBI, commonly seen in Veterans, can lead to PTE, where patients suffer from epileptic seizures that are the result of aberrant neuronal activity. In addition, Veterans may suffer from seizures that are non-epileptic (PNES), which lack epileptiform activity on an electroencephalogram but are otherwise comparable to epileptic seizures. PNES are thought to be the result of traumatic experiences, such as those seen in combat. With the help of an FY16 ERP IDA, Dr. William Curt LaFrance, his collaborator Dr. Jerzy Szaflarski, and their colleagues are investigating the neural circuitry of PTE and PNES through a longitudinal neuroimaging study of Veterans. Specifically, Dr. LaFrance's team will perform magnetic resonance imaging before and after patients receive cognitive and behavioral therapy for seizures, which in preliminary studies reduced seizure burden in patients with PNES. In addition, these findings will be compared to patients who have received a TBI, but have not had PTE or PNES. Dr. LaFrance and his team are working to find neural signatures that differentiate PNES from PTE and TBI in Veterans, with the hope that these discoveries may lead to better treatments for both PNES and PTE.

Diffuse and Focal Brain Injury in a Large Animal Model of PTE: Mechanisms Underlying Epileptogenesis

John A. Wolf, Ph.D., University of Pennsylvania

Many Service members and civilians who receive a TBI later develop spontaneous recurrent seizures (i.e., PTE). During the time between the TBI and the development of PTE, the brain undergoes changes that make it prone to seizures, a process known as epileptogenesis. The mechanisms of epileptogenesis are not fully understood. There has been some research success in this area using animal models of PTE. The most common models rely on focal injury in rodents. While these models replicate some of the hallmarks of PTE, they may not adequately model the complex focal and diffuse brain injuries typically seen in PTE patients.[4]

With the support of an FY15 ERP IDA, Dr. John Wolf is investigating different injury models in a novel PTE animal model, namely swine. The swine brain more closely resembles human neuroanatomy than that of rodents, as it has significantly more white matter as well as the presence of gyri and sulci, unlike the smooth cortical surfaces seen in mice and rats. The larger brains of swine also make the induction of diffuse injury more feasible, while still enabling the types of focal injuries performed in rodent models.

Dr. Wolf and his team are first comparing purely focal, purely diffuse, and combination injuries in this swine model in order to better understand the injury modalities that lead to PTE and determine which best replicates the clinical hallmarks seen in patients. Next, to investigate the underlying epileptogenic processes following injury, the researchers are implanting electrodes in the hippocampus, a brain region prone to epilepsy due to its circuitry involving a high concentration of excitatory connections, and more superficial electrodes to continuously measure cortical neuronal activity. This continuous electrographic monitoring following injury will enable analysis of neuronal activity before spontaneous recurrent seizures begin, during seizures, and between seizures. In addition, the group is investigating changes in neuronal circuitry and the utility of previously known TBI blood biomarkers. With the abundance of data being collected, Dr. Wolf and his team hope to uncover novel circuitry alterations, electrophysiological markers, and blood biomarkers that will lead to a much deeper understanding of the fundamental mechanisms of epileptogenesis and thus will likely form the basis for future preclinical treatment development and clinical investigations in patients with PTE.

[4] Lucke-Wold BP, Nguyen L, Turner RC, et al. 2015. Traumatic Brain Injury and Epilepsy: Underlying Mechanisms Leading to Seizure. *Seizure* 33:13-23.

Deconstruction and Control of Neural Circuits in Post-Traumatic Epilepsy

Jeanne Paz, Ph.D., Gladstone Institute of Neurological Disease

After TBI, there is a latent period between the injury and the onset of spontaneous seizures in PTE. Although no one knows what leads to development of PTE, during the latent period, the brain is thought to undergo a number of changes that predispose it to epilepsy, a process known as epileptogenesis. Dr. Jeanne Paz received an ERP FY15 IDA to study specific neural circuits that may be most vulnerable to changes that lead to PTE. She seeks to understand where and when epileptogenesis takes place, in the hope that this knowledge will lead to new therapeutic approaches. Her work so far has pinpointed hot spots of inflammation and neural network hyperexcitability located in the cortex around the site of the injury and in the part of the brain that senses touch and pressure called the "somatosensory thalamus." Dr. Paz's team has discovered that those hot spots form before the onset of PTE and persist during PTE. They have also shown that C1q, an immune molecule involved in regulating synaptic connectivity, is an important marker of these hot spots, and that blocking C1q can prevent chronic inflammation after TBI. The group is now testing whether blocking the C1q pathway after TBI can prevent PTE. If successful, new interventional strategies could be designed that harmonize immune-neuronal interactions after TBI to prevent PTE.

"The Epilepsy Research Program is comprised of a passionate, highly committed collection of scientific researchers, clinical professionals, and those whose daily lives are affected by post-traumatic epilepsy. A gunshot wound to the head while serving in Iraq sowed the seeds of post-traumatic epilepsy in my husband, which we still live with today. The ERP honors my husband's service and sacrifice by its mission; to better understand how trauma transforms the brain and disturbs cognitive function. This program is tasked to find and eliminate mechanisms that start the epileptogenic process, which means a better chance for survival, rehabilitation, and quality of life for the next generations of Veterans. DoD's funding for epilepsy research allows my husband's sacrifice to continue to improve the lives of everyday citizens and fulfills this country's promise; to care for those wounded while protecting our freedoms."

Patricia Horan
CURE | Citizens United for Research in Epilepsy

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