DoD Psychological Health/Traumatic Brain Injury (PH/TBI) Research Program

Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.

Year	PH/TBI Research Contributions	Additional Information and Hyperlinks
2007	Three multidisciplinary research consortia, Strong Star, INTRuST, and Mission Connect, were established to advance research in Posttraumatic Stress Disorder (PTSD) and/or Traumatic Brain Injury (TBI). The spectrum of studies range from basic science to clinical research and trials.	
2007	Corticosterone Administration to Promote Fear Memory Forgetting in an Animal Model of PTSD. Based on evidence that glucocorticoid can enhance the memory-forgetting process in both healthy humans and animals, Dr. He Li hypothesized that the administration of glucocorticoid prior to or following stress could promote the traumatic memory-forgetting process and, potentially, prevent traumatic memory retrieval in PTSD patients. Dr. Li found that long-lasting efficacy of corticosterone applied 30 minutes prior to or after a traumatic stress episode mitigated the innate exaggerated acoustic startle response (ASR) lasting up to 21 days or 14 days respectively in an animal model of PTSD.	• Jia M, Smerin SE, et al. 2015. Corticosterone mitigates the stress response in an animal model of PTSD. J Psychiatr Res 60:29-39. • Li H, Li X, et al. 2014. Mitochondrial gene expression profiles and metabolic pathways in the amygdala associated with exaggerated fear in an animal model of PTSD. Front Neurol 5:164. • FY07 PTSD Concept Award
2007	Dr. Jeffrey Pyne developed virtual-reality stress inoculation biofeedback training as a predeployment intervention to reduce PTSD development and related mental health problems.	• FY07 Intramural PTSD Investigator-Initiated Research Award
2007	Dr. Liying Zhang developed an idealized three-dimensional human head model to examine the blast phenomena and determined that the maximum peak pressure transmitted to the scalp, skull, and brain is higher than the blast pressure received by the head.	
2007	Dr. Paul Kizakevich developed an easy-to-use Personal Health Monitor for longitudinal data collection to study signs, symptoms, triggers, and behaviors in PTSD and mild Traumatic Brain Injury (mTBI) patients. The device allows for the collection of comprehensive physical and physiological data while minimizing subject burden.	• FY07 PTSD Concept Award
2007	Dr. Mikulas Chavko determined that pressure detected in the rat brain following exposure to blast overpressure is contingent on the orientation to the blast direction, suggesting that pressure waves enter the protective tube and body by diffraction, moving in the opposite direction of the blast wave.	
2007	Dr. Michael Vitek measured the safety and toxicity of COG1410 in rats and dogs to form the basis of an Investigational New Drug application to the FDA for the treatment of TBI. COG1410 is a mimetic of the wild-type apoE protein, but it is very small and therefore crosses the blood-brain barrier and exerts anti-inflammatory and neuroprotective activities similar to wild-type apoE.	

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2007	Design of Effective Therapeutic Interventions for mild TBI/PTSD Using Interactive Virtual World Environments. Dr. Charles Levy leveraged combat veterans' comfort and familiarity with communications technology and immersive environments to build a prototype virtual-world grocery store in which to conduct rehabilitation of cognition emotional control for returning combat Veterans with mTBI/PTSD. The store (V-Mart) includes virtual humans that interact with the user verbally. A therapist directs the experience with a second computer which controls multiple parameters of the experience. Dr. Levy and his team of investigators have demonstrated that therapeutic virtual-world environments are feasible and show great potential to expedite and expand care to Veterans and Service Members with mTBI/PTSD. The work continues with funding support from the Veterans Administration's Rehabilitation Research and Development Service.	• PH/TBI Video Highlight • FY07 TBI Concept Award
2007	Dr. Nicholas Webster identified the lead drug, 5E5, and 38 other promising compounds for the treatment of brain injury based on their ability to activate the TrkB receptor.	• PH/TBI Research Highlight
2007	Dr. Roger Pitman found that propranolol blocks reconsolidation of fear conditioning in a rat animal model. Human studies show that propranolol plus traumatic memory activation reduces symptoms of chronic PTSD.	• FY07 Intramural PTSD Advanced Technology-Therapeutic Development Award
2007	Dr. Donald Stein developed a set of analogs specifically to maintain the neuroprotective properties of progesterone while increasing solubility following TBI.	
2007	Dr. Peter Bergold determined that minocycline and N-acetylcysteine synergistically improve behavioral performance following moderate controlled brain injury in rats.	
2007	Drs. James Tour and Thomas Kent of the Mission Connect Consortium synthesized potent antioxidant nanomaterials that use small carbon nanotubes to carry antioxidants for the treatment of oxidative stress following TBI, representing an entirely new class of treatment for TBI.	• PH/TBI Video Highlight • PH/TBI Research Highlight
2007	STRONG STAR Consortium: Brief Cognitive Behavioral Treatment of Deployment-Related PTSD in Primary Care Settings. The initial pilot study involved four-to-six 30-minute treatment sessions consistent with emotional processing theory and showed a significantly improved PTSD severity. Using the pilot study treatment protocol, a follow-on randomized clinical trial has been conducted. The trial is expected to be completed by September 2016.	• PH/TBI Research Highlight • STRONG STAR Consortium
2007	Prazosin for Treatment of Patients with PTSD and Comorbid Alcohol Dependence. Dr. Petrakis investigated if the effectiveness of Prazosin for PTSD might extend to PTSD populations with comorbid alcohol use disorders (AUD). Multiple studies of this alpha-1 adrenergic antagonist have demonstrated effectiveness in PTSD, however these studies typically exclude participants with AUD even though these disorders commonly co-occur. In the present study, the investigators recruited participants with both PTSD and AUD and found that the drug prazosin now failed to reduce the symptoms of PTSD and sleep disturbances. While the lack of effectiveness of this promising treatment in this population was disappointing, the work by Dr. Petrakis highlights the need to incorporate common comorbidities in studies of drug efficacy to better test effectiveness in 'real world' patients.	• FY07 Intramural PTSD Advanced Technology-Therapeutic Development Award

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2007	Dr. Murray Raskind of the VA Puget Sound Health Care System and VA and DoD collaborators conducted a randomized, controlled clinical trial of an FDA-approved medication, prazosin, for combat trauma nightmares, sleep quality, global function, and overall symptoms in active-duty Service Members with PTSD. Prazosin was superior to the placebo in all primary outcomes. The findings of this highly successful trial and others regarding prazosin's safety and efficacy have subsequently influenced the clinical practice guideline for treating PTSD sleep issues and related nightmares. Dr. Raskind is currently studying prazosin as an augmentation treatment for alcohol use disorders in active duty soldiers with and without PTSD.	• PH/TBI Video Highlight • FY07 Intramural PTSD Investigator-Initiated Research Award
2007	Dr. Michael McCrea found that the Military Acute Concussion Evaluation (MACE) is a reliable and valid measure for measuring cognitive function following military-related TBI. The study also found that the MACE is a valuable tool to rapidly assist in clinical decision-making following mTBI.	
2007	Dr. Jamshid Ghajar developed a military ready, portable, ruggedized goggle-style device (EYE-TRAC) to assess eye-movement deficits related to mTBI.	
2007	Dr. Steven Thorp's study of prolonged exposure therapy (PE) for PTSD demonstrated clinically significant improvements when delivered either in-person or by video conference. The telemedicine-based delivery may be advantageous for Veterans with PTSD living in remote areas.	• FY07 Intramural PTSD Investigator-Initiated Research Award
2007	Dr. Mark George, an INTRuST investigator, conducted a pilot safety and feasibility study of transcranial magnetic stimulation to rapidly stabilize patients with PTSD and/or mTBI exhibiting suicidality.	
2007	Dr. Harvey B. Pollard and his team at the Uniformed Services University of the Health Sciences have discovered PTSD-specific proteins in cerebrospinal fluid and plasma that can represent the causal, consequential, or compensating central mechanisms of PTSD. Patients suffering from PTSD, but not healthy controls, have fluctuating ratios of proteins known as chemokines depending on the time of day. The team's findings suggest that this differential chemokine ratio could serve as a biomarker for early PTSD diagnosis. In addition, Dr. Pollard's team has shown that microRNAs are also differentially expressed in PTSD patients. Previous research has shown that miRNAs regulate the expression of specific genes. Dr. Pollard plans to use these findings as a roadmap to uncover candidate targets for the early diagnosis and treatment of PTSD.	• PH/TBI Research Highlight • FY07 Intramural PTSD Investigator-Initiated Research Award
2007	Individual versus Group Cognitive Processing Therapy for Combat-Related PTSD. To evaluate an effective group treatment for combat-related PTSD, Dr. Patricia Resick compared Cognitive Processing Therapy (CPT) with Present-Centered Therapy in a randomized clinical trial. Although both group therapy treatments resulted in large decreases in PTSD severity, CPT was found to have a greater impact on PTSD symptoms as well as depression. A comparison of individual versus group CPT is currently underway.	• PH/TBI Research Highlight • STRONG STAR Consortium • FY07 PTSD Multidisciplinary Research Consortium Award

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2007	Prolonged Exposure for PTSD among OIF/OEF Personnel: Massed vs. Spaced Trials; Dr. Edna Foa, University of Pennsylvania. The purpose of this study is to enhance the efficiency of treatment for PTSD with PE, an efficacious treatment for PTSD, which is typically administered in weekly sessions, by evaluating whether massing 10 PE sessions in 2 weeks is as efficacious as the standard administration of PE. The treatment phase of the study is completed, and follow up assessments and data collection will be completed by the end of June 2016. Data analysis is ongoing.	• STRONG STAR Consortium • FY07 PTSD Multidisciplinary Research Consortium Award
2007	INTRuST Clinical Consortium: Concussion Treatment After Combat Trauma (CONTACT): The Effect of Telephone Follow-up on Outcome for Service Members with mild TBI/PTSD. A randomized prospective trial of a telephone-based counseling intervention called problem-solving treatment (PST) versus usual care (UC) for 356 Service Members with mTBI to treat the persisting psychological and physical symptoms of concussion and thus improve recovery and overall quality of life. As compared to UC, PST led to improvements in psychological distress, but not post-concussive symptoms, at 6 months post-PST, with effects no longer present at 12 months. Additionally, there was a significant beneficial effect on depression, PTSD symptoms, sleep, and physical functioning. Change in sleep quality occurred, at least in part, by reducing the subjective burden of comorbidities that affect and modulate sleep quality (especially pain, depression, and PTSD), as well as by providing practical, easily applicable advice for sleep quality improvements. Further study is needed to evaluate strategies such as more prolonged treatment or relapse prevention to sustain improvements.	• INTRuST Clinical Consortium
2007	INTRuST Clinical Consortium: Brain Indices of Risk for PTSD after mTBI. A longitudinal cohort study to evaluate associations between baseline measures of brain structure and function and PTSD symptoms 6 months post injury in Service Members with mTBI or extracranial injuries without TBI (non-TBI injured controls). A secondary aim is to evaluate differences associated with TBI due to blast or non-blast events.	• INTRuST Clinical Consortium
2007	INTRuST Clinical Consortium: A Randomized Clinical Trial of Glyburide for TBI. A randomized, blinded placebo-controlled, proof-of-concept trial to determine the efficacy of glyburide as a TBI therapeutic and evaluate its safety and tolerability in subjects with complicated mild, moderate, or severe TBI. Glyburide has been shown to prevent brain swelling and enhance neuroprotection in stroke and is FDA-approved for Type 2 diabetes. Preliminary magnetic resonance imaging (MRI) analyses reveal reduced edema in patients that took glyburide over a 72-hour period, within 10 hours of sustaining injury.	• INTRuST Clinical Consortium

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2007	INTRuST Clinical Consortium: Improving Walking and Balance in Veterans with TBI. This pilot study evaluated the feasibility and dosage of Intensive Mobility Training (IMT) by determining if participants with chronic, mild-to-moderate TBI show significant improvements in measures of locomotion and balance. Individuals with chronic TBI demonstrated gains in fast gait speed, mobility, and dynamic, functional balance activities following IMT, with gains improving as the number of 3-hour treatment sessions increased, but not doubling the outcomes assessed after 20 days of therapy versus 10 days of therapy. Rehabilitative gains in fast gait speed and mobility were sustained at 3 months.	• INTRuST Clinical Consortium
2007	INTRuST Clinical Consortium: Novel Functional and Structural Biomarkers of Neuroinflammation and White Matter Change in TBI: A Potential New Diagnostic and Therapeutic Approach. This pilot study acquired positron emission tomography (PET) images and MRI of complicated mTBI patients and age- and sex-matched control subjects recruited in the acute phase of injury. Inflammation, axonal injury, and micro-hemorrhage in the brain were measured with advanced neuroimaging techniques [diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI)]. All three abnormalities were correlated with cognitive/neuropsychological and behavioral measures to provide insight into neuro-inflammation associated with TBI and lead to more accurate and specific TBI diagnosis. Additional imaging biomarkers increased in complicated mTBI patients compared to healthy controls in the acute phase of injury (1-2 weeks) with PET imaging and DTI imaging techniques. After 3 months, the PET marker decreased, suggesting a reversal/recovery process. SWI revealed increased micro-hemorrhages in complicated mTBI patients at both time points.	• INTRuST Clinical Consortium
2007	INTRuST Clinical Consortium: Reliability and Initial Validation of the INTRuST Structured Assessment for Evaluation of Traumatic Brain Injury (SAFE-TBI). The purpose of this study was to develop SAFE-TBI, an instrument to (1) improve and systematize the manner in which information about a potential mTBI is ascertained, and (2) increase the degree of confidence that someone had an mTBI. Based on this project, the SAFE-TBI shows moderately good test-retest reliability when used by both experienced TBI clinicians and trained research coordinators, and good sensitivity and specificity compared to the gold standard of experienced TBI clinicians performing a thorough evaluation shortly after injury. Data from the VA cohort suggests that the current screening questions identify an appropriately broad population of military personnel at risk for previous exposure to an mTBI, but that almost one in four (24%) of those who screen positive have weak or no evidence of TBI on more detailed examination with the SAFE-TBI.	• INTRuST Clinical Consortium

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2007	INTRuST Clinical Consortium: Ganaxolone in PTSD: Proof-of-Concept Randomized Controlled Trial Investigating a Neuroactive Steroid Analog. This proof-of-concept, multisite, double-blind, placebo-controlled clinical trial investigated the efficacy of ganaxolone, an analog of a neuroactive steroid known to affect a host of neurological pathways and structures for which many published studies indicate it is an excellent candidate for a first-line medicine to treat PTSD. Although the results did not demonstrate efficacy for ganaxolone, ongoing analyses indicate that subpopulations of the patients experienced different blood concentrations of ganaxolone, and therefore, it may not have been sufficiently concentrated in the brain to affect PTSD symptoms. The research team continues to evaluate these results in order to determine appropriate next steps.	• INTRuST Clinical Consortium
2007	INTRuST Clinical Consortium: Initial Randomized Controlled Trial of Acceptance and Commitment Therapy (ACT) for Deployment-related Distress and Impairment. A randomized controlled clinical trial that compared two psychotherapeutic interventions, ACT and Present Centered Therapy (PCT). Findings showed participants in either ACT or PCT displayed clinically significant improvement, but there were no group differences other than ACT being associated with greater improvement in insomnia. Positive clinical results were observed regardless of head injury status. Within the small subgroup of women in the trial, ACT was associated with greater reductions general distress and PTSD symptoms than was PCT.	• INTRuST Clinical Consortium
2007	INTRuST Clinical Consortium: Randomized Controlled Trial of Galantamine, Methylphenidate, and Placebo for the Treatment of Cognitive Symptoms in Patients with mTBI and/or PTSD. This pilot study found clinically and statistically significant effects in improved attention and cognitive processing speed with the medication methylphenidate in contrast to galantamine and placebo. The most notable effects were in patients with PTSD. Future examination of methylphenidate is warranted.	• INTRuST Clinical Consortium
2007	INTRuST Clinical Consortium: A Double-Blind, Placebo-Controlled, Flexible-Dose Pilot Clinical Trial of Once-Daily Extended-Release Tramadol for the Treatment of PTSD. This pilot clinical trial compared Tramadol, an opioid medication having a low abuse potential and anxiolytic properties, with a placebo in PTSD patients. The results demonstrated that men who received Tramadol showed significant reductions in PTSD symptoms at some time points; methodological issues limit conclusions about women. Tramadol is a promising medicine for the treatment of PTSD and larger clinical trials should be conducted.	• INTRuST Clinical Consortium
2007	INTRuST Clinical Consortium: A Pilot Safety and Feasibility Study of High Dose Left Prefrontal Transcranial Magnetic Stimulation (TMS) to Rapidly Stabilize Suicidal Patients with PTSD. Delivering high doses of left prefrontal repetitive TMS over three days to suicidal inpatients is possible and safe, with few side effects and no worsening of suicidal thinking. Although there were no overall differences between TMS and sham, TMS appears to have led to earlier symptom reduction. This suggestion of a rapid anti-suicide effect needs to be replicated in a larger sample before implementation.	• INTRuST Clinical Consortium

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2009	Dr. Mikulas Chavko used a rat model of blast injury to reveal that pressure detected in the rat brain is contingent on the orientation to the blast direction.	
2009	Dr. Ksenia Ustinova developed a low-cost, virtual reality-based system to be used in physical rehabilitation of subjects experiencing motor coordination defects post-TBI. Data analysis indicated all subjects demonstrated improved motor function after utilization of the training regimen.	
2009	Dr. Jed Hartings and Dr. Raj Naryan developed a smart brain catheter to continuously and accurately measure biochemical, physiological, and electrophysiological characteristics of excess cerebral fluid resulting from TBI.	
2009	Dr. Charles Wilkinson found clinical evidence for increased post-traumatic hypopituitarism (diminished production of hormones from the pituitary gland) in Veterans with a history of blast mTBI.	
2010	Dr. David Poulsen demonstrated low-dose methamphetamine is neuroprotective following TBI in a rat model of TBI. Intravenous administration acutely following TBI resulted in improved neuron survival and improved neurobehavioural outcomes compared to control.	
2011	AnthroTronix (Dr. Corinna Lathan) received FDA clearance for the Defense Automated Neurobehavioural Assessment (DANA) mobile application. The DANA is a computerized cognitive test battery that can assist healthcare professionals in assessing various brain health concerns in a clinical setting. The tool is a phone or tablet app, which can be deployed on both iOS and Android operating systems.	
2011	Dr. Meis' team is studying Veterans in trauma-focused treatment for PTSD to understand how families influence treatment adherence. Preliminary findings indicate Veterans are more likely to stay in treatment when they tell others about it and when families encourage facing fears. Findings suggest strategies are needed to improve family support for treatment so Veterans can get the most from their care. While early findings are encouraging, they could change once the project is complete.	• PH/TBI Research Highlight • FY11 Basic Psychological Health Award
2012	The DoD and the VA collaborated to establish two new consortia focused on developing more effective diagnoses and treatment of PTSD and mTBI. The Consortium to Alleviate PTSD (CAP), led by Dr. Alan Peterson, and the Chronic Effects of Neurotrauma Consortium (CENC), led by Dr. David Cifu, are dedicated to improving the health and welfare of our nation's Service Members, Veterans, and their family members.	• PH/TBI News Release
2013	TBI Endpoints Development (TED) Award established a collaborative, multi-disciplinary research team to advance clinically validated endpoints which can support regulatory approvals of TBI diagnostics and therapeutics. The team is led by Dr. Geoffery Manley at the University of California, San Francisco.	

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2013	DoD funding began to support entry of data from completed PH/TBI studies (from previous funding cycles) into the Federal Interagency TBI Research (FITBIR) informatics system. FITBIR is a joint DoD and NIH-developed platform to share data generated from funded TBI studies and to facilitate and enhance collaboration, and it supports the National Research Action Plan (NRAP). Access to these "legacy" data will greatly enhance the immediate utility of FITBIR.	