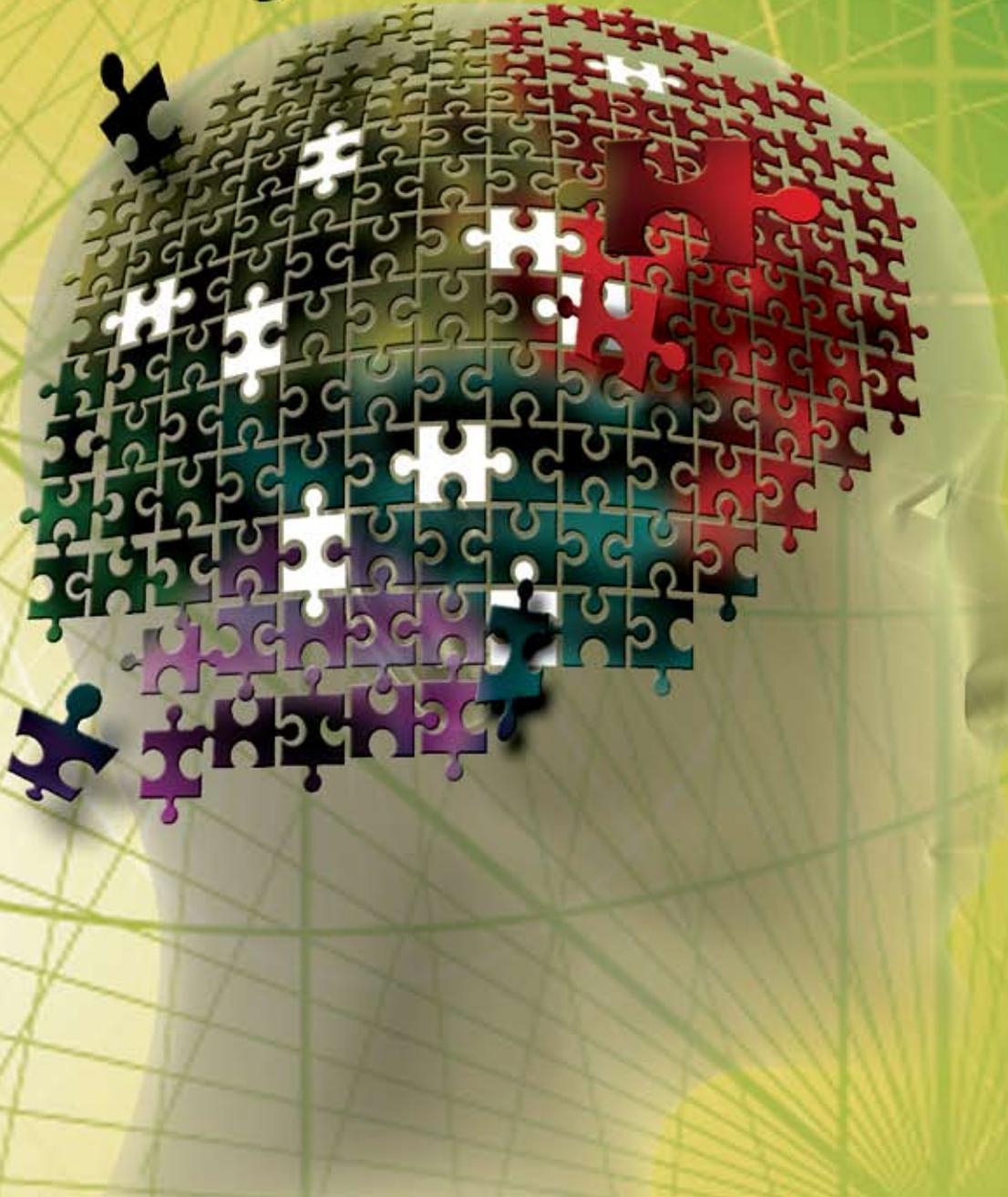


# X. Psychological Health and Traumatic Brain Injury Research Program





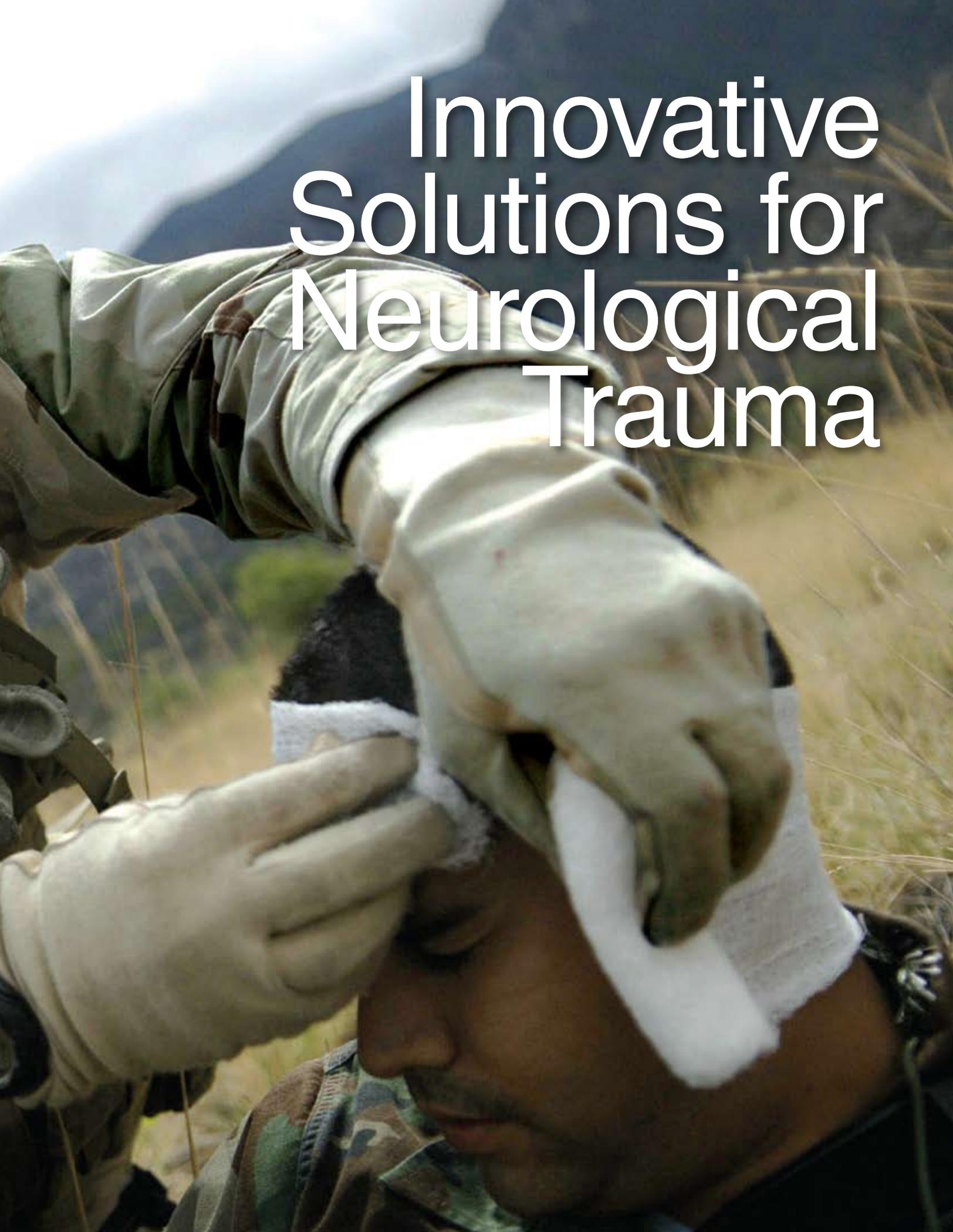
“Recent research on U.S. service members returning from Iraq and Afghanistan highlights the significant risk of military deployment on the psychological health of these combat veterans. The development and evaluation of evidence-based interventions for the prevention and treatment of combat-related PTSD [post-traumatic stress disorder] in our active-duty military and recently discharged veterans is of significant national importance. The STRONG STAR Multidisciplinary PTSD Research Consortium will leverage the combined expertise of civilian, military, and Veterans Affairs clinicians and researchers to make major scientific advances in the prevention and treatment of combat-related PTSD.”

**Dr. Alan Peterson**

**University of Texas Health Science Center at San Antonio**



# Innovative Solutions for Neurological Trauma

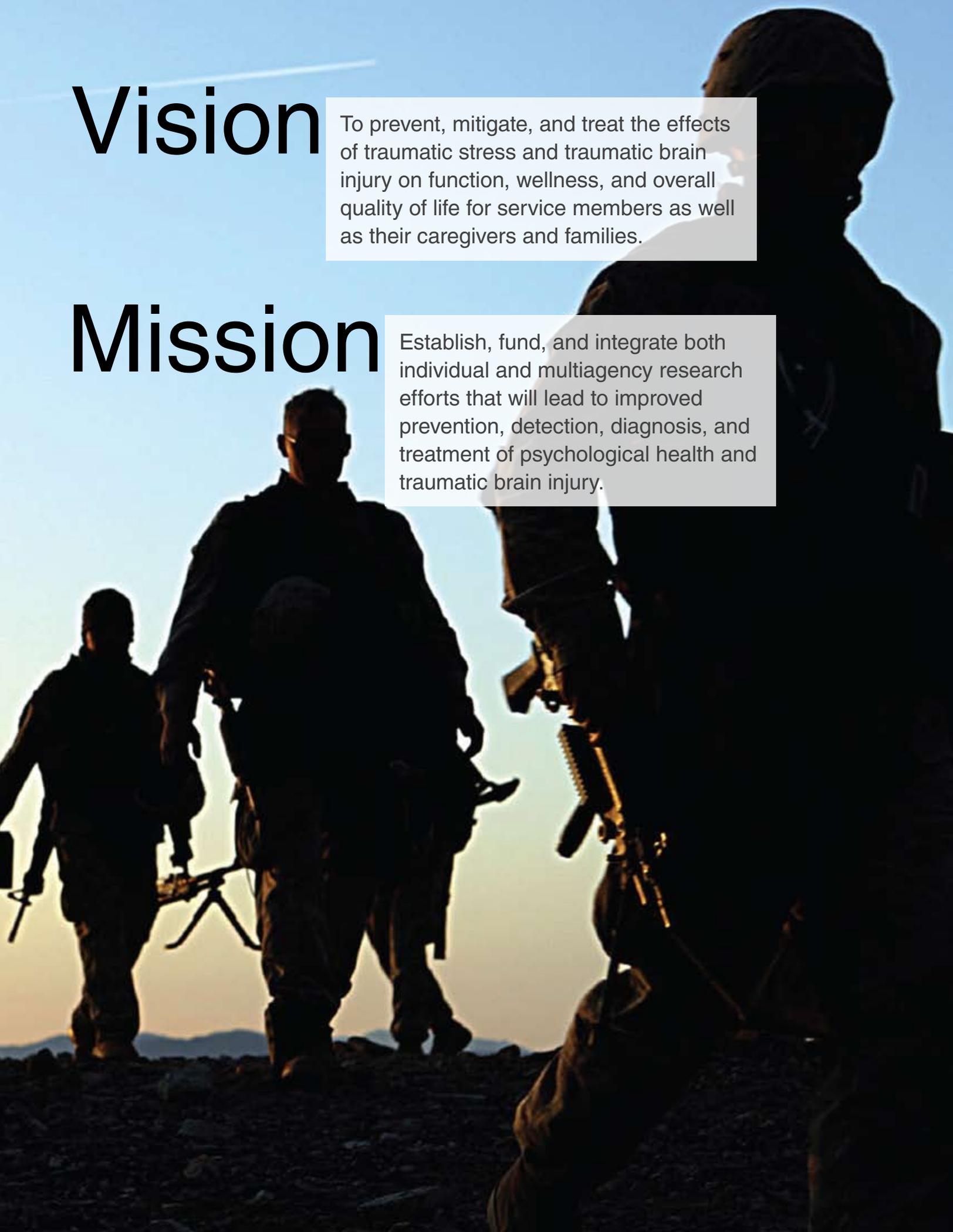


# Vision

To prevent, mitigate, and treat the effects of traumatic stress and traumatic brain injury on function, wellness, and overall quality of life for service members as well as their caregivers and families.

# Mission

Establish, fund, and integrate both individual and multiagency research efforts that will lead to improved prevention, detection, diagnosis, and treatment of psychological health and traumatic brain injury.



# Program Background

The Congressionally Directed Medical Research Programs (CDMRP) began managing the Department of Defense (DOD) Psychological Health and Traumatic Brain Injury (PH/TBI) Research Program, formerly called Post-Traumatic Stress Disorder (PTSD) and TBI Research Programs, in response to the U.S. Troop Readiness, Veterans’ Care, Katrina Recovery, and Iraq Accountability Appropriations Act, Public Law 110-28, which provided \$150 million (M) for research on PTSD and \$150M for research on TBI. An additional \$1M was provided for research on PTSD in Public Law 109-289. Of the \$301M, \$45M was assigned to the Defense Centers of Excellence (DCoE) for Psychological Health and Traumatic Brain Injury (information about the DCoE can be found at <http://www.dcoe.health.mil>). This \$301M congressional special interest funding was aimed at promoting a better standard of care for PTSD and TBI in the areas of prevention, detection, diagnosis, treatment, and rehabilitation. The program provides research to benefit service members and their family members, veterans, and other beneficiaries of the Military Health System.

A stakeholders meeting was held in June 2007 where more than 100 expert scientists and clinicians from academia, industry, and the military assembled to assess the state of science for the purposes of identifying gaps in the fields of PTSD and TBI research. A vision-setting meeting was conducted by a Joint Program Integration Panel (JPIP) to prioritize the research gaps identified by the stakeholders (Tables X-1a and X-1b), establish program goals and objectives, and recommend an investment strategy (Table X-2).

Table X-1a. PTSD Research Gaps

PTSD Research Gaps
Treatment and Intervention
Prevention
Measures in Screening Detection and Diagnosis
Epidemiological Studies
Families/Caregivers
Neurobiology/Genetics

Table X-1b. TBI Research Gaps

TBI Research Gaps
Treatment and Clinical Management
Neuroprotection and Repair Strategy
Rehabilitation/Reintegration Strategies
Field Epidemiology of TBI (with emphasis on mild TBI [mTBI])
Physics of Blast as It Relates to Brain Injury

Table X-2. Investment Strategy

Funding Mechanisms	Allocation
<b>Fast-Track Intramural</b>	<b>\$74M</b>
Advanced Technology - Therapeutic Development	
Investigator-Initiated Research	
<b>Extramural</b>	<b>\$150M</b>
Investigator-Initiated Research	\$10M
New Investigator	\$6M
Concept	\$8M
PTSD/TBI Clinical Consortium (Coordinating Center and Study Sites)	\$60M
Advanced Technology – Therapeutic Development	\$16M
Multidisciplinary Research Consortia	\$50M
<b>DCoE</b>	<b>\$45M</b>
<b>Total</b>	<b>\$269M</b>

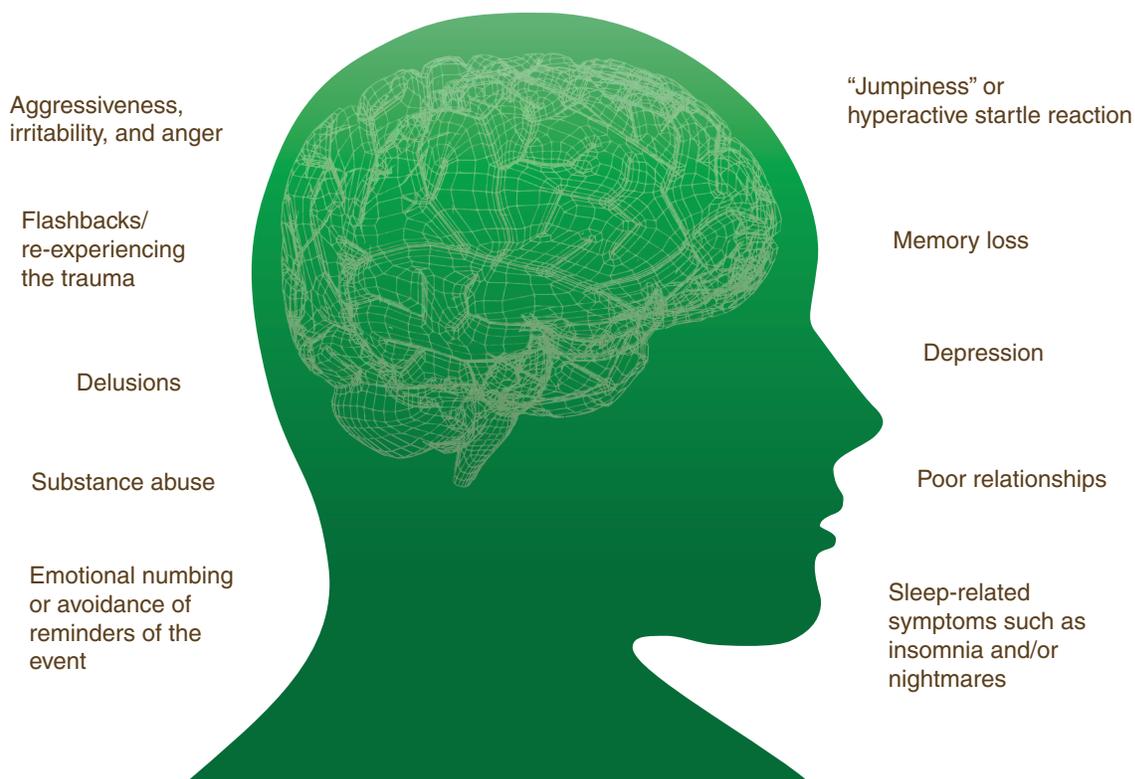
# The Diseases

## Post-Traumatic Stress Disorder

Military personnel are often subject to traumatic and life-threatening events. While many survivors of a traumatic event return to normal over time, some develop psychological symptoms that impair their daily functioning. PTSD is a major military health concern marked by distinct neurobiological and physiological changes. Statistics indicate that as many as 17 percent of military personnel returning from Iraq and 11 percent of military personnel returning from Afghanistan suffer from PTSD.<sup>1</sup> Thus, this is a major national health care concern. Through research, scientists and physicians are addressing the health and well-being of our service members, veterans, and their family members and striving to develop new treatments and ways to deal with this insidious vestige of combat.

## Signs and Symptoms

PTSD symptoms typically manifest within 3 months after a traumatic event although in rare instances symptoms can develop years later. Some indicators of PTSD may include the following:



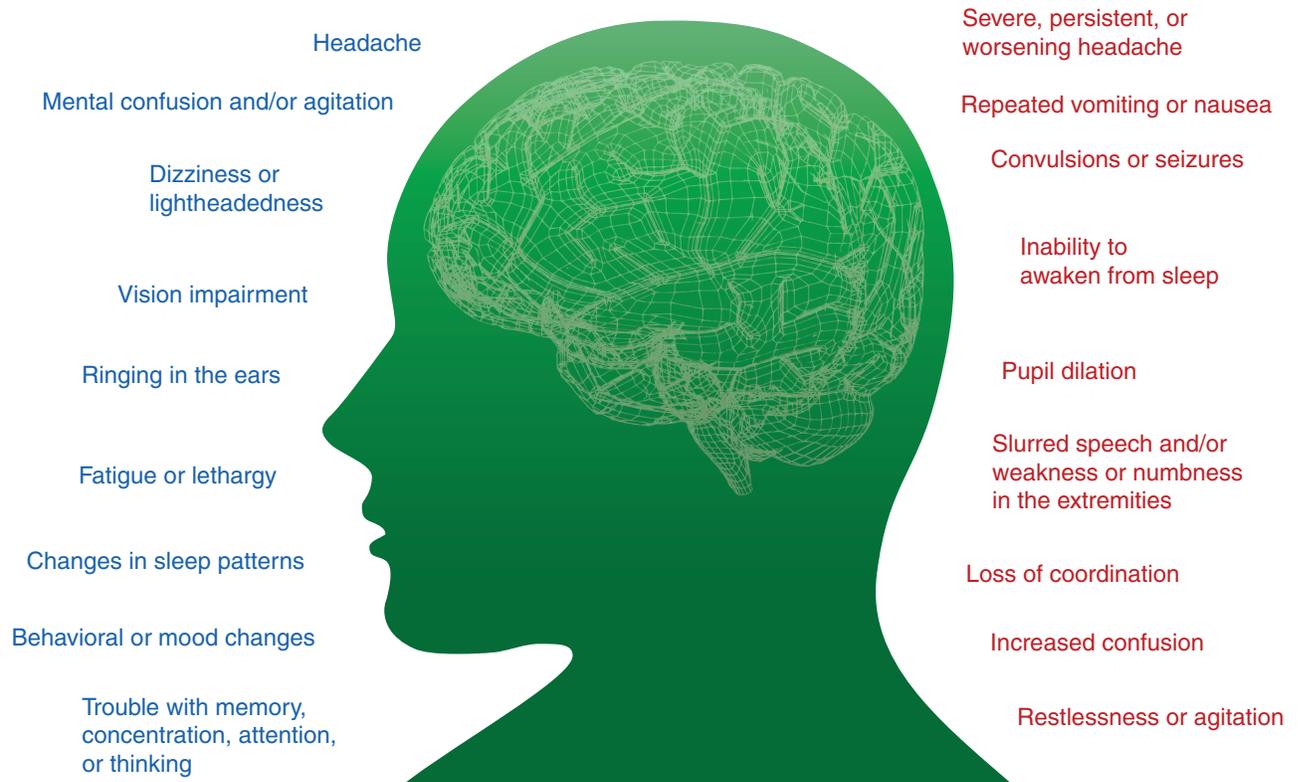
<sup>1</sup> Hoge CW, Castro CH, Messer SC, et al. 2004. Combat Duty in Iraq and Afghanistan, Mental Health Problems, and Barriers to Care. *New England Journal of Medicine* 351(1):13-22.

# Traumatic Brain Injury

Soldiers are subjected to a wide range of potentially injurious hazards, including falls, penetrating and nonpenetrating projectile impacts, and exploding shells or bombs. TBI is typically classified as resulting from a penetrating head injury, a closed head injury, or a blast head injury. Of note, TBI is often linked to psychological health (PH) issues. Because it accounts for a large proportion of casualties, TBI has been called the “signature injury of the Iraq War.” Statistics indicate that the incidence of TBI among wounded military personnel is approximately 20 percent. TBI can have a profoundly negative impact on productivity and quality of life and result in long-term disability. Identification of TBI is challenging because the condition does not always present the same, especially in the case of an mTBI.

## Signs and Symptoms

TBI severity is classified as mild, moderate, or severe, depending on the duration of loss of consciousness, period of post-traumatic amnesia, and Glasgow Coma Scale score. A person with mTBI may remain conscious or may experience a loss of consciousness for less than 1 hour while a person with moderate or severe TBI typically loses consciousness for up to or longer than 24 hours, respectively. Individuals with moderate or severe TBI may show the same symptoms as someone with mTBI but may also experience additional symptoms. Some specific indicators of mTBI are shown in blue. Some specific indicators of moderate or severe TBI are shown in red.



# Partnering for Success

The PH/TBI Research Program recognizes the contributions of many individuals whose commitment and innovative approaches to research have made a large impact in the fields of PH and TBI. Partners of the PH/TBI Research Program include Congress, DOD, Department of Veterans Affairs (VA), Department of Health and Human Services, peer review panel members, consumer advocates, and the scientific community, all of which joined efforts to address the needs of those with PH and TBI challenges.

## Peer Review Panel Members

The peer review panels for the PH/TBI Research Program were composed of esteemed scientists, clinicians, and consumers (those individuals and family members suffering from PH and/or TBI) who provided unbiased, expert advice on the scientific and technical merit of the proposals. The consumers provided broad perspectives on issues critical to addressing PH and TBI among warfighters. More than 275 scientists, clinicians, and consumers participated in the peer review process for the PH/TBI Research Program. For additional details about peer review, refer to Section I, Overview.

## Scientific Community

The scientific community is an integral part of the PH/TBI Research Program. Scientists and clinicians provided their expertise in setting the program's vision and reviewing proposals, and funded researchers are now conducting the necessary laboratory and clinical studies to tackle the complex challenges associated with PH and TBI.

“Being a part of this was a huge honor. I had the opportunity to see and speak with so many great minds—all of whom had come together with one common goal, to support the Soldiers who had been injured as they fought for their country. I am grateful to have had this opportunity.”

**Richard Flores**

**FY07 Psychological Health Consumer Peer Review Panel Member**



“What an experience! Panel members treated me with respect. They listened to my expressions of consumer views about proposed research and priorities. They treated me as a colleague. All this while I participated in a dialogue that seemed equivalent to an up-to-date progress report on present TBI knowledge and research direction. Panel members discussed proposal merits and limitations in a way that expanded my view and appreciation for what we know about TBI and the value of research discovery in improving quality of life. Participation in a peer review panel as a consumer representative was a rewarding and fulfilling experience. If given a chance to participate, take it!”

**Ken Rich**

**FY07 Traumatic Brain Injury Consumer Peer Review Panel Member**



“Astute and unbiased peer review is critical to the success of any program designed to support high-quality scientific research. The CDMRP continues to work assiduously to evaluate and improve their peer review process. It is a challenge and a privilege to participate in the peer review process for the Psychological Health/Traumatic Brain Injury program of the CDMRP.”

**Douglas Dewitt, M.D.**  
The University of Texas  
Medical Branch



“I was proud to participate as a reviewer for the CDMRP FY07 Psychological Health/Traumatic Brain Injury program. The dedication, efficiency, and professionalism of the CDMRP staff were impressive. The quality of applications was excellent and I am confident that outstanding work will be performed because of this important program.”

**Neil Grunberg, M.D.**  
Uniformed Services University of  
the Health Sciences



## JPIP Members

Distinguished members of the four military services, the Office of the Assistant Secretary of Defense (Health Affairs), Uniformed Services University of the Health Sciences, VA, and National Institutes of the Health comprised the program's first JPIP. The JPIP provided programmatic and strategic direction for the PH/TBI Research Program and served as a recommending body to the final approval authority, the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness.

### **Karl Friedl, Ph.D.**

(JPIP Chair)  
Colonel, U.S. Army  
U.S. Army Medical Research and Materiel Command

### **Michael Leggieri, M.S.**

(JPIP Alternate Chair)  
U.S. Army Medical Research and Materiel Command

### **Loree Sutton, M.D.**

Brigadier General, U.S. Army  
(DCoE Director)  
DCoE for PH and TBI

### **Russell Shilling, Ph.D.**

Commander, U.S. Navy  
(Alternate to DCoE Director)  
DCoE for PH and TBI

### **Bruce Barnes, B.S.**

U.S. Marine Corps

### **James Bloom, M.D.**

Captain, U.S. Navy

### **Tony Carter, M.D.**

Colonel, U.S. Army  
Office of the Assistant Secretary of Defense for Health Affairs

### **Salvatore Cirone, D.V.M., M.P.V.M.**

Office of the Assistant Secretary of Defense for Health Affairs

### **Mary Erickson, M.A.O.L., B.S.O.T.**

Colonel, U.S. Army  
Office of the Surgeon General

### **Douglas Forcino, Ph.D.**

Captain, U.S. Navy  
Office of Naval Research

### **Joseph Francis, M.D., M.P.H.**

Department of Veterans Affairs

### **Robert Ireland, M.D.**

Colonel, U.S. Air Force  
Office of the Assistant Secretary of Defense for Health Affairs

### **Chuck Isler, Ph.D.**

Major, U.S. Air Force

### **Michael Jaffee, M.D.**

Colonel, U.S. Air Force

### **Jonathan Jaffin, M.D.**

Colonel, U.S. Army  
U.S. Army Medical Research and Materiel Command

### **Steve Kaminsky, Ph.D.**

Uniform Services University of the Health Sciences

### **Robert Koffman, M.D., M.P.H.**

Captain, U.S. Navy

### **Walter Koroshetz, M.D.**

U.S. Department of Health and Human Services

### **Bart Kuhn**

Office of the Deputy Undersecretary of Defense for Science and Technology

### **Debra Malone, M.D.**

Lieutenant Colonel, U.S. Air Force  
U.S. Air Force Division of Science and Technology

### **Rodger Martin**

Colonel, U.S. Army  
U.S. Army Medical Research and Materiel Command

### **Garrett Polhamus, Ph.D.**

Air Force Research Laboratory

### **Keith Prusaczyk, Ph.D.**

Naval Medical Research Center

### **Elsbeth Ritchie, M.D., M.P.H.**

Colonel, U.S. Army  
Office of the Surgeon General

### **William Tanner, M.D.**

Commander, U.S. Marine Corps

### **James Wargo, Ph.D., P.E.**

Joint Improvised Explosive Device Defeat Organization

# Innovative Solutions...

## Through Collaborative Multi-Institutional and Multidisciplinary Approaches



### The Post-Traumatic Stress Disorder/Traumatic Brain Injury Clinical Consortium

Murray Stein, M.D.

University of California, San Diego

The overarching goal of establishing the PTSD/TBI Clinical Consortium is to combine the efforts of the nation's leading investigators to bring to market novel treatments or interventions that will ultimately decrease the impact of militarily relevant PTSD and TBI and improve the function, wellness, and overall quality of life for service members, as well as their families and caregivers and the American public. Dr. Murray Stein will lead the consortium, which comprises a Coordinating Center at the University

of California, San Diego and 10 clinical sites, each of which will participate in clinical trials in PTSD and/or TBI. The PIs of the 10 sites recommended for funding are Dr. Howard Eisenberg (University of Maryland), Dr. David Benedek (Henry M. Jackson Foundation/USUHS), Dr. Ross Zafonte (Spaulding Rehabilitation Hospital), Dr. Thomas McAllister (Dartmouth College), Dr. Nancy Temkin (University of Washington), Dr. Raj Narayan (University of Cincinnati), Dr. Gerald Grant (Duke University), Dr. Raul Coimbra (University of California, San Diego), Dr. Mark George (South Carolina Research Authority/Medical University of South Carolina), and Dr. Gregory Gahm (Geneva Foundation/Madigan Army Medical Center).

“The Clinical Consortium is focused on finding and validating new treatments for military personnel and civilians who suffer from the neurological, psychological, and cognitive after-effects of traumatic stress and injury. We recognize that existing treatments for these conditions—which include PTSD and mTBI—are inadequate, and it is our mission to bring novel and better treatments to the patients who need them.”

“We will be bringing together psychologists, psychiatrists, neurologists, neurosurgeons and trauma surgeons, and rehabilitation specialists to design and conduct studies that help us answer questions about what really happens with people who suffer mild head injuries such as concussions.”

“This will help us better understand how we should be following up and providing appropriate care. Moreover, both PTSD and TBI frequently occur in the same patient after an injury. The Clinical Consortium will be devoting special efforts to understand and develop treatments for the overlap between these two conditions.”

**Murray Stein, M.D.**  
University of California, San Diego



### The Psychological Health Multidisciplinary Research Consortium

#### The STRONG STAR Multidisciplinary Consortium

Alan Peterson, Ph.D.

University of Texas Health Science Center at San Antonio

The Psychological Health Multidisciplinary Research Consortium, called STRONG STAR (South Texas Research Organizational Network Guiding Studies on Trauma and Resilience), is dedicated to the development and evaluation of the most effective early interventions for the detection, prevention, and treatment of combat-related PTSD in active-duty military and recently discharged veterans. The STRONG STAR consortium will evaluate the impact of comorbid conditions (burns, chronic pain, alcohol abuse, amputation, traumatic brain injury, and insomnia) on the etiology, prevention, and treatment of PTSD. Epidemiology, neurobiology, imaging, and genomics studies will be conducted to better understand PTSD risk, resilience, and prevention and to stimulate novel approaches to treatment development, selection, and response. In addition, the consortium will train multidisciplinary scientists to pursue careers devoted to the detection, prevention, and treatment of combat-related PTSD. The STRONG STAR team is being led under the direction of Dr. Alan Peterson and includes nine partnering PIs: Dr. Edna Foa (University of Pennsylvania School of Medicine), Dr. Patricia Resick (National Center for PTSD/VA Boston Healthcare System), Dr. Robert Gatchel (University of Texas at Arlington), Dr. John Roache (University of Texas Health Science Center at San Antonio), Dr. David Riggs (USUHS), Dr. Randy Strong (University of Texas Health Science Center at San Antonio), Dr. Brett Litz (National Center for PTSD/VA Boston Healthcare System), Dr. Peter Fox (University of Texas Health Science Center at San Antonio), and Dr. Michael Escamilla (University of Texas Health Science Center at San Antonio). A team of 85 leading investigators will take a multidisciplinary approach to developing and evaluating effective early interventions for the treatment of PTSD in active-duty and recently discharged veterans of Operation Iraqi Freedom and Operation Enduring Freedom.



### The Traumatic Brain Injury Multidisciplinary Research Consortium

#### Mission Connect Mild TBI Translational Research Consortium

Alex Valadka, M.D.

University of Texas Health Science Center at Houston

The TBI Multidisciplinary Research Consortium is composed of premier TBI investigators from four academic institutions and from all of the major trauma facilities in the Houston-Galveston area, all operating within an existing cooperative framework, The Mission Connect Mild TBI Translational Research Consortium. The goal of the joint efforts between these clinical and basic scientists is to reduce the number and severity of disabilities caused by mTBI by focusing on improving the diagnosis and treatment of mTBI. Specifically, the consortium will focus on standardization of animal models of mTBI using clinically relevant neurobehavioral end points, improvement of the diagnosis of acute and chronic mTBI, and development of new and innovative treatment strategies for mTBI, to include providing the preclinical and Phase I and II testing of treatments that have been found to improve outcomes. These innovative studies have the potential to lead to immediate improvements in the diagnosis and treatment of mTBI. The consortium's lead PIs are Dr. Alex Valadka, University of Texas Health Science Center at Houston; Dr. Jose Perez-Polo and Dr. Ping Wu, University of Texas Medical Branch at Galveston; Dr. Brent Masel, Transitional Learning Center at Galveston; Dr. Pramond Dash, Dr. Raymond Grill, Dr. Ponnada Narayana, Dr. Andrew Papanicolaou, and Dr. Paul Swank, The University of Texas Medical School; Dr. James Tour, Rice University's Smalley Institute for Nanoscale Science and Technology; and Dr. Michael Friedlander, Dr. Thomas Kent, Dr. Stephen LaConte, Dr. Harvey Levin, Dr. Eli Mizrahi, Dr. Matthew Rasband, Dr. Claudia Robertson, Dr. Stelios Smirnakis, Dr. Andreas Toliias, and Dr. Kimberly Toliias, Baylor College of Medicine.

# Innovative Solutions Across the Spectrum of Prevention, Detection, Diagnosis, and Treatment of PH and TBI

## Addressing the Needs of Children and Families of Combat Injured

Stephen Cozza, M.D.

Uniformed Services University of the Health Sciences

More than 27,000 Soldiers, Sailors, Marines, and Airmen have been injured in the Iraq war. Many of these injured service members have families that may be dramatically affected by longer term injury adjustment challenges.

The proposed study aims to (1) identify the immediate impact of parental combat injury on children and families; (2) assess the progressive impact of injury on child, parent, and family function; and (3) determine the appropriateness of developing intervention strategies for this population. Urgency exists to better understand the impact of parental combat injury on children and families. Further scientific effort in this area will benefit not only the military population but also the extremely large number of U.S. children whose parents sustain serious traumatic injury.

## Telemental Health and Cognitive Processing Therapy for Rural Combat Veterans with PTSD

Leslie Morland, Psy.D.

Pacific Islands VA Health Care System

Treatment of combat-related PTSD among military troops returning from Iraq/Afghanistan and residing in rural and remote areas presents a significant challenge. A potential solution to the problem of accessing care in remote areas can be telemental health technologies such as video-conferencing (VTC).

The proposed project is the first prospective, randomized clinical trial designed to evaluate the clinical effectiveness of delivering evidence-based cognitive behavioral group intervention specifically treating PTSD via VTC. This project will (1) train PTSD clinicians on the use of the VTC modality and the standardized Cognitive Processing Therapy (CPT) protocol, (2) conduct assessments at multiple study intervals to determine maintenance of treatment effects, and (3) test the effectiveness of a novel mode of mental health service delivery (VTC) versus a traditional mode (in-person) for providing specialized mental health intervention (CPT) to combat veterans with PTSD.



### Dissemination of Evidence-Based Cognitive Behavioral Therapy Intervention Components: Online, Self-Administered Training for Providers Treating Military Deployment-Related PTSD

Joseph Ruzek, Ph.D.

Palo Alto Institute for Research and Education

A systematic, cost-effective training program is needed to teach mental health providers how to deliver short-term, efficacious, evidence-based treatments for significantly increasing numbers of military personnel who suffer from PTSD and other problems associated with exposure to military deployment-related trauma.

The proposed study will (1) create web-ready text for core components of PTSD-related Cognitive Behavioral Therapy, (2) translate text into an innovative web methodology, (3) implement a telephone and web-based supervision/consultation to ensure that skills are implemented competently in routine clinical care, (4) develop a cost-effective, feasible methodology for measuring training impact, and (5) conduct a rigorous randomized control trial on the effectiveness of these training dissemination methods.



### Deployment, PTSD Symptoms, and Comorbid Mental Health Conditions in the Active Force and Reserve Components

Laurel Hourani, Ph.D.

Research Triangle Institute

The goal of this research is to develop models of PTSD risk from a wide array of deployment, stress, trauma, and mental health factors. Specifically, this study will (1) identify the underlying structure of PTSD co-occurring with mental and substance-use disorders among active-duty and reserve-component military personnel using latent class analysis and (2) examine variation in the

underlying structure across subgroups defined by military and individual characteristics using logistic regression models. Findings should advance our understanding of the prevalence of disorders co-occurring with PTSD and how individual and military factors may influence the risk of both PTSD and co-occurring mental and substance-use disorders.



### Cognitive Behavioral Social Rhythm Therapy for Sleep and Mood Disturbances in Veterans with PTSD

Patricia Haynes, M.D.

University of Arizona, Tucson

Depression and sleep problems are highly prevalent in PTSD. Unfortunately, veterans who suffer from these additional disorders have much worse outcomes than veterans with PTSD alone. The purpose of this study is to test the efficacy of Cognitive Behavioral Social Rhythm Therapy (CBSRT) in male veterans and active-duty personnel who have PTSD, major depressive disorder (MDD), and sleep or scheduling problems. Specifically, the study aims to (1) test whether group CBSRT is superior to an active control condition (Present-Centered Therapy [PCT]) in improving depression symptoms from baseline to the end of treatment and 6 months post-treatment in patients with PTSD, MDD, and sleep or social rhythm disturbances; (2) test whether group CBSRT is superior to PCT in improving sleep; (3) test whether CBSRT is superior to PCT in improving PTSD symptoms; and (4) gather preliminary data testing CBSRT in men returning from military operations in Iraq or Afghanistan.

Regardless of outcomes, this project will provide important data that will increase the ability of VA clinicians to effectively treat veterans afflicted with these disturbances.



### Stable Intravenous Fluorohydrocarbon Emulsion with High Oxygen Capacitance Combined with Hyperbaric Oxygen for the Acute Salvage of Tissue Injury After TBI

John R. Sims, M.D.

Massachusetts General Hospital, Boston, Massachusetts

Oxygen delivery is critically impaired in severe traumatic brain injury (TBI) and is the primary cause of secondary injury. Thus, an easy-to-carry, safe, and stable “blood substitute” with high oxygen-carrying capacity is needed for the battlefield. Such compounds have been developed. An example is Perfluorooctyl bromide (PFOB), a substance that carries 20 times more oxygen than blood, but its ability to bring oxygen to the brain is limited by how much oxygen is present in the environment. On the other hand, oxygen provided under high pressures (hyperbaric oxygen therapy [HBOT]) can deliver more oxygen than breathing even 100 percent oxygen at sea level. However, since oxygen does not dissolve well in the fluid of the blood, this therapy has limited impact on increased oxygen delivery to the brain. The goal of this study is to test a combination of intravenous PFOB with HBOT in the setting of TBI and a polytrauma hemorrhage model. Specifically, this study will (1) determine the greatest delay (time) from TBI to onset of treatment that maintains both tissue sparing and functional improvement effects, (2) determine the minimal dose of PFOB at 60 minutes after TBI that maintains both tissue sparing and functional improvement effects, (3) determine the lowest partial pressure of oxygen at the highest effective dose of PFOB at 60 minutes that maintains both tissue sparing and functional improvement effects, and (4) determine the efficacy of PFOB and HBOT for tissue sparing and functional improvement in TBI combined with hemorrhage.



### Sensors to Assess Pressure-Mediated Effects on Blast-Induced TBI

Mikulas Chavko, Ph.D.

Naval Health Research Center

The detonation of any powerful explosive generates a blast wave, which is a sudden and extreme difference in pressure that leads to significant neurological injury with unknown mechanisms.

This study aims to (1) implant, fix, and test sensors in rats; (2) measure blast energy transmission into the rats’ brains; and (3) perform neurohistopathology studies that will allow correlation of the degree of neuronal disruption with the intensity level of brain pressure.

### The Effects of Hypoxia on Cognitive Function in Aviators and Complex System Operators Who Have Had mTBI

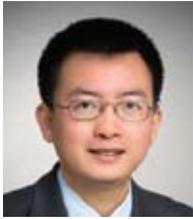
Leonard Temme, Ph.D.

U.S. Army Aeromedical Research Laboratory

Preliminary observations suggest that individuals with mTBIs, which is usually asymptomatic, may experience functional deficits only under stressful physiological condition.

The hypothesis that mild to moderate hypoxia reversibly uncovers neurological deficits in individuals who have experienced mTBI will be tested by evaluating a group of asymptomatic patients who have a history of mTBI and a matched control group of individuals with no history of mTBI under stressful conditions. Outcome measures will include reflex eye movements, a neurocognitive battery, and standardized self-report of altitude-related symptoms.

If hypoxia does uncover deficits in patients with a history of mTBI, important follow-up studies should be conducted to answer questions concerning the impact of other physiological stressors (e.g., sleep deprivation, fatigue, drug use, and alcohol consumption).



### Brain Tissue Regeneration After Traumatic Brain Injury

Ning Zhang, Ph.D.  
Clemson University

Despite tremendous effort in neuroprotection and in managing tissue damage and inflammation following TBI, current therapies have led to clinical failure in improving the mortality and neurological outcome, largely due to the inability of these treatments to revascularize and repopulate the lesion with functional neural cells.

The objective of this project is to revascularize and repopulate the TBI lesion cavity with functional neural cells for sustained structural and functional recovery. Specifically, this study aims to (1) pre-engineer the lesion cavity with vasculature network, (2) mobilize endogenous neural stem cells (NSCs) from their natural reservoir in the brain subventricular zone and site-specific recruitment to the vasculature network, and (3) perform in situ differentiation induction of the recruited NSCs into functional neural cells.

The overall hypothesis of this study is that a combined strategy based on localized, site-specific delivery of signaling growth factors for the mobilization, site-specific recruitment, and functional differentiation of endogenous NSCs in the brain to the TBI lesion that is pre-engineered with a vasculature network would promote neural repopulation of the lesion cavity, leading to significant improvement in neurological outcome in TBI.



### Advanced MRI in Blast-Related TBI

David Brody, M.D., Ph.D.  
Washington University

TBI and its effects on brain functional connectivity are very difficult to directly detect and quantify in living patients using conventional magnetic resonance imaging (MRI) and computed tomography.

However, new advances in MRI technology, such as diffusion tensor imaging (DTI) for detecting axonal injury and resting-state functional MRI for investigating brain functional connectivity, may help to overcome these challenges.

The objective of this proposal is to test these two advanced MRI methods, DTI and resting-state functional MRI, in active-duty, military blast-related TBI patients immediately after injury and correlate findings with TBI-related clinical outcomes 6–12 months later. Specifically, this prospective observational study intends to (1) assess the extent of acute blast TBI-related abnormalities that are not apparent on conventional MRI scans using DTI and resting-state functional MRI, (2) determine specific patterns of imaging abnormalities that predict specific TBI-related clinical outcomes, and (3) develop acute imaging predictors of overall 6- to 12-month clinical outcomes.

The proposed project, if successful, will have a major impact on the care of TBI patients, their families and caregivers, and the American public.

### A Multifunctional Blood Substitute for Field Resuscitation of Polytrauma Combat Casualties with Brain Injury and Concomitant Hemorrhagic Shock

Daniel Freilich, M.D.  
Naval Medical Research Center

TBI and hemorrhagic shock can result from multiple injuries and are the most common causes of trauma death, with the most deaths occurring prior to hospital arrival as a result of limited pre-hospital treatment.

The clinical objectives of this study are to develop a multifunctional blood substitute containing a vasoactivity-attenuated hemoglobin-based oxygen carrier that improves cerebral perfusion pressure, brain oxygenation, and survival in polytrauma casualties with TBI and hemorrhagic shock by extending in-hospital capabilities to pre-hospital situations.

## Additional PTSD and TBI Projects

In addition to the FY07 PH/TBI Research Program investment, the CDMRP has funded PTSD and TBI research through the Peer Reviewed Medical Research Program. These projects are well aligned with the FY07 priorities identified by the FY07 PH/TBI Research Program stakeholders and include:

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A Phase III evaluation 30 years post-injury to examine delayed effects of head injury on health and nervous system function.

---

Evaluation of agents in the treatment and prevention of seizures following TBI.

---

Investigation of the use of propranolol following combat memory reactivation to weaken traumatic combat memories.

---

Determination of whether alterations of diurnal cortisol concentrations and specific risk genes can predict the development of PTSD.

---

Investigation into whether a new type of cellular therapy in an animal model can be used to promote protection and repair after TBI.

---

A controlled trial of citalopram for anxiety disorders following TBI in Soldiers returning from combat.

---

A controlled trial using fluoxetine as an early intervention for PTSD and comorbid symptoms in recently redeployed Soldiers.

---

Identifying biochemical markers in cerebrospinal fluid, blood, and/or urine that are capable of accurately characterizing penetrating ballistic brain injury in a preclinical rodent model.

---

Evaluation of an Internet-based, nurse-assisted, cognitive behavioral self-management program for individuals with PTSD related to Operation Iraqi Freedom or Operation Enduring Freedom.

---

Identification of the longitudinal risk and resilience factors that may predict psychiatric disruption, mental health service utilization, and military retention in Operation Iraqi Freedom National Guard troops.

---

Evaluation of an evidence-based cognitive behavioral anger intervention for the secondary prevention of PTSD-related anger problems.

---

Evaluation of prazosin for combat-stress-related nightmares, sleep disturbance, and overall function in combat-exposed returnees from Operation Iraqi Freedom and Operation Enduring Freedom.

---

Evaluation of prazosin and an evidence-based behavioral sleep intervention for reducing PTSD-related sleep disturbances.

---

Evaluation of neuroendocrine factors before and after a cognitive behavioral intervention (prolonged exposure) to assess risk factors that increase the probability of developing PTSD following trauma.

---

Development and preclinical testing of novel resuscitation strategies of combined TBI and hemorrhagic shock.

## PH/TBI Research Program In the News

### Pentagon Spends \$300M to Study Troops' Stress, Trauma Unprecedented Sum Will Fund Research on Prevalent Injuries of Iraq, Afghanistan Wars

By Gregg Zoroya, USA TODAY, Aug. 5, 2008

The Pentagon is spending an unprecedented \$300 million this summer on research for post-traumatic stress disorder and traumatic brain injury, offering hope not only for troops but hundreds of thousands of civilians. The money—the most spent in one year on military medical research since a \$210 million breast cancer study in 1993—will fund 171 research projects on two of the most prevalent injuries of the Iraq and Afghanistan wars.

Gregory O'Shanick, national medical director for the Brain Injury Association of America, says the funding initiative is “without a doubt an all-time high” for spending by the government on posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI). He says civilian victims will benefit directly from the military studies.

“It is huge,” says Ross Bullock, director of neurotrauma at the University of Miami School of Medicine and lead investigator in a Pentagon-funded study of a drug designed to improve oxygen flow to damaged brain cells. “It is the just the most enormous thing that has happened in traumatic brain injury research.”

An estimated 1.4 million Americans suffer TBI each year, leaving 235,000 hospitalized and 50,000 dead, according to the Centers for Disease Control and Prevention. The majority are mild cases that can often lead to recovery. Many others suffer lasting damage to their short-term memory and problem solving abilities, researchers say.

The new research focuses considerable attention on mild TBI, says Navy Capt. E. Melissa Kaime, head of the Congressionally Directed Medical Research Programs office, which is distributing the funds. The studies should be completed in 18 months to five years, she says. Projects range from the development of an eyeglasses-like device that can detect brain injury through eye movement to coordinated studies of troops and veterans at locations across the country, Kaime says. The Pentagon also will target new ways of delivering therapy to PTSD victims living in remote areas of the USA and reducing the stigma that can keep victims from seeking help, she says. The military funding will go toward evaluating up to 20 different medications for TBI, she says, and studying ways of regenerating damaged brain cells.

Congress has provided an additional \$273.8 million this year to study battlefield injuries, some of which will also go toward researching PTSD and TBI.

A study released in April by the RAND Corp. think tank estimates 300,000 current or former combat troops have PTSD or depression, and up to 320,000 may have suffered a brain injury.

#### **DoD allocates \$25 million to study PTSD**

A randomized, controlled trial will test two behavioral treatments.

By Christopher Munsey, Monitor staff

#### **Smart Combat Helmet Is Goal of Researchers**

Technology - redOrbit - March 7, 2008

#### **Shell Shock Revisited: Solving the Puzzle of Blast Trauma.**

By Yudhijit Bhattacharjee; published by AAAS,  
from www.sciencemag.org - January 28, 2008

# The Program Today

## FY07 Summary

The fiscal year 2007 (FY07) PH/TBI Research Program received congressional appropriations of \$151M for research on PTSD and \$150M for research on TBI. Program Announcements for 4 intramural and 12 extramural award mechanisms recommended by the JPIP challenged the scientific community to design innovative research that would foster new directions, address identified research gaps, and bring new investigators into the fields of PTSD- and TBI-focused research. Additionally, DCoE solicited proposals focused on complementary and alternative medicine (CAM) and also received several PH/TBI-focused unsolicited proposals through a U.S. Army Medical Research and Materiel Command (USAMRMC) Broad Agency Announcement (BAA).

Because the CDMRP recognizes the need for personal scientific development, certain mechanisms allowed for multiple independent Principal Investigators (PIs) to submit a single proposal that, in collaboration, addressed a single project in PTSD and/or TBI. Although they were working collaboratively on a single project, each PI received a separate award (funds) that was in line with their contribution to the project.

Of the 2,110 proposals received across the award mechanisms, 1,826 represented individual projects aligned by gap area. All subsequent data reported represent proposals funded/received. Of the 2,110 proposals received, 201 were funded, as shown in Tables X-3–5. The FY07 investment portfolio for PH and TBI is illustrated in Figures X-1–4. The data are represented by gap areas (Figures X-1 and X-3) and clinical categories (Figures X-2 and X-4).

*Table X-3. PH/TBI Clinical Consortium Funding Summary*

Categories and Award Mechanisms	Proposals Received	Awards	Investment
<i>PH/TBI Clinical Consortium</i>			
Coordinating Center	12	1	\$60.0M
Study Site	32	0	\$0M
<b>TOTAL</b>	<b>44</b>	<b>1</b>	<b>\$60.0M</b>

Note: Ten Study Sites will be subawards under the Coordinating Center.

“Trauma is the number one killer of children and young adults in this country. It is the number one cause of loss of years of productive life.

Traumatic injuries to the brain explain most of the morbidity and mortality of trauma and account for the single largest share of the overall expense of trauma, adding up to many billions of dollars.

However, research funding for trauma as a function of its impact on society lags far behind that of other common diseases. Mission Connect was created over a decade ago to bring together investigators from different disciplines and institutions. The goal was to reverse the effects of central nervous system injury. The existing Mission Connect structure formed the perfect foundation to create the mild traumatic brain injury consortium. The goal of the consortium is to make discoveries that will ultimately allow intervention with the most effective early therapy before a mild traumatic brain injury results in a chronic problem. The consortium’s work is driven by the high prevalence of mild traumatic brain injury in soldiers, but the conclusions of the research also will benefit civilians who have suffered concussions.”

**Alex Valadka, M.D.**

**University of Texas Health Science Center at Houston**



Table X-4. PH Funding Summary

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Concept	245	33	\$7.09M
Intramural Advanced Technology – Therapeutic Development	14	4	\$15.75M
Intramural Investigator-Initiated Research	98	24	\$27.27M
New Investigator	119	10	\$4.19M
Investigator-Initiated Research	146	10	\$10.46M
Advanced Technology – Therapeutic Development	25	0	0
Multidisciplinary Research Consortium (MRC)	72	10	\$34.07M
CAM	53	8	\$3.95M
BAA	2	1	\$0.07M
<b>TOTAL</b>	<b>774</b>	<b>100</b>	<b>\$102.85M</b>

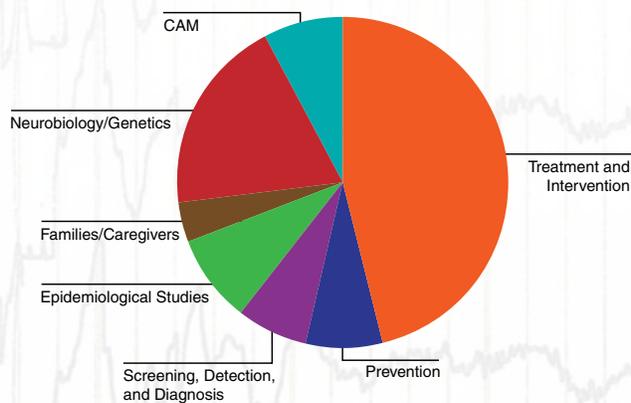


Figure X-1. PH Funded Projects by Gap Area

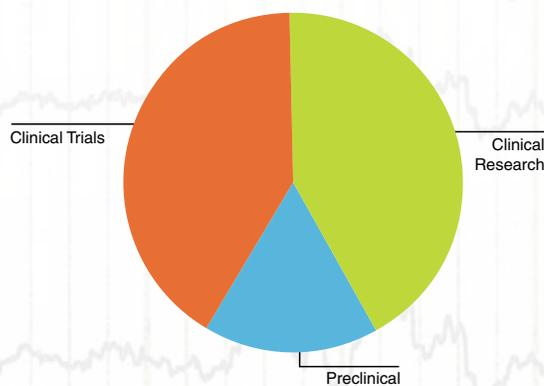


Figure X-2. PH Clinical Categories

Note: Clinical Consortium Coordinating Center (one project) and Study Sites (five projects) are part of the Treatment and Intervention research gap. The funded BAA submission is focused on Prevention.

Table X-5. TBI Funding Summary

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Concept	445	26	\$5.35M
Intramural Advanced Technology – Therapeutic Development	29	7	\$25.92M
Intramural Investigator-Initiated Research	106	22	\$22.50M
New Investigator	194	11	\$4.47M
Investigator-Initiated Research	219	9	\$9.28M
Advanced Technology – Therapeutic Development	67	3	9.94M
MRC	200	20	\$35.99M
CAM	30	2	\$1.04M
BAA	2	0	0
<b>TOTAL</b>	<b>1,292</b>	<b>100</b>	<b>\$114.49M</b>

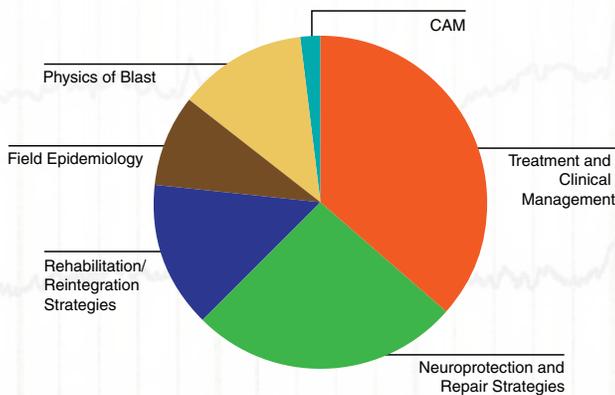


Figure X-3. TBI-Funded Projects by Gap Area

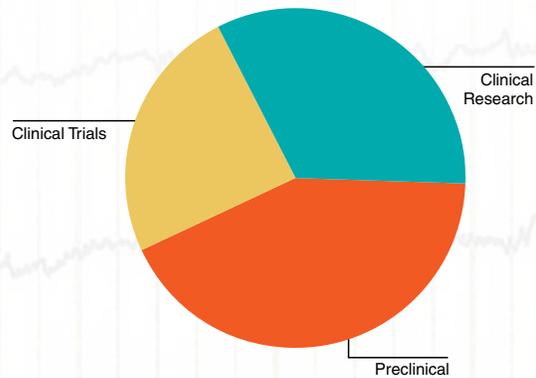


Figure X-4. TBI Clinical Categories

Note: Clinical Consortium Study Sites (five projects) are part of the Treatment and Clinical Management research gap.

### The PH/TBI Team

**Barbara Terry-Koroma, M.S., Ph.D.**  
Program Manager

**Holly Campbell-Rosen, Ph.D.**  
Grants Manager

**Tammy Crowder, Ph.D.**  
Grants Manager

**Kimberly del Carmen, Ph.D.**  
Grants Manager

**Inna Williams, M.S.**  
Program Specialist, Azimuth

**Margaret Young, R.N.**  
Program Specialist, Azimuth

**Meropi Athanasiou, Ph.D.**  
Program Coordinator, SAIC

**Tomy Gover, Ph.D.**  
Biomedical Scientist, SAIC

**Nicole Williams, Ph.D.**  
Program Coordinator, SAIC

**Herbert Avila, Ph.D.**  
Peer Review Coordinator  
SRA International

**Ronald Hostutler, M.B.A., Ph.D.**  
Peer Review Coordinator  
SRA International

**Steven Goldberg, M.B.A., Ph.D.**  
Peer Review Coordinator  
SRA International

**Steve Gallo, Ph.D.**  
Peer Review Coordinator  
American Institute of  
Biological Sciences

**William Daniels, Ph.D.**  
Peer Review Coordinator  
American Institute of  
Biological Sciences