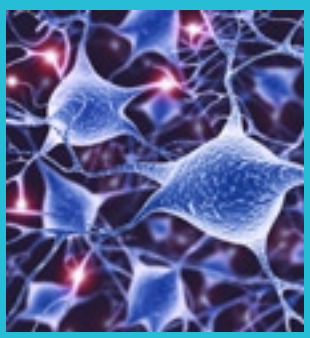
CDMRP

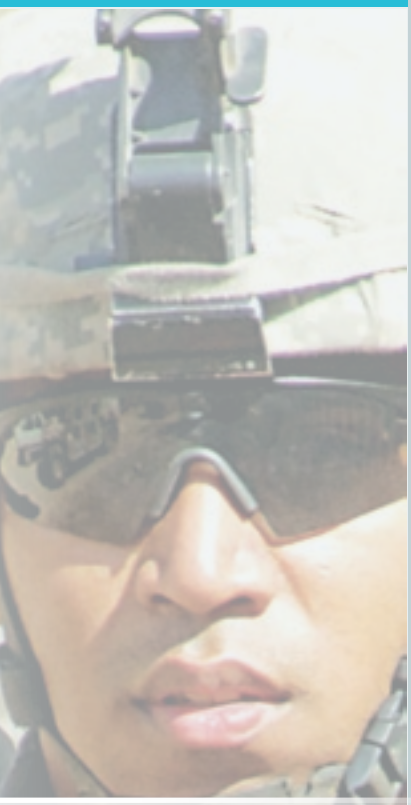
Department of Defense

Psychological Health/ Traumatic Brain Injury Research Program





U.S. Army Medical Research and Materiel Command



In combat, TBI accounts for 20-25% of surviving injuries and is one of the most common causes of chronic disability

Approximately one of every six returning OIF/ OEF veterans has symptoms of PTSD

VISION

Prevent, mitigate, and treat the effects of traumatic stress and TBI on function, wellness, and overall quality of life for service members as well as their caregivers and families

MISSION

Establish, fund, and integrate both individuals and multi-agency research efforts that will lead to improved prevention, detection, and treatment of PH and TBI

Congressionally Directed Medical Research Programs

History of the CDMRP

The Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community that convinced Congress to appropriate funds for breast cancer research. This enabled a unique partnership among the public, Congress, and the military. In fiscal year 1993 (FY93), the CDMRP was created as an office within the U.S. Army Medical Research and Materiel Command (USAMRMC) to manage these funds. Since that time, the CDMRP has grown to encompass multiple targeted programs and has received approximately $6 billion in appropriations from FY93 through FY10. Funds for the CDMRP are added by Congress to the Department of Defense (DOD) budget where support for individual research programs is allocated via specific guidance from Congress. The CDMRP manages these programs, under the support of USAMRMC, from receipt of funds, through competitive selection of proposals and individual project performance, to award closeout.

Psychological Health and Traumatic Brain Injury Research Program

History of the PH/TBI Research Program

The PH/TBI Research Program is one of the medical research programs administered by the CDMRP. This program was established in FY07 for the purpose of complementing ongoing DOD efforts toward promoting a better standard of care for PH (including Post-Traumatic Stress Disorder [PTSD]) and TBI in the areas of prevention, detection, diagnosis, treatment, and rehabilitation. This includes research to benefit service members, their family members, veterans, and other beneficiaries of the Military Health System. Through FY10, $351.6 million (M) has been assigned to the USAMRMC Office of the CDMRP for management oversight. A total of $45M was assigned to the Defense Centers of Excellence (DCoE) for PH and TBI for investment; information about the DCoE can be found at http://www.dcoe.health.mil.

Program Management

The CDMRP uses a unique two-tier review process for proposal evaluation recommended by the Institute of Medicine. This model has received high praise from the scientific community, advocacy groups, and Congress. The first tier is the scientific peer review of proposals against established criteria for determining scientific and technical merit. The second tier, programmatic review, is conducted by the PH/TBI Research Integration Panel, that compares submissions and recommends proposals for funding based on both scientific merit and the program's goals. Both levels of review involve a dynamic interaction between scientists, clinicians, and consumer reviewers.

Consumer reviewer participation at both levels of review is a critical factor. The unique experience of the consumer advocates helps scientists and clinicians understand the human dimension and their voice brings a sense of urgency to find the best research to make a positive impact on the lives of those affected. For the PH/TBI Research Program, consumers may be service members who have suffered a TBI, are working to overcome PH issues, or are family members supporting veterans who have suffered a TBI and or are experiencing PH issues.

Dr. Guilio Pasinetti of Mount Sinai School of Medicine served as a member of the FY09 PH/TBI Research Program Peer Review Panel. His laboratory is currently focused on translational research toward developing clinically assessable biomarkers to improve early detection of neurological disorders and lifestyle/dietary approaches for treating neurological disorders. Dr. Pasinetti is also working toward identifying and characterizing blood biomarkers of concussive brain injuries among OEF/OIF veterans. Dr. Pasinetti commented that *"a review committee comprised of scientists from multidisciplinary expertise together with public advocates provides the best format to ensure new, publicly supported researchers will be directed toward using the best science to address issues with significant impact to patients' quality of life."*

FY07 and FY09 Scientific Peer Reviewer, **Dr. Helen Bramlett** of the University of Miami, School of Medicine, first became involved in traumatic brain injury research as a graduate student. Having worked in the field of traumatic brain injury for the past 17 years, Dr. Bramlett's research currently focuses on understanding and developing viable treatments in a model of polytrauma. In addition, her work also concentrates on post-traumatic epilepsy and potential therapies to attenuate this consequence of TBI. Of her experiences in serving on the PH/TBI peer review panel, Dr. Bramlett notes that *"this program has been instrumental in funding much needed research in the area of psychological health and TBI that impacts our warfighters. The hope is that the results from this program will be able to provide treatments in several different areas of trauma that our wounded warriors experience."*

Dr. Steve Kaminsky has served on the PH/TBI Research Program Integration Panel from FY07–FY10. Dr. Kaminsky is the Vice President for Research and Director of Research Administration at the Uniformed Services University of the Health Sciences (USUHS). In his current capacity, he is responsible for developing and implementing policies that promote and enhance research in USUHS's school of medicine. Dr. Kaminsky commented that *"The Leadership at the Congressionally Directed Medical Research Programs has assembled some of the best scientists in this country to set the goals and standards for the science being funded in the Psychological Health and Traumatic Brain Injury research portfolio. The CDMRP staff have worked across federal agency boundaries to take all views into consideration as they work to solve the immediate problems associated with head injury in military medicine. The scope of what they have been charged to do is daunting but with each program announcement and review they make tremendous progress in fulfilling their commitment to fund the best research for unraveling the mysteries of brain injury."*

The PH/TBI Research Program is supporting our service members through innovative research addressing…

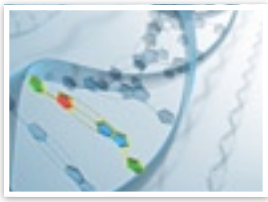
Psychological Health

Screening, Detection, and Diagnosis

- Identification of biomarkers for PTSD using state-of-the-art proteomic technologies to aid in diagnosis and to serve as objective surrogate end points for therapy.
- Developing an easy-to-use, handheld data collection system to assess treatment response in PTSD and TBI patients. The system will enable investigators to monitor symptoms in real-life situations and reduce patient burden.
- Evaluation of pre-deployment predictors of PTSD to identify Soldiers at greatest risk for developing PTSD. Concurrently, investigators are assessing pre-deployment resiliency interventions that may benefit Soldiers at risk to potentially prevent PTSD.

Treatments and Interventions

- The STRONG STAR PTSD Multidisciplinary Research Consortium, composed of 100 collaborating investigators at 20 institutions, is evaluating the use of cognitive-behavioral interventions for PTSD in primary care clinics and deployment settings.
- The PTSD/TBI Clinical Consortium, INTRuST, is a collaboration of numerous investigators and 10 clinical sites poised to conduct clinical trials of novel treatments for military-relevant PTSD and TBI.
- Telemedicine and virtual reality strategies for PTSD treatment are under investigation to improve access to care for veterans and active duty Soldiers.
- Since patients with comorbid PTSD and pain have increased symptom severity and poorer prognosis for both conditions, the effect of comorbid pain on the diagnosis and treatment of PTSD in OIF/OEF veterans is currently being evaluated.
- Prazosin is being evaluated in OIF/OEF veterans to augment the treatment of PTSD symptoms, which include nightmares and sleep disturbances.
- PTSD is twice as likely to occur in women; however, there is paucity in combat PTSD-related research in females. Investigators are evaluating novel treatments such as Propanolol, a beta-adrenergic receptor blocker, in female OIF/OEF veterans. Additional studies are aimed at understanding the prevalence of PTSD and use of health service utilization in female veterans.



Neurobiology and Genetics

- Models of PTSD are being used to elucidate the role of neurotransmitters and sex hormones in stress response and fear conditioning, informing the development of new drug candidates.
- Optical stimulation of various brain regions in a model of PTSD is being used to identify neural targets whose stimulation or silencing could prevent or treat PTSD.
- Genetic differences in PTSD patients and healthy controls are being examined to improve understanding of fear dysregulation seen in PTSD.

Prevention

- A combination treatment using glucocorticoid and beta-adrenergic receptor blockers administered immediately following trauma is being tested in a novel model of PTSD.
- A pre-deployment military mindfulness training program designed to improve Soldiers' capacity to recover from stress-related impairments and reduce the incidence of PTSD is being evaluated.

Families and Caregivers

- A longitudinal study is under way to examine the impact of combat injuries on military children and evaluate differences in family functioning, from the perspectives of both parent and child.
- As approximately 33% of Reserve and National Guard personnel are 25 years old or younger, many are single and rely on their families of origin for support. In light of this, the mental health needs of single, adult Reservists and Guard personnel and their families of origin are being assessed, and family-based interventions are in development.

Epidemiology

- The first longitudinal registry of combat-exposed men and women with PTSD is being created.
- Reservists have increasingly become central to recent operations, but there is limited understanding of the detriment of mental health among these forces. Investigators are currently assessing the prevalence of PTSD and health service utilization to determine factors that may act as stressors or that may engender resilience among these forces.

Traumatic Brain Injury

Physics of Blast

- To assist in the development of more effective protective helmets for Soldiers, a cranial-only blast injury apparatus producing repeatable, dose-dependent blast-TBI, independent of transthoracic mechanisms of injury to the brain has been developed and tested.
- Development of three-dimensional numerical model capturing the physics of shock wave propagation to evaluate and further understand the effects of blast pressure on the human skull and brain tissue.
- For improved protection against the effects of blast injury, animal models of blast injury are being used to identify pathways by which blast energy is transferred to the brain and body.

Rehabilitation and Reintegration

- As physical rehabilitation has been shown to have significant influence on the brain in stroke patients, investigators are using an animal model of TBI to determine if motor rehabilitation strategies can affect the reorganization and healing of the injured brain.
- Investigators are examining the efficacy of a cognitive training augmentation of supported employment to improve cognitive performance and work outcomes in veterans with mild to moderate TBI who are unemployed and want to return to work.
- Telerehabilitation and virtual reality therapies are being evaluated for the treatment of OIF/OEF veterans who have suffered a TBI.

Neuroprotection and Repair

- Evaluation of the neuroprotective effects of brain stimulation and investigational drugs to identify potential therapeutic targets using wireless brain stimulators in animal models of TBI.
- Comparison of blast-induced and mechanically induced TBI neural and behavioral sequelae in veterans and civilians via combination of neurobehavioral techniques and magnetic resonance imaging (MRI).
- Clinicians are testing the safety and tolerability of an investigational compound that increases tissue oxygenation in patients with severe nonpenetrating TBI to determine improvements in brain oxygen delivery and patient outcome.

Treatment and Clinical Management

- Pair-wise combinations of FDA-approved drugs are being evaluated for additive or synergistic neuroprotective effects in TBI models to develop a multidrug cocktail for the treatment of TBI.
- Diffusion tensor imaging is being combined with validation by resting-state functional MRI to reveal brain abnormalities in individuals who have experienced TBI.
- Valproate is being evaluated in individuals with TBI and alcohol dependence to help improve daily function and reduce alcohol intake.
- A sensitive rapid eye-tracking device for the diagnosis of mTBI in the field has been developed and is currently being tested.
- Mission Connect, the mTBI Multidisciplinary Research Consortium, is a collaboration of investigators at five institutions studying mTBI in the laboratory and clinic. In one study, the investigators are conducting a clinical trial of atorvastatin in TBI patients to study the effects on brain function recovery.

Families and Caregivers

- An integrated cognitive and motor training protocol is being implemented to help veterans who experienced a TBI to reintegrate and restore life role participation.
- A Multi-Family Group Intervention for veterans with TBI and their families is being evaluated to improve overall health and quality of life.

Field Epidemiology

- Epidemiological studies are being conducted to determine the prevalence of, and identify predictive factors of, post-concussive syndrome after TBI to assist in the development of targeted secondary prevention, medical, and rehabilitative strategies.
- The validity of multiple state-of-the art modeling approaches is being evaluated using serum and cerebrospinal fluid markers associated with TBI to establish comprehensive biomarker modeling algorithms for diagnosis, prognosis, and management of patients in the field.

Personal Monitoring for Ambulatory PTSD Assessment

Paul Kizakevich, M.S., P.E., RTI International, Research Triangle Park, North Carolina

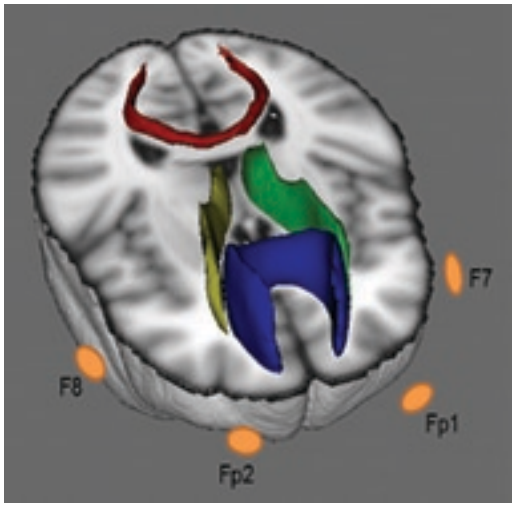
Active duty men and women diagnosed with PTSD are typically only monitored on a weekly or monthly basis. These infrequent evaluations are often biased by recent events in the patient's life that prevent a complete and accurate characterization of symptoms by caregivers. Mr. Paul Kizakevich has received an FY07 Psychological Health and Traumatic Brain Injury PTSD Concept Award to develop a Personal Health Monitor (PHM) for ambulatory PTSD assessment. The handheld system will collect longitudinal data on PTSD signs, symptoms, triggers, and behaviors during daily life.

The instrument will collect PTSD symptom data on flashbacks, dreams, avoidance stimuli, sleep difficulties, irritability, concentration issues, diet, and substance use. The system will also conduct heart rate variability analysis to assess stress and use 3-axis accelerometry to assess body movement and respiration during sleep. The integrated data will be saved on the PHM Pocket PC or smart phone in a secure database and offloaded for analysis and clinical assessment. Based on their evaluations, clinicians and research investigators will also be able to customize survey and sensor modalities to improve patient compliance and treatment. The device is designed to fit in a hip-pack to reduce patient burden, and project staff will also conduct pilot tests to enhance device usability. Currently, Mr. Kizakevich is completing the PHM prototype and evaluating device software. When finished, the PHM will enable psychological health assessments on a more continuous basis than traditional clinical encounters, and it will offer researchers a better understanding of the longitudinal fluctuations and progression of PTSD symptoms. The device will also increase user privacy and anonymity, which may improve the quality, frequency, and accuracy of the psychometric assessments.

The Effects of Explosive Blast as Compared to Post-Traumatic Stress Disorder on Brain Function and Structure

Scott R. Sponheim, Ph.D., Veterans Affairs Medical Center, Minneapolis, Minnesota; University of Minnesota, Twin Cities

Individuals experiencing blast-related TBI and those suffering from PTSD display similar clinical presentations. Characterization of the neurological effects of blast-related TBI is often complicated by the emotional and cognitive sequelae of accompanying psychological trauma. The inability for clinicians to clearly demarcate the symptoms of explosive blast exposure and combat stress has made it difficult to prescribe therapies that are effective in returning Soldiers to full functioning. Dr. Scott Sponheim received an FY07 Intramural TBI Investigator-Initiated Research Award to characterize the changes in neural structure and function following blast-related TBI in a sample of military personnel that were deployed to Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF). Dr. Sponheim is recruiting subjects into one of four experimental groups, PTSD (PTSD, No Blast Exposure), Blast (Blast Exposure, No PTSD), PTSD and Blast, and Control (neither PTSD nor Blast), to differentiate the effects of combat-related PTSD and blast-induced TBI. Emotional health is being evaluated using both clinical interviews and self-reporting measures. MRI and quantitative electroencephalography (EEG) is being used to evaluate brain structure and function, respectively. To date, clinical, MRI, and EEG data have been collected on 112 military personnel that returned from OIF/OEF deployment. Preliminary analyses of quantitative EEG data revealed diminished synchronization of activity across the frontal lobes of the brain in individuals with blast-related mild TBI. The diminished EEG synchronization in subjects with blast-related mild TBI was also associated with the lower structural integrity of white matter connections to the frontal lobes of the brain (fractional anisotropy as measured through diffusion tensor imaging). Final results of this study will inform the differential diagnosis of blast-related TBI and PTSD thereby leading to better treatment and recovery in our fighting forces.



Virtual Reality Exposure Therapy to Battle PTSD

Gregory Gahm, Ph.D., and Greg Reger, Ph.D., Madigan Army Medical Center, Tacoma, Washington

Prolonged Exposure Therapy (PE) is one of the most effective treatments for PTSD. However, PE requires the patient to revisit their traumatic memory in an emotionally engaging way. Soldiers face unique barriers to care compared to civilian populations. Following combat deployments, many Soldiers suffering from PTSD are emotionally detached and avoid the painful memories associated with the traumatic event, which can limit their ability to engage in the PE treatment process. In addition, some Soldiers report concerns about stigma associated with seeking help through traditional "talk therapies." Virtual Reality Exposure Therapy (VRET) holds the potential to provide effective therapy for PTSD and to improve access to care for Soldiers who might otherwise avoid treatment due to stigma. VR works by immersing a participant in a realistic computer-generated world that simulates the sources of combat stress. By revisiting the traumatic event in a sensory-rich environment, the investigators hypothesize that participants may experience heightened physiological arousal, and clinical outcomes may be significantly improved compared to those from traditional PE. Dr. Gregory Gahm and Dr. Greg Reger are conducting a randomized clinical trial comparing VRET to traditional PE in the treatment of combat-related PTSD in OIF/OEF Soldiers. Returning Soldiers diagnosed with PTSD will be randomized to receive 10 sessions of either VRET or PE or a waitlist control group (that will wait several weeks to be placed in a treatment group). The study will compare the efficacy of the two treatments and will also compare psychophysiological arousal during VRET and PE treatment sessions. These data will help demonstrate whether the multisensory nature of VRET increases arousal and whether increased arousal contributes to better treatment outcomes. Perceptions of stigma, patient satisfaction, and treatment adherence will be evaluated for the two treatments. The investigators hope that Soldiers will find the gaming aspect of VRET appealing and lessen the stigma associated with seeking help. The study is in collaboration with the Department of Psychology at Madigan Army Medical Center and is currently recruiting Soldiers from that facility. In addition, the investigators are planning to extend the study to Soldiers at Womack Army Medical Center at Fort Bragg, North Carolina.

Treatment of Active Duty Military with PTSD in Primary Care: PTSD-PC Program Early Findings

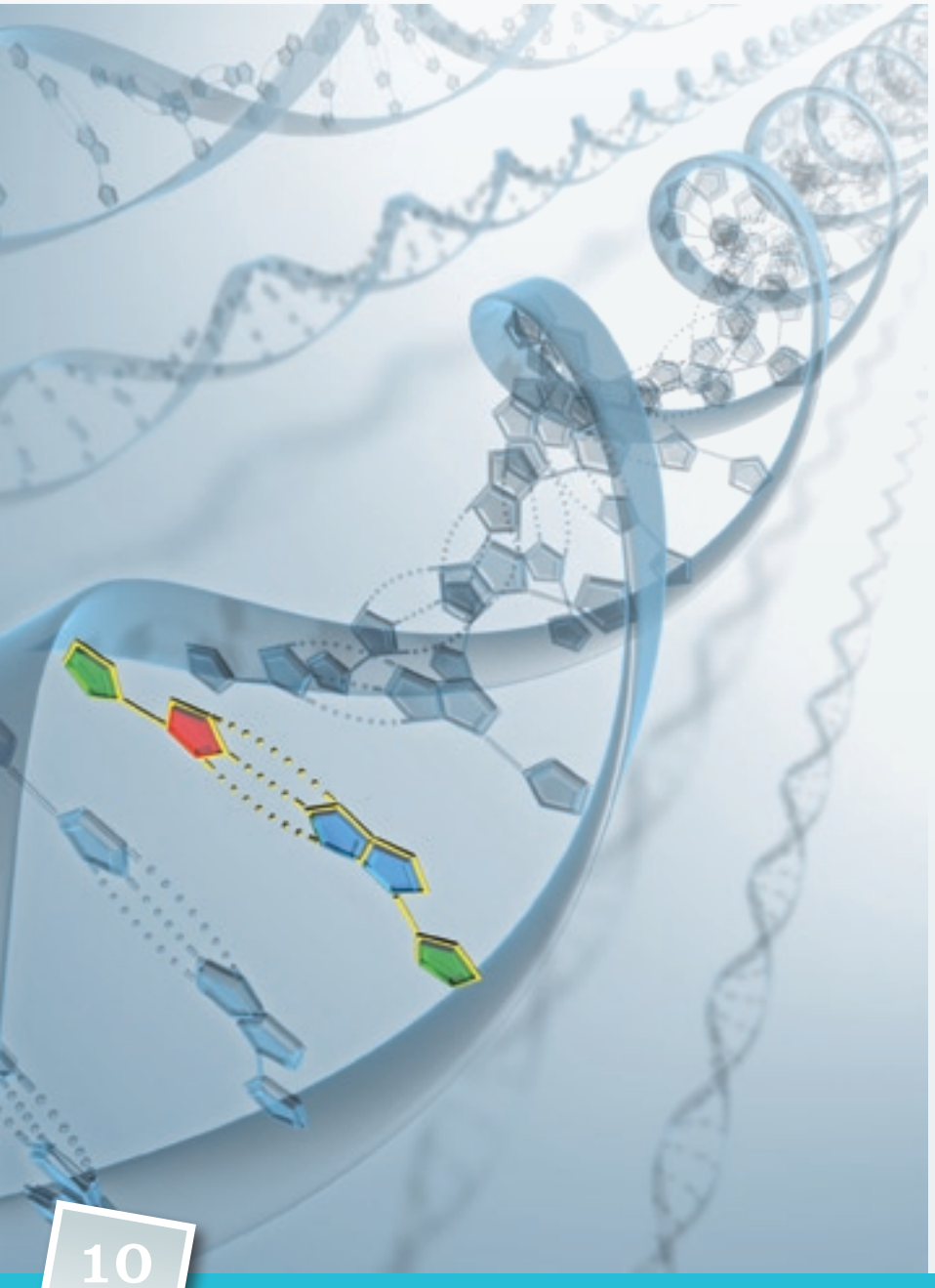
Lt Col Jeffrey Cigrang, Ph.D., Wilford Hall Medical Center, San Antonio, Texas; Sheila Rauch, Ph.D., VA Ann Arbor Healthcare System and University of Michigan Medical School, Ann Arbor Michigan; and Laura Avila, Ph.D., Brooke Army Medical Center, San Antonio, Texas

The South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR), a multidisciplinary and multi-institutional research consortium focusing on PTSD, received a DOD FY07 PTSD Multidisciplinary Research Consortium Award. Under this award, Lt Col Jeffrey Cigrang and his partnering investigators, Drs. Sheila Rauch and Laura Avila, have been exploring a psychotherapy treatment for deployment-related PTSD. A substantial number of veterans of the wars in Iraq and Afghanistan are currently affected by PTSD, yet many report having received no professional help or inadequate help in the past year. Concern that one's military peers and leadership may negatively judge mental health help-seeking can be a significant barrier to accessing care in a specialty mental health clinic. The primary care (PC) clinic may be a more favorable environment for treatment of PTSD in terms of reduced stigma and increased reach to military members. PC is also an ideal setting for offering relatively brief, first-line help to service members with PTSD as part of a larger stepped model of care. These investigators are conducting an ongoing pilot study of a cognitive-behavioral treatment (CBT) designed for use by psychologists working in an integrated PC clinic that see active-duty military with deployment-related PTSD. The CBT protocol is composed of four to six individual 30-minute appointments with a PC psychologist and practice assignments conducted over 6 to 8 weeks. Treatment content is primarily based on an exposure model but includes elements of both prolonged exposure and cognitive processing therapies. Participants were recruited for the pilot study trial from the population of patients referred to the PC psychologist by their PC manager during routine clinical care. Participants are active-duty or activated reserve OIF/OEF veterans seeking help for deployment-related PTSD symptoms with a PCL-M (scaled self-report PTSD questionnaire) score >32, and interest in treatment for PTSD in PC. Those with moderate to severe suicide risk, current alcohol dependence, psychotic disorder, or severe traumatic brain injury were not eligible to participate. To date, 10 participants have completed treatment and a 1-month post-treatment evaluation. At 1-month post-treatment, five participants (50%) no longer met criteria for PTSD. Six- and 12-month follow-up evaluations are currently being conducted. Psychological assessments given at follow-up indicated that the average PTSD symptom severity was significantly reduced from baseline as measured by both interviewer-administered and self-report inventories, the average depression symptom severity was also significantly reduced, and overall mental health functioning was increased. These early findings are highly encouraging for the use of PTSD-PC as a viable first-step treatment protocol in the context of PC. Further, this intervention may help overcome barriers to care, such as stigma regarding mental health treatment, and meet the needs of many active-duty OIF/OEF veterans seeking help for PTSD.

Genetic Screen for PTSD-Prone Soldiers

Clare M. Bergson, Ph.D., Medical College of Georgia Research Institute, Augusta, Georgia

A subset of individuals exposed to combat stress and trauma develop PTSD. Studies of Vietnam veterans demonstrated that PTSD is concordant in twins, indicating a possible genetic predisposition for PTSD. While genetic factors have been shown to influence risk of trauma exposure, suggesting a role for traits such as neuroticism and impulsivity, no specific PTSD susceptibility loci have been identified. Data emerging from human and animal studies suggest that the calcyon gene, associated with attention deficit hyperactivity disorder, may also play a role in the development of PTSD. Dr. Clare M. Bergson received an FY07 PTSD Concept Award to investigate the relationship between calcyon and PTSD in active military personnel and veterans.



Dr. Bergson, in collaboration with Dr. Dewleen Baker, M.D., and Caroline Neivergelt, Ph.D., of the San Diego Department of Veterans Affairs (VA) Medical Center, will ascertain phenotype and genotype information from a total of 500 active duty military personnel and veterans with mild to severe combat exposure. With respect to phenotype, each participant is extensively evaluated with respect to trauma exposure, social support, medical history, personality traits and symptoms by Dr. Baker, a clinician specializing in PTSD. Subjects will be genotyped for variations in the calcyon gene and ethnic ancestry using cell lines established from their lymphocytes. Together these data will be used to assess the association of calcyon to PTSD and gene-environment interaction studies on susceptibility to PTSD related to combat exposure. The study currently includes 328 participants. The results of this study may provide unbiased prognostic information about PTSD and in turn could influence the treatment of Soldiers exposed to traumatic combat situations.

Roles of the Medial Prefrontal Cortex and HPA Axis in the Generation of PTSD-Like Symptoms

Israel Liberzon, M.D., University of Michigan, Ann Arbor, Michigan

Clinical manifestations of PTSD include an intrusive and recurrent recollection of traumatic events, avoidance of normal social interactions, and the perception that emotions including fear, anger, and anxiety are beyond patient control. Previous research has implicated abnormalities in medial prefrontal cortex (mPFC) function centrally, as well as altered hypothalamus-pituitary-adrenal (HPA) axis function, in PTSD. The mechanisms that link PTSD symptom generation, mPFC function, and stress axis abnormalities, however, have not been established. Dr. Israel Liberzon, of the University of Michigan, has developed an animal model of PTSD using single prolonged stress (SPS), which induces PTSD-specific, HPA axis changes, and the behavioral arousal characteristics of PTSD. Further, preliminary data from Dr. Liberzon's laboratory suggest that SPS induces deficits in extinction, avoidance of social interactions, and deficits in modulation of aversive responses. Thus, with funding from an FY07 Intramural PTSD Investigator-Initiated Research Award, Dr. Liberzon is investigating whether SPS-induced deficits in these PTSD-like symptoms are caused by SPS-induced effects on HPA and mPFC function. To date, Dr. Liberzon has investigated the effect of SPS on the concentrations of the major excitatory (glutamate) and inhibitory (GABA) neurotransmitters in brain regions including the mPFC, hippocampus, and amygdala. Results from this study have recently been published in *Neuroscience Letters* and demonstrate that glutamate levels were decreased only in the mPFC with no significant changes in GABA levels found in any brain region tested. Future investigations will assess the effect of selective serotonin reuptake inhibitors (SSRIs) to alleviate SPS-induced behavioral alterations and the role of mPFC/amygdala function and HPA/glucocorticoid function in this process. Together, data generated from this study will contribute to the current understanding of PTSD and may offer insight into SSRIs as a treatment for emotional regulation in patients with PTSD.

Post-Stress Combined Administration of Beta-Receptor and Glucocorticoid Antagonists as a Novel Preventive Treatment in an Animal Model of PTSD

David Morilak, Ph.D., University of Texas Health Science Center at San Antonio, Texas

Some symptoms of PTSD, including "flashbacks," social withdrawal, stress sensitization, and generalized anxiety, may be considered manifestations of a pathological and persistent memory of the traumatic event. The immediate response to stress includes glucocorticoid secretion and norepinephrine release in the brain, which act on receptors in the amygdala to enhance conditioned fear and anxiety and to strengthen emotional memories of stressful events. Dr. David Morilak of the University of Texas Health Science Center at San Antonio hypothesizes that combined treatment with glucocorticoid and beta-adrenergic receptor antagonists immediately following trauma will attenuate the strength of traumatic and stressful memories, reducing the likelihood of developing PTSD. Dr. Morilak received an FY07 PTSD Concept Award to test the effectiveness of this combined treatment as protection against PTSD-like symptoms in a rat model.

During this award, Dr. Morilak established a reliable set of behavioral tests that evaluate key PTSD-like symptoms in rats including social withdrawal, generalized anxiety, and stress sensitization, enhanced fear conditioning, and compromised extinction of conditioned fear. Following consultation with military and medical colleagues, a new rat model of adult traumatic stress called Chronic + Acute Prolonged Stress (CAPS) was developed and tested. CAPS involves chronic intermittent cold stress applied over a 2-week period followed by a single prolonged stress session consisting of 30 minutes of immobilization, 20 minutes of social defeat, and 10 minutes of swim stress. Dr. Morilak feels that CAPS is a better model of human PTSD than those that currently exist, given that combat deployment creates a context of chronic stress, but it is often a single traumatic event within this context that triggers the development of PTSD. To begin testing of drug treatment paradigm, rats were given the beta-adrenergic antagonist, propranolol, and/or the glucocorticoid antagonist mifepristone, following the single prolonged stress component of the CAPS protocol. Preliminary results suggest that mifepristone modestly reduced the negative effect of CAPS on conditioned fear extinction, but propanolol did not have an effect on fear conditioning or extinction. Dr. Morilak is encouraged by these early results using the CAPS model and plans to use it in ongoing and future studies of the neurobiology of PTSD and its treatment.

Spouse Telephone BATTLEMIND: A Telephone Support Program for Spouses to Help Soldiers Transition Home

Linda Nichols, Ph.D., and Jennifer Martindale-Adams, Ed.D., VA Medical Center, Memphis, Tennessee

The BATTLEMIND Training System was originally developed by the Walter Reed Army Institute of Research to help Soldiers reintegrate and adapt their combat skills back into civilian life. Although reintegration difficulties and mental health symptoms increase during the first year for returning veterans, face-to-face training for spouses of OEF/OIF service members has typically been offered on a one-time basis, which does not provide ongoing support as new reintegration challenges appear. Dr. Linda Nichols and Dr. Jennifer Martindale-Adams at the VA Medical Center in Memphis are expanding the Spouse BATTLEMIND training program into a year-long, telephone-based support group to investigate its effectiveness. The program provides telephone support group sessions to spouses that are designed to educate, build coping skills, improve access to services for veteran and family, and serve as a source of shared support. So far, 60 spouses have been enrolled in the feasibility trial, plus the recent addition of 26 Wounded Warrior Project spouses. Over the period of 1 year, each group of 6–10 spouses and a trained Group Leader have hour-long structured telephone sessions once a month. The content of the session includes ways the returning service member, spouse, and family may have changed during deployment, with emphasis placed on compromise and negotiation in personal relationships; strategies to reduce or eliminate reunion and reintegration difficulties; strategies to support the returning Soldier; and cues to alert spouses when to seek mental health services for the Soldier, children, or themselves. The investigators are evaluating participant satisfaction and changes in spouse self-report of depression, anxiety, relationship satisfaction, and family communication. If successful, the investigators hope to disseminate the program for use across the DOD and the Department of Veterans Affairs. The Army's recent change from the BATTLEMIND rubric will provide more flexibility in session topics and in how sessions are scheduled, and in the future will be called Spouse READI (Resilience Education and Deployment Information.)

Building Warrior Resilience with Mindfulness Training

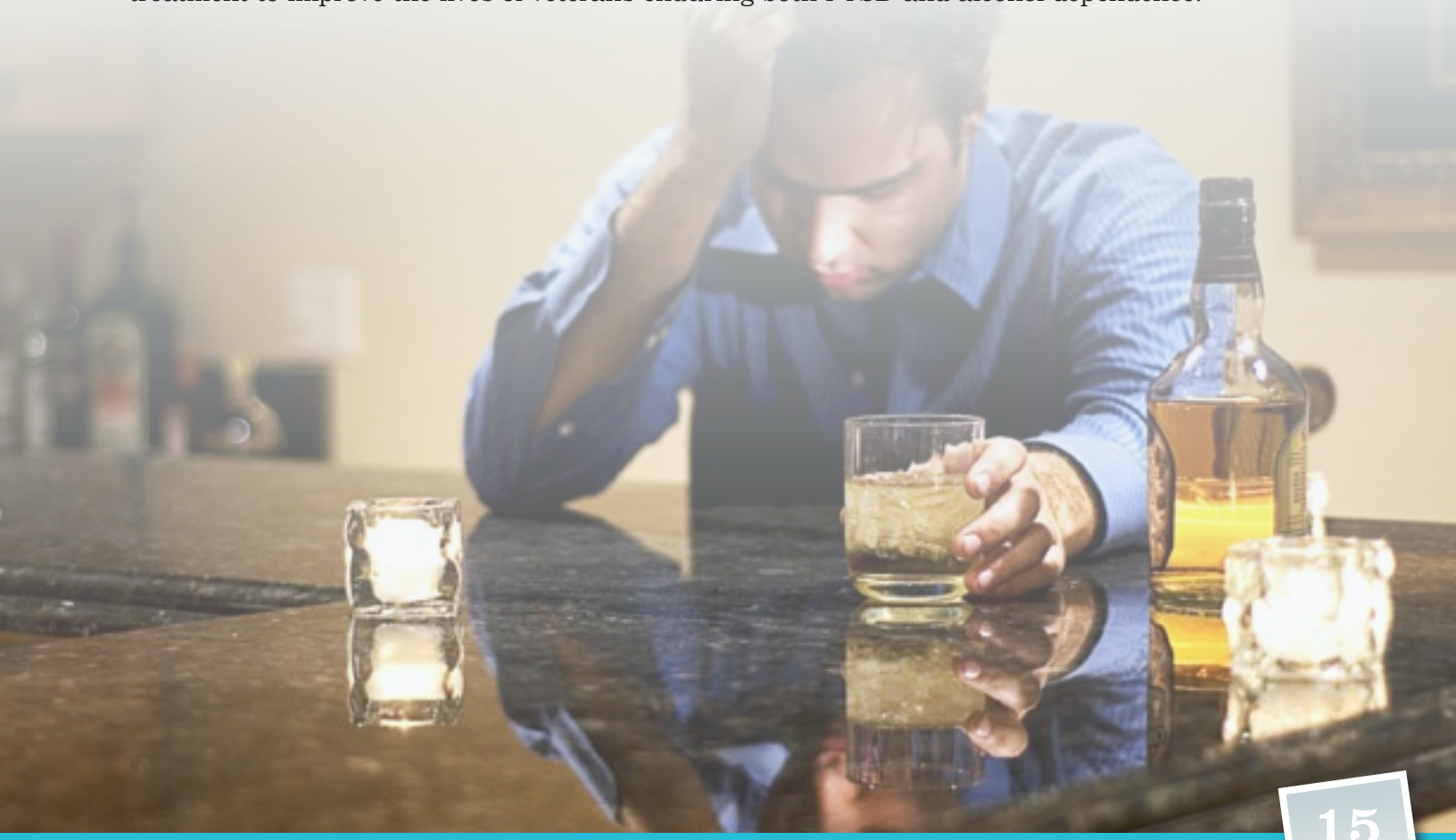
Amishi Jha, Ph.D., University of Miami, Miami, Florida

Recent military deployments have resulted in a range of psychological health issues and turned attention to the development of protective measures to mitigate the negative effects of prolonged and repetitive stress. Dr. Amishi Jha has spearheaded a research program to investigate if psychological resilience can be trained and strengthen with mental training techniques. She has been investigating a protocol—"mindfulness-based Mind Fitness Training" (MMFT, pronounced M-Fit)—designed to build resilience in Soldiers, which was developed and delivered by her collaborator Dr. Elizabeth Stanley from Georgetown University. The program is based on civilian mindfulness training protocols that have been used successfully for stress reduction in other contexts. The MMFT program teaches Soldiers techniques and exercises to enhance mind fitness including mental agility, emotion regulation, attention, focus, and situational awareness, which are crucial for military effectiveness. These skills are thought to equip warriors with "mental armor" to both optimize their performance and enable them to handle the challenges and stressors of deployment. Dr. Jha has conducted a pilot study of MMFT in 31 U.S. Marine reservists who were set to deploy to Iraq. These results were recently published in the journal *Emotion* (Jha et al., 2010). During the 8-week MMFT course, troops learned about the stress reaction cycle and its effects on the mind and body. They were instructed in how mind fitness can boost resilience to this stress. They were also taught mindfulness training exercises that they could practice outside of the course. The training exercises were to be practiced 30 minutes a day in groups or individually. Before and after the training, Marines participated in a battery of behavioral tasks to measure their cognitive capabilities, including attention and working memory, and completed affective self-report questionnaires on mood and perceived stress. Marines who spent more time engaging in mind fitness exercises (~10 hours outside of class) had an improvement in working memory performance and positive mood and decreased levels of negative mood compared to Marines who spent less time on the exercises (~2 hours or less outside of class). After returning from deployment to Iraq, the Marines participated in the same behavioral tests and were interviewed. While the results of the testing are in progress, many of the Marines in the study reported that they had personalized their approach to the daily MMFT exercises once deployed. Some incorporated the exercises into their physical fitness regimes, others used them to remain alert and focused while on missions, while others used the exercises at bedtime to quiet their minds and fall asleep. The results of this pilot study show promise that the pre-deployment MMFT intervention may be an effective program for improving operational effectiveness and decreasing the psychological injury that occurs under the extreme stress of deployment. Dr. Jha is currently conducting the next phase of research on MMFT in a USAMRMC-funded project referred to as the STRONG project that involves training and research on several predeployment Army platoons. Her current project is indexing brain function in addition to behavioral performance and survey results. In addition, mindfulness-based training is being compared to resilience building interventions involving positive psychology.

Conquering Co-morbidities: Prazosin for the Treatment of PTSD and Alcohol Dependence

Ismene Petrakis, M.D., Yale University, New Haven, Connecticut

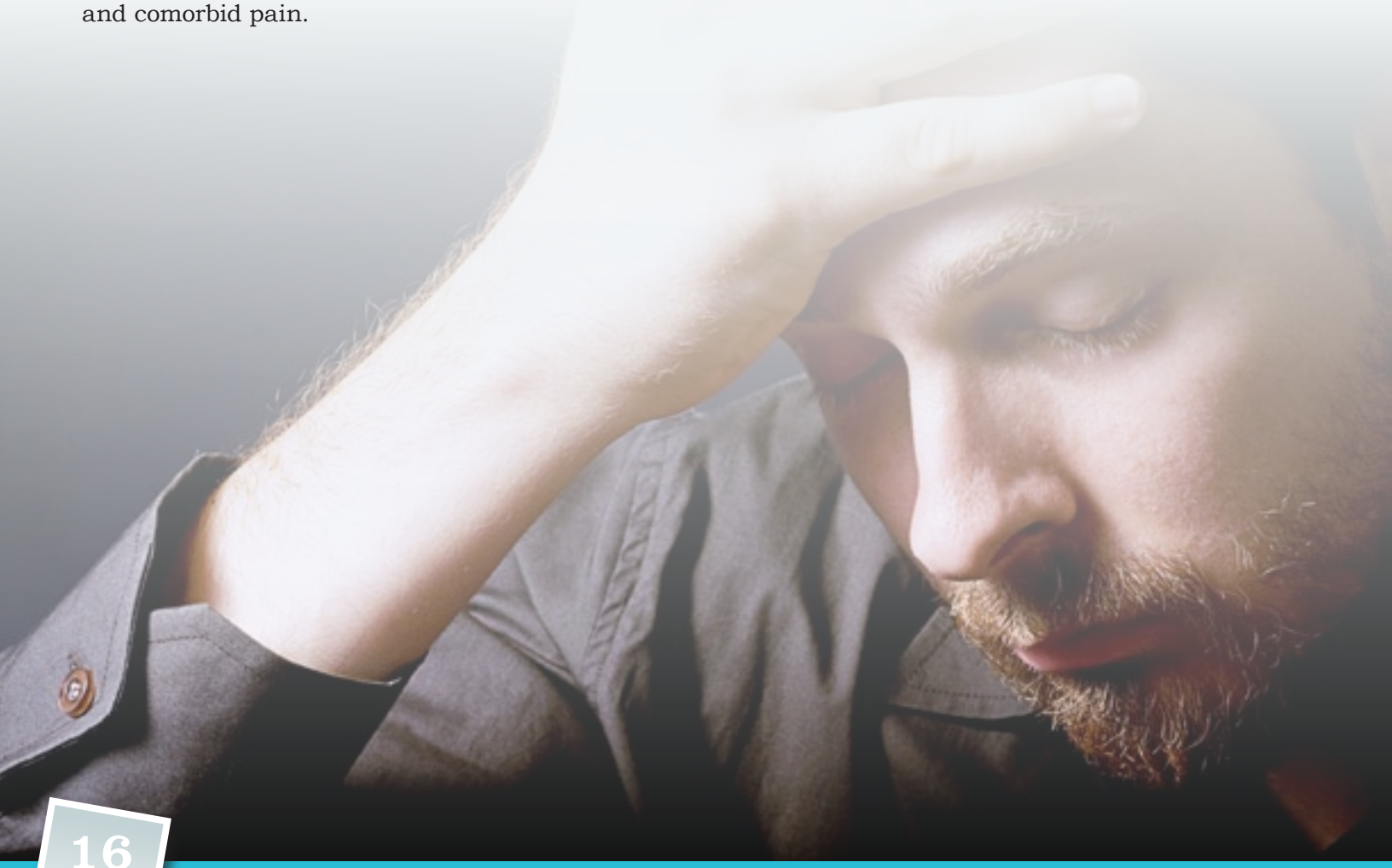
Alcohol dependence is one of the most common co-morbid diagnoses among men with PTSD. This co-morbidity is associated with more severe PTSD symptoms, higher rates of alcohol relapse, higher rates of psychosocial and medical problems, and psychiatric hospitalization in comparison to non-co-morbid patients with PTSD. There is evidence of a common biological mechanism underlying PTSD and alcohol dependence that involves abnormalities in the noradrenergic system. Prazosin, an alpha-1 adrenergic receptor antagonist that targets the abnormalities in this system, has shown promise in the treatment of PTSD, nightmares, sleep disturbances, and alcohol dependence in pilot studies. Dr. Ismene Petrakis, recipient of an FY07 PTSD Advanced Technology/Therapeutic Development Award, is conducting a double-blind randomized clinical trial of this promising drug in 120 veterans with PTSD and co-morbid alcohol dependence. Veterans are currently being recruited from the VA Connecticut Healthcare System and the Bedford, Connecticut VA Hospital. Prazosin or placebo will be administered to patients for 12 weeks. During follow-up, PTSD symptoms, including nightmares and sleep disturbances, and alcohol intake will be evaluated through various assessments to determine the effectiveness of the treatment. Ultimately, the investigators are hopeful that prazosin will be an effective treatment to improve the lives of veterans enduring both PTSD and alcohol dependence.



Post-Traumatic Stress Disorder and Pain Comorbidity in Veterans

Erin Krebs, M.D., Indiana University, Indianapolis, Indiana

PTSD is frequently complicated by the presence of comorbid chronic pain. Previous investigations of Vietnam veterans enrolled in VA PTSD treatment programs indicated that a majority of the Soldiers with PTSD also had coexisting chronic pain disorder. Patients with comorbid PTSD and pain also experience increased symptom severity and a poorer prognosis for both conditions. Thus, Dr. Erin Krebs, recipient of an FY07 PTSD Concept Award, is currently investigating the relationship between PTSD and chronic pain among veterans receiving care in the VA health care system. To accomplish this, Dr. Krebs is extracting longitudinal clinical and health care utilization data of veterans from the Veterans Integrated Service Network 11 to assess whether pain affects the diagnosis and treatment of PTSD and to evaluate the effects of PTSD/pain comorbidity on the utilization of mental health, primary care, and pain-related health services. In addition, Dr. Krebs is investigating the importance of several potential covariates, including psychiatric diagnoses, medical comorbidity, VA clinical site, race, gender, and era of service on the utilization of VA health care services and medications. Ultimately, data obtained from these studies may help to determine what targeted interventions are needed to improve the outcomes of veterans with PTSD and comorbid pain.



Cognitive Behavioral Therapy for Nightmares in OEF/OIF Veterans

Richard Ross, M.D., Ph.D., and Gerlinde Harb, Ph.D., Philadelphia Research and Education Foundation, Philadelphia VA Medical Center, Philadelphia, Pennsylvania

A large number of veterans returning home from OIF/OEF have psychological symptoms related to traumatic combat exposures, including recurring nightmares and insomnia. These nightmares are highly distressing, typically do not respond adequately to treatment, and often persist after the resolution of other symptoms of PTSD. Imagery rehearsal (IR) is a form of psychotherapy in which patients use imagery to alter disturbing aspects of the recurring nightmare and then rehearse the new dream daily. Dr. Richard Ross from the Philadelphia Research and Education Foundation and the Philadelphia VA Medical Center received an FY07 Intramural PTSD Investigator-Initiated Research Award to investigate the efficacy of IR in treating nightmares and insomnia in OIF/OEF veterans.

Drs. Ross and Harb will recruit 160 OIF/OEF veterans enrolled in treatment for PTSD at the Philadelphia VA Medical Center and the VA Connecticut Health Care System in West Haven, Connecticut for this study. Participants will complete a battery of baseline assessments, including neuropsychological testing, to evaluate PTSD, nightmares, and sleep quality. Evidence of mild to moderate TBI will be obtained. Participants will then be randomized to receive one of two treatments weekly for 6 weeks: (a) psychoeducation about PTSD and nightmares and standard cognitive behavioral therapy for insomnia (PPCI). The investigators will collect follow-up data from participants immediately following the end of treatment and again after 3 and 6 months. A possible peripheral biomarker of the sleep disturbances in PTSD (salivary alpha-amylase as an indicator of sympathetic nervous system activity) will be measured before and after the treatment intervention. Currently, the investigators have received approval from the Philadelphia VA Medical Center, and they have been recruiting participants. The results of this study will enhance the understanding of the effectiveness of cognitive-behavioral therapy for recurring nightmares and insomnia in PTSD, will indicate whether TBI is a significant moderating factor, and may help in explaining the biological mechanisms of the sleep disturbances in PTSD. Positive results would suggest that IR with PPCI could reduce the intensity and frequency of nightmares and improve quality of life for OIF/OEF veterans.

Family-Based Intervention with Traumatized Service Members and Their Young Children

Ellen R. DeVoe, Ph.D., Boston University, Boston, Massachusetts

The ongoing wars in Iraq and Afghanistan (OEF/OIF) have been especially challenging for military families with very young children (birth–5 years) due to more frequent and lengthier deployments and a higher exposure to combat among deployed personnel. Young children and parents in OEF/OIF families are faced with prolonged deployment-related separation, and the child-parent relationship may be compromised when a service member parent returns from war with combat stress or other deployment-related difficulties. Thus, with funding from an FY07 Intramural PTSD Investigator-Initiated Research Award, Dr. Ellen DeVoe is investigating the impact of PTSD and deployment separation on very young children in OEF/OIF families.

The primary aim of this project is to develop and test the effectiveness of a home-based reintegration program entitled Strong Families Strong Forces to mitigate the impact of deployment separation and the legacy of combat in service members returning from war on young children and on the child-parent relationship. Dr. DeVoe and her team have conducted over 80 interviews with service members, their spouses and partners, and with key informants to explore the effects of war zone-related trauma on reintegration, parenting, and child-parent relationships. Findings from these interviews have informed the development of the Strong Families Strong Forces Program, and a pilot test of the program has been completed. A randomized clinical trial is under way in which 128 OEF/OIF families with young children are assigned either to the treatment group or to a wait-list comparison group. Assessments, including a videotaped structured play observation of the service member parent and his or her young child, are conducted pre-, post-, and 3 months following treatment to evaluate the quality of child-parent relationships, parental mental health, parenting, and child developmental status. The outcomes of this research will assist in elucidating the impact of war-related trauma and deployment separation on very young children and their relationships with their military parent(s), and will result in a military relevant intervention that may benefit parents with PTSD and their young children.

A Longitudinal Study of PTSD Trajectory, Comorbidity and Mental Health Care Service Utilization in Reserve and National Guard Forces

Sandro Galea M.D., Columbia University Medical Center New York, New York
Robert Ursano M.D., Uniformed Services University of the Health Sciences, Bethesda, Maryland

Reserve forces and the Army and Air National Guard have become essential to operations in recent OIF/OEF operations, taking on key combat and supporting roles for longer periods of time. Despite this increasing role in combat operations, there is a limited understanding of determinants of mental health and service utilization among these members of the Armed Forces. These service members face unique stressors such as potentially unanticipated departure from families and regular employment. However, they are also in a unique situation that may potentially provide resilience such as the social support of family and friends, military unit cohesion, and reintegration into workplace upon return. Despite a growing number of studies on the impact of combat on military personnel, there has been little research on the determinants of mental health and mental health service utilization among members of the Reserve and National Guard. To address this, Dr. Sandro Galea at Columbia University Medical Center and Dr. Robert Ursano at Uniformed Services University of the Health Sciences are developing, piloting, and implementing a structured survey in these service members. The overall goal of this project is to assess the prevalence of PTSD and other mental illnesses as well as health service utilization among a representative sample of Reserve forces (Dr. Galea) and National Guard troops (Dr. Ursano). The surveys were developed to take into account life course experiences together with combat history, other military experience and civilian traumatic event experience as determinants of mental health. The trajectories of PTSD and comorbidities over time will also be documented. Using this standardized survey, the investigators will have a comprehensive lifecourse perspective to assess potential determinants of mental health and mental health service utilization in this group. Thus far, 1,000 Reserve Soldiers and 1,000 National Guard troops have completed the survey. Preliminary analysis of the data and continued follow-up is under way. The investigators hope that the findings from this work will guide efforts to enhance any protective factors that are identified and buffer any potential adverse consequences in these groups. This study is the first major step in the scientific field to fill this important gap in knowledge.

Assessing Pressure-Mediated Effects on Blast-Induced Traumatic Brain Injury

Mikulas Chavko, Ph.D., Naval Health Research Center, Silver Spring, Maryland

Many troops involved in active combat are at risk of developing disabling, neurological disorders from blast waves. As such, a direct recording of pressure waves inside the brain during exposure to blast can potentially be useful in discriminating between contributions of different mechanisms resulting in injury. Thus, with funding from an FY07 Intramural TBI Investigator-Initiated Research Award, Dr. Mikulas Chavko at the Naval Health Research Center is focusing on the identification of potential pathways in which blast energy is transferred to brain tissue using microfiber pressure sensors in addition to detecting blast wave propagation through the body using a rat model of blast injury. To date, Dr. Chavko's studies characterizing blast energy transmission into the brain in rats exposed to a moderate level of blast overpressure (BOP) in three orientations—head facing the blast wave, one side of the body exposed to the blast wave, or with back to the blast—have revealed a differential effect of blast exposure in animals with respect to their orientation to BOP. Measurement of the pattern of the shock wave in animals has indicated higher shock wave amplitude in the brain with the head-on orientation as well as differences in the shape of the shock wave with respect to the orientation of the head when exposed to BOP, suggesting that shock waves can enter the body and tissues from different angles and are reflected by surrounding tissues and change shape. Dr. Chavko has also investigated whether pressure wave diffraction is a significant source of pressure inside the body. Here, animals were placed inside PVC tubing to protect against BOP, exposed to blast, and the shock wave was measured in the brain. Data from this study revealed that pressure detected in the rat brain is contingent on the orientation to the blast direction and further suggested that pressure waves enter the protective tube and body by diffraction, moving in an opposite direction to the blast wave. Ultimately, the data generated from the current and future investigations can be applied to the better design of protection against the effects of BOP on the brain and body.

Designing Effective Therapeutic Interventions for Mild TBI/PTSD Using Interactive Virtual World Environments

Charles Levy, M.D., North Florida/South Georgia Veterans Health System, Gainesville, Florida

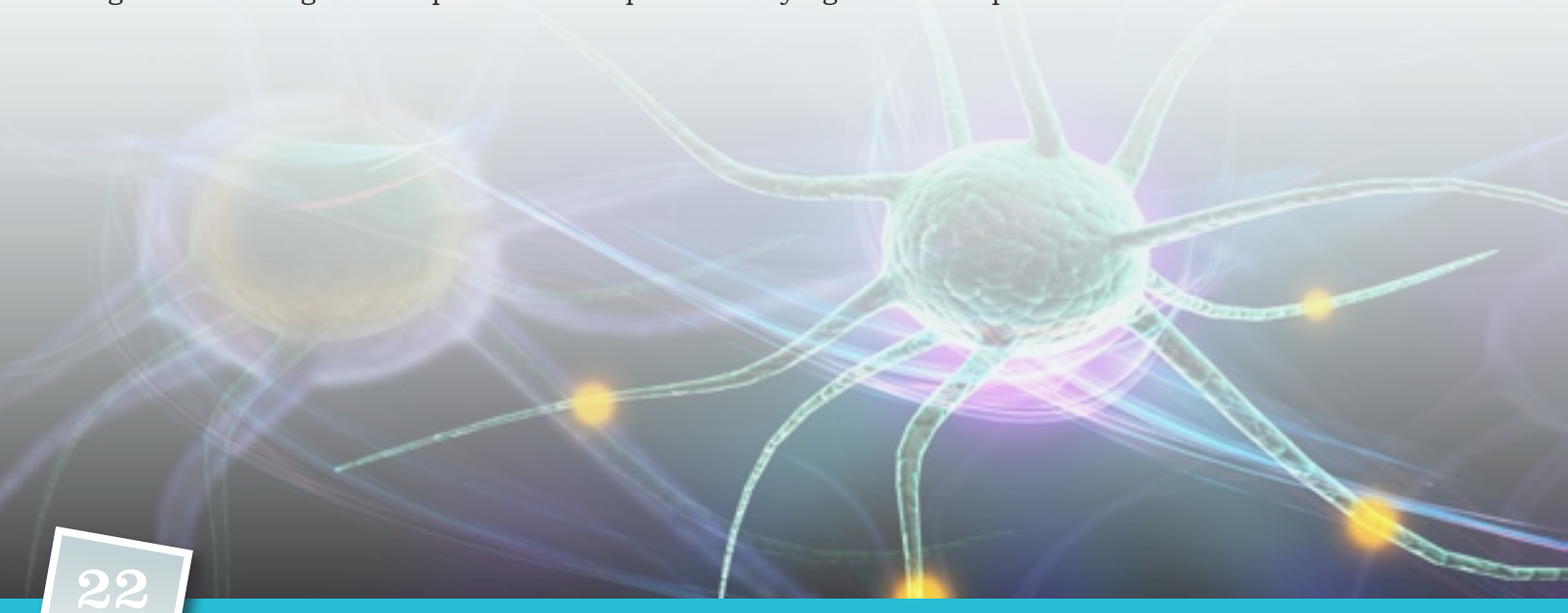
Treatment for mild traumatic brain injury (mTBI) and PTSD typically consists of medication and traditional psychotherapy, often demanding frequent travel to a clinic, a potential hardship for many veterans. Thus, with funding from an FY07 TBI Concept Award, Dr. Charles Levy sought to leverage combat veterans' comfort and familiarity with communications technology and immersive environments (through cell phones, the Internet, and video games) and build a prototype of a virtual world environment (VWE) in which to conduct therapy. To initiate the development of a working prototype VWE, Dr. Levy first assembled clinical and technology teams as well as an advisory panel consisting of national experts in virtual reality, telehealth, and mental health. Following the establishment of overall project goals and the roles and responsibilities of each team, different virtual scenarios were considered including a grocery store, home environment, and a virtual Iraq. Of these, the grocery store was the preferred virtual scenario. A virtual grocery store was constructed that allowed a patient and a therapist to simultaneously occupy different avatars in the store from separate personal computers. Avatars could select grocery carts, navigate the store, choose items from shelves, open a wallet, and check a personal digital assistant within the VWE. The therapist accompanying the veteran in the store could select the number of shoppers, their ethnic appearances, the amount of money in the wallet, and could arrange a collision with another shopper. The final prototype was deemed relevant by clinicians treating returning combat veterans with mTBI/PTSD to provide multiple levels and types of cognitive tasks and emotional challenges. Future investigations will further refine and ultimately test the utility of VWEs in assisting combat veterans to overcome barriers that block successful social reintegration.

Small Molecule Activators of the TRK Receptors for Neuroprotection

Nicholas J. Webster, Ph.D., Veterans Medical Research Foundation of San Diego

TBI is one of the major causes of mortality and morbidity in children and young adult civilians as well as among active duty military personnel. TBI usually results in the loss of neurons within the region of the brain known as the hippocampus, an effect that can occur over a period of many days following the insult. Despite improvements in surgical treatment of the primary insult, there are currently no therapies that provide neuroprotection to mitigate this secondary or delayed damage subsequently leading to poor prognosis and chronic cognitive impairment. It is well known that the neurotrophins acting through the nerve growth factor Trk receptors promote survival of multiple neuronal cell types and stimulate in vitro neuronal regeneration. Although preclinical and clinical findings suggest that neurotrophins are a promising therapy for TBI, they are not good drug candidates due to their poor pharmacokinetic behavior and bioavailability at the desired targets. So a lot of effort has been devoted to the search for novel small-molecule activators that will mimic the desired neuroregenerative responses of neurotrophins.

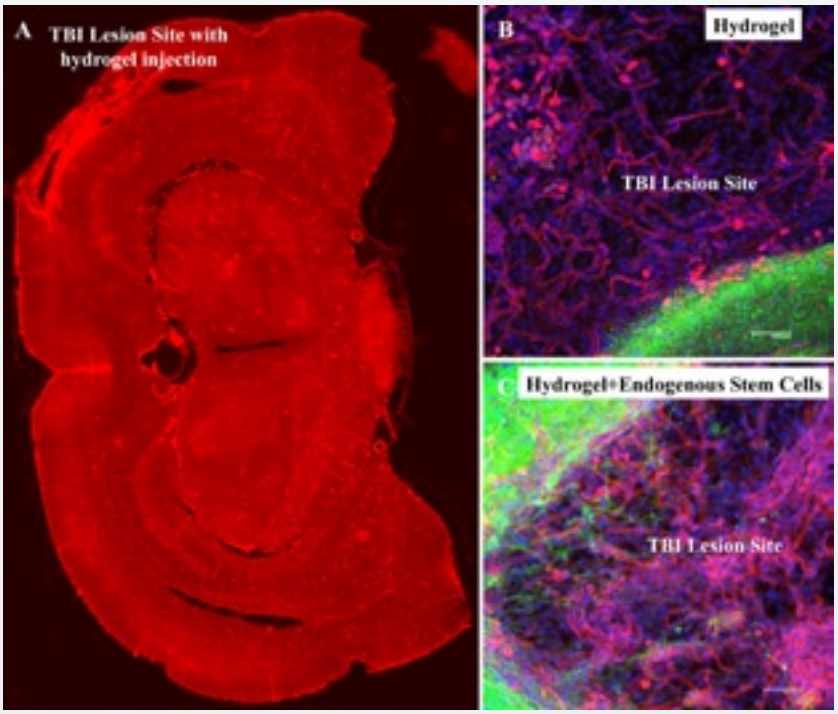
Dr. Webster, a recipient of an Intramural TBI Investigator-Initiated Research Award, is focusing on the development of neuroprotective drugs that will activate the Trk receptors to prevent the neuronal cell death following TBI and improve cognitive function. To date, Dr. Webster and his colleagues, Dr. Stan Krajewski at the Burnham Institute for Medical Research and Dr. Michael Pirrung at the University of California, Riverside, have (1) identified the lead drug 5E5 and 38 other promising compounds based on their ability to activate the TrkB receptor, (2) completed an in vivo evaluation of the neuroprotective effects of 5E5 utilizing two mouse models of neurodegeneration, and (3) tested their lead drug 5E5 in a controlled cortical impact model for brain injury. The in vivo results indicated that treatment with 5E5 delayed the onset of cognitive impairments and improved the ability of the mice to learn spatial information when given before or after the onset of symptoms in both models of neurodegeneration. The drug also exerted a neuroprotective effect, reduced the magnitude of the brain injury as measured by a smaller contusion area, and improved motor skills in the cortical impact model of TBI. With funding from an FY09 Investigator-Initiated Research Award, Dr. Webster, Dr. Krajewski, and Dr. Pirrung will continue preclinical development studies of neuroprotective agents activating Trk receptors in the hope of identifying novel therapeutic modalities for TBI.



Brain Tissue Regeneration After Traumatic Brain Injury

Ning Zhang, Ph.D., Clemson University, Clemson, South Carolina

Currently, millions of individuals in the United States are suffering from TBI. Following a TBI, brain tissue injury and inflammation result in the swelling of brain structures within a finite space. Prolonged cell dysfunction and poor neural regenerative repair at the TBI site can lead to the formation of a lesion or cavity that is associated with prolonged neurological impairment. Despite tremendous effort in neuroprotection and managing tissue damage and inflammation following TBI, current therapies have not been successful in improving mortality rate and neurological outcome. This is largely due to the inability of these treatments to revascularize and repopulate the lesion with functional neural cells. With funding from an FY07 TBI Concept Award, Dr. Ning Zhang of Clemson University sought to structurally repair the post-TBI brain tissue lesion site pre-engineered with a complete vasculature network (Figures A and B) using a specially designed injectable neural biocompatible hydrogel system. By delivering a spectrum of signaling molecules, a sequential neuro-regenerative response is stimulated to regenerate brain tissue from endogenous neural stem cells (NSCs).



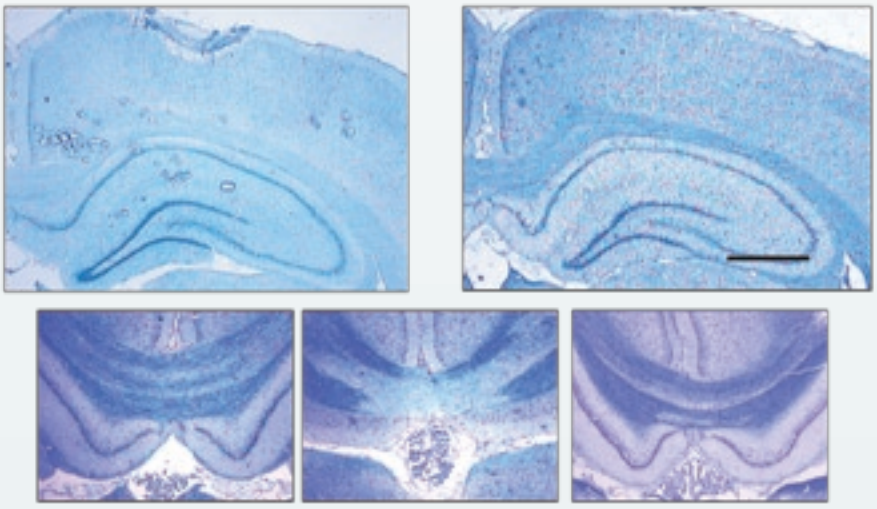
Dr. Zhang has designed, synthesized, and optimized a series of synthetic hydrogel systems that could successfully be utilized for neural applications. The recruitment efficiency of endogenous neural stem cells using signaling molecule-loaded hydrogels was examined in brain tissue after TBI, with data revealing that signaling molecule-loaded hydrogel recruited more endogenous neural stem cells and differentiated into neural cells at TBI site (Figure C). With respect to the formation of the vasculature network, hydrogel was injected into the lesion site 2 days following TBI in adult male rats. Data generated from immunohistochemical and histological analyses revealed that the maximal number of site-specific recruited endogenous NSCs at the TBI lesion cavity occurred in animals administered special-signaling molecule-loaded nanoparticles and hydrogel. These cells survived better and accumulated at the lesion, leading to improvements in the neurological outcome in the rats compared to other groups. Here, Dr. Zhang demonstrated that nanoparticles could release neurotrophic factors for up to 8 weeks with growth factors determined to be bioactive and able to induce endogenous neural stem cells to differentiate into neurons. Future investigations will focus on translating these findings into a clinical setting in an effort to develop medical products utilized for the structural and functional recovery of TBI patients.

Multidrug Treatment of Traumatic Brain Injury

Peter Bergold, Ph.D., SUNY Downstate Medical Center, Brooklyn, New York

There are currently no drugs available to effectively treat TBI despite a growing need in the military for neuroprotective interventions. Past studies have focused on single drug therapies that have had little clinical success. Dr. Peter Bergold of SUNY-Downstate Medical Center received an FY07 TBI Concept Award to develop a multidrug cocktail for the treatment of TBI.

Dr. Bergold initially established a set of neurobehavioral tasks that discriminates between mild and moderate TBI in rats. Drugs, singly and in combination, were screened by dosing them 1 hour after injury in the controlled cortical impact animal model of TBI. One week later, drug combinations were tested for synergy on the hierarchy of behavioral tests. As monotherapy, only minocycline improved acquisition of the massed version of active place avoidance that required memory lasting less than 2 hours. Minocycline-treated animals, however, were impaired during the spaced version of the same avoidance task that required 24-hour memory retention. Co-administration of n-acetylcysteine (NAC) with minocycline improved spaced learning suggesting a synergistic enhancement of memory. Examination of brain histology 2 weeks after injury suggested that minocycline plus NAC preserved white, but not grey matter, since lesion volume was unaffected, yet myelin loss was attenuated. Dr. Bergold recently received additional FY09 funding from the PH/TBI Research Program to continue these studies with the ultimate goal to get this drug combination into clinical trials.



Multi-Family Group Intervention for OEF/OIF Traumatic Brain Injury Survivors and Their Families

Deborah Perlick, Ph.D., VA Medical Center, Bronx, New York

It has been estimated that close to one-quarter of Soldiers wounded in combat during OEF/OIF have a TBI. While the VA has a developed a system of care to improve the diagnosis and treatment of veterans with TBI, less emphasis has been placed on educational and support programs for caregivers. Family caregivers of TBI patients do not always have the skills and access to resources to allow them to appropriately adjust to the situation and often experience depression, anxiety, poor physical health, financial difficulties, and social isolation. A Multi-Family Group Treatment (MFGT) model, originally developed for schizophrenics and their families, was recently adapted for use with civilian TBI patients (MFGT-TBI). Dr. Deborah Perlick of the VA Medical Center in Bronx, New York, received an FY07 TBI New Investigator Award to evaluate the feasibility and effectiveness of MFGT-TBI in a veteran population.

The MFGT-TBI model consists of a 1-day skills workshop followed by regular meetings of six to eight TBI patients and their families with two clinicians to improve communication and problem-solving skills for 9 months. To adapt the MFGT-TBI to veterans, the 1-day skills workshop was modified to include information on military service, and the overall pace of the intervention will be increased. All participants will be interviewed at baseline and will be reassessed every 3 months during the intervention program and at 3 months following completion of MFGT-TBI to evaluate the program's efficacy at reducing psychiatric symptoms, problem behaviors; increasing reintegration and quality of life among veterans; and reducing caregivers' distress, isolation, and burden. Separate focus groups of veterans, caregivers, and clinicians will be formed following the end of treatment to assess the efficiency of and satisfaction with MFGT-TBI.

Epidemiological Study of Mild Traumatic Brain Injury Sequelae Caused by Blast Exposure During Operations Iraqi Freedom and Enduring Freedom

William Walker, M.D., McGuire Research Institute, Richmond, Virginia

Blast-related TBI is a source of morbidity with an estimated 20% of service members sustaining a mTBI during OIF/OEF. Often mTBI is unrecognized and subsequently may persist as post-concussive syndrome (PCS). Although many returnees report ongoing cognitive, emotional, and somatic symptoms consistent with PCS, the impact of this condition on military and veteran health care services is unknown. As such, with funding from an FY07 Intramural TBI Investigator-Initiated Research Award, Dr. William Walker is conducting epidemiological studies aimed at determining the prevalence and early factors predictive of PCS after blast injury. The persisting effects of blast-related mTBI will also be studied by identifying cognitive and neurological impairments and assessing the utility of quantitative electroencephalography for detecting neurophysiologic abnormalities. To further clarify the scope of residual injury, symptom trajectory and social/vocational functioning in PCS stemming from blast-related mTBI will also be determined. Ultimately, the identification of factors predisposing service members to PCS following blast-related mTBI, as well as the characterization of impairments related to PCS, will assist in the development of targeted secondary prevention, medical, and rehabilitative strategies.

Epigenetic Patterns of TBI: DNA Methylation in Serum of OIF/OEF Service Members

Jennifer Rusiecki, Ph.D., Uniformed Services University of the Health Sciences, Bethesda, Maryland

TBI is being called the “signature injury” of OIF/OEF. While it is known that there is an immediate inflammatory response to TBI, the molecular changes that occur following this type of injury remain largely uncharacterized. Epigenetic mechanisms that are linked to regulation of gene expression, such as DNA methylation, may play an important role in the pathophysiology of TBI. Dr. Jennifer Rusiecki at the Uniformed Services University of the Health Sciences received an FY07 TBI Concept Award to investigate patterns of DNA methylation following varying degrees of TBI in OIF/OEF veterans.

Dr. Rusiecki will identify TBI cases among OIF/OEF veterans using a clinical patient database at Walter Reed Army Medical Center. Control individuals who never received a diagnosis of TBI also will be identified. DNA from serum samples collected prior to first OIF/OEF deployment and upon return from that deployment will be isolated. Methylation will be evaluated in specific promoter regions of several inflammatory cytokines and in repetitive elements throughout the genome. Patterns of DNA methylation will be compared pre- and post-deployment between TBI cases stratified for injury severity and controls. Currently, Dr. Rusiecki is collecting samples for the study. The results of this study will begin to elucidate the molecular mechanism that underlie TBI and could identify potential therapeutic targets.

Deployment-Related Mild Traumatic Brain Injury (mTBI): Incidence, Natural History, and Predictors of Recovery in Soldiers Returning from OIF/OEF

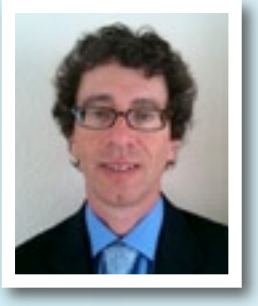
Karen Schwab, Ph.D., Defense and Veterans Brain Injury Center, Walter Reed Army Medical Center, Washington, DC; COL Heidi Terrio, M.D., M.P.H., Evans Army Community Hospital, Fort Carson, Colorado; MAJ Steven C. Lewis, M.D., Womack Army Medical Center, Fort Bragg, North Carolina

Data collected from OIF/OEF veterans at Fort Bragg and Fort Carson indicate that approximately 14%–23% of Soldiers sustain a TBI during deployment. The majority of these injuries are classified as mTBI. While most individuals with mTBI recover within days to a couple of months following the injury, some report injury-related sequelae persisting beyond 3 to 6 months. The high prevalence of mTBI among OIF/OEF veterans highlights the need to better understand the effect of pre-existing and comorbid conditions on the natural history and prognosis of mTBI. Dr. Karen Schwab at the Defense and Veterans Brain Injury Center at Walter Reed Army Medical Center received an FY07 Intramural TBI Investigator-Initiated Research Award to perform a prospective longitudinal study of deployment-related mTBI.

The study investigators plan to collect data from a total of 750 OIF/OEF veterans with mTBI and 750 uninjured Soldiers from Fort Bragg and Fort Carson. All individuals returning from deployment are routinely screened for TBI, and the results of these questionnaires will be used to identify potential cases for the study. Participation in this study will not interfere with routine medical care, and Soldiers with mTBI will receive the usual standard of care treatment. Once enrolled in this study, subjects will participate in a clinical interview, and additional information will be collected related to TBI, neuropsychological status, and pre-existing or comorbid conditions. Telephone interviews will be conducted at 3, 6, and 12 months after baseline assessment to collect follow-up data on the status of TBI sequelae, issues with employment or functional status, depression, anxiety, and PTSD. Currently, the study has recruited a significant population at Fort Carson and is awaiting final approval to move forward with recruitment at Fort Bragg. The data collected in this study will provide important epidemiologic information about the long-term functional effects of deployment-related mTBI among Army Soldiers.

Making Major Advancements Through Collaboration

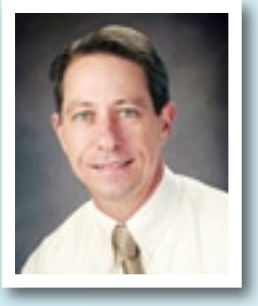
In FY07, the PH/TBI Research Program supported the development of three multi-institutional consortia to address military relevant PH and TBI research gaps. Through the combined efforts of investigators across the country, all three consortia are making an impact on the field. Although several consortia investigators were highlighted within this book, more information can be found in the PH/TBI Research Program Consortia Book.



PTSD/TBI Clinical Consortium:

The mission of the INTRuST (INjury & TRaumatic STress) Clinical Consortium is to improve functioning, wellness, and quality of life for U.S. service members, their families, and caregivers by developing and evaluating novel treatments or interventions to ultimately decrease the impact of military-relevant PH problems and TBI. Dr. Murray Stein, at University of California San Diego serves as Director of the INTRuST Clinical Consortium that is a network composed of a clinical coordinating center at UCSD and 10 clinical sites that will participate in conducting of clinical trials to decrease the impact of military-relevant PTSD and TBI.

- Since no treatment has been proven effective for military personnel returning from deployment displaying a complex array of symptoms resulting from combat exposure, Dr. Ariel Lang is evaluating the effectiveness of a cognitive behavioral therapy called Acceptance and Commitment Therapy (ACT) in veterans suffering from depression, anxiety, and/or postconcussion syndrome.
- Drs. Chris Marx and Ann Rasmusson are conducting a Phase II clinical trial of ganaxolone, a neurosteroid analog that has an established safety profile, in individuals with PTSD, which could be rapidly translated into clinical use if it is shown to be effective in reducing symptoms.
- Dr. Mark George is investigating the novel application of noninvasive Transcranial Magnetic Stimulation of the brain to reduce suicidality in patients with PTSD.
- The self-management of chronic health conditions, such as heart disease, has been shown to improve health outcomes and reduce utilization of emergency health care resources. Dr. Kathleen Bell is conducting a randomized prospective trial to evaluate the impact of individualized scheduled telephone counseling that teaches military personnel self-management techniques to help improve recovery time and return to duty rates in individuals with mTBI and PTSD.



PTSD Multidisciplinary Research Consortium:

The PTSD Multidisciplinary Research Consortium, STRONG STAR (South Texas Research Organizational Network Guiding Studies on Trauma and Resilience), is dedicated to the development and evaluation of the most effective interventions for the detection, prevention, and treatment for combat-related PTSD. The STRONG STAR team is a collaboration of nine partnering investigators led by Dr. Alan Peterson at University of Texas Health Science Center at San Antonio. The ultimate goal of the STRONG STAR consortium is to apply a multidisciplinary approach to improve the lives of service members and veterans by preventing chronic PTSD, thereby contributing to the resilience and long-term health of our fighting forces. The STRONG STAR consortium will conduct 11 clinical studies at 7 sites.

- Preliminary results from a pilot study led by Lt Col Jeffrey Cigrang, investigating the use of a cognitive-behavioral treatment designed for use in integrated primary care clinics demonstrate that 50% of participants no longer met criteria for PTSD 1-month following treatment. A larger follow on clinical trial is planned to further validate this exciting finding.

- Dr. Randy Strong is using a preclinical model to study the impact of early life stressors on vulnerability to PTSD in adulthood. Early results from this study indicate that prenatal stress programs a characteristic neurochemical phenotype, sensitizes the adult to traumatic stress, and prevents the extinction of conditioned fear.

- Dr. Edna Foa will investigate the use of a condensed time line for administration of the empirically validated prolonged exposure (PE) therapy for PTSD in active duty military personnel and recent veterans to meet the demand for more effective and efficient treatments for the growing number of Soldiers that return home with symptoms of PTSD.

- Dr. Patricia Resick also will address the need for more efficient treatments for our fighting forces in a randomized clinical trial evaluating the effectiveness of individual and group-based cognitive processing therapy (CPT) for combat-related PTSD.

- While the military deploys hundreds of mental health professionals to provide services to deployed troops, there is little data on the effectiveness of psychotherapy in deployment/combat settings. Dr. Alan Peterson is leading a pilot study to investigate the use of two different psychotherapies (CPT and PE) in military personnel deployed in Afghanistan that display symptoms of combat operational stress reactions.

TBI Multidisciplinary Research Consortium

The Mission Connect Consortium, led by Dr. Claudia Robertson at the Baylor College of Medicine and Dr. John Holcomb at the University of Texas Health Science Center at Houston, is composed of more than 20 TBI investigators who are combining efforts to reduce disabilities caused by mTBI by focusing on improving diagnosis and treatment of mTBI. Mission Connect scientists and clinicians are addressing the spectrum of research from basic science through clinical trials.

- In an effort to improve mTBI diagnosis and to mitigate the secondary complications of traumatic injuries, consortium investigators are performing baseline neurobehavioral assessments on mTBI patients within 24 hours post-injury. Patients diagnosed with mTBI are being enrolled into a Phase II clinical trial of atorvastatin to determine if delivery of the drug within 24 hours after injury will improve post-concussive symptoms. Secondary outcome measures such as EEG, MRI, and DTI will be performed to determine if these may provide a biomarker for prognosis.

- Studies have shown that outcomes for patients who have suffered a TBI are severely worsened when coupled with hemorrhagic shock. To develop therapies to improve outcomes for these patients, Dr. Claudia Robertson has developed a novel model of mTBI complicated by hemorrhagic hypotension and is testing the neuroprotective effects of erythropoietin (Epo) and the Epo derivative ARA290.

- Dr. Thomas Kent at Baylor College of Medicine and Dr. James Tour of Rice University have developed a new class of treatment using small carbon nanotubes that carry antioxidants and have identified carbon nanotube-based materials that are more potent than current medications for reducing free radical damage caused by traumatic insult to the brain. The investigators are currently testing the safety and toxicity in animal models of mTBI combined with hypotension.

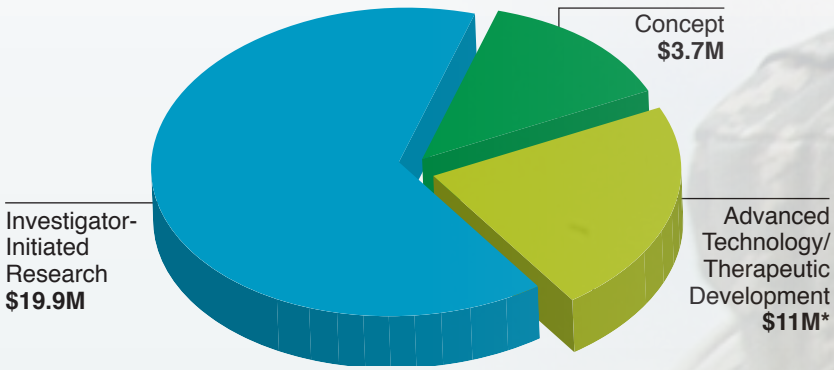
- Dr. Jose Perez-Polo is investigating whether blockade of IL-1 or TNFα receptor signaling using the FDA-approved drugs Kineret (IL-1 receptor antagonist) or Etanercept (antibody to TNFα) in rat models of mTBI will reduce mTBI-induced cognitive and behavioral deficits by decreasing injury-induced acute inflammation in the brain.

- Given the role of the Wnt-GSK-3β/β-catenin signaling pathway in neural growth and development, Dr. Pramod Dash is testing the efficacy of two FDA-approved drugs and GSK-3β inhibitors, valproic acid and lithium chloride, in reducing alterations in cognitive and motor function induced by TBI.

On the Horizon

FY09

In FY09, the PH/TBI Research Program invested $51.1M of the FY09 PH/TBI Appropriation in innovative projects aimed at improving the function, wellness, and overall quality of life for warriors, veterans, families, and caregivers. The majority, $34.6M, was awarded across 3 award mechanisms with $30.5M applied to projects solicited by the FY09 PH/TBI Research Program and $4.1M applied to PH/TBI focused projects solicited through the Defense Medical Research and Development Program (note following figure). Additionally, six applications to the Deployment Related Medical Research Program addressing the PH/TBI topic area were funded for a total of $15.9M. Finally, due to outstanding progress and exceptional scientific merit, $0.6M was applied to 5 FY07 PH/TBI awards.



Funding by Award Mechanism

*Two Advanced Technology/Therapeutic Development projects submitted to the Defense Medical Research and Development Program were funded with FY09 PH/TBI funds.

FY10

For FY10, the PH/TBI Research Program offered the Cognitive Rehabilitation for TBI Clinical Trial Award mechanism. This award is intended to encourage the rapid implementation of clinical trials to assess the efficacy of cognitive rehabilitative therapy for TBI for members or former members of the Armed Forces. Approximately $10M was assigned to the USAMRMC CDMRP for management oversight of these awards.

For more information, visit:
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12-2010