Office of the Assistant Secretary of Defense for Health Affairs

Defense Health Program

Defense Medical Research and Development Program Execution

CDMRP

Department of Defense





U.S. Army Medical Research and Materiel Command

Defense Health Program
Defense Medical Research and Development Program

The Defense Medical Research and Development Program (DMRDP) is a core research program of the Department of Defense (DoD) within the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]) and the focal point for Defense Health Program (DHP) execution of research, development, test, and evaluation (RDT&E) funds. The program's efforts help to fulfill the DHP priority to advance medical research and development (R&D) for wounded warriors and expedite the delivery of products and solutions to service members and their families and advance the state of medical science in areas of the most pressing need. Since fiscal year 2010 (FY10) the DMRDP has funded R&D projects spanning basic research through advanced clinical development.

DMRDP Objectives:

1. To discover and explore innovative approaches to protect, support, and advance the health and welfare of military personnel, families, and communities.
2. To accelerate the transition of medical technologies into deployed products.
3. To accelerate the translation of advances in knowledge into new standards of care for injury prevention, treatment of casualties, rehabilitation, and training systems that can be applied in theater or in the clinical facilities of the Military Health System.

"Our men and women in combat; our wounded warriors; the chronically ill—these are our priorities and these service members and families need our greatest attention."

Jonathan Woodson, M.D.
Assistant Secretary of Defense for Health Affairs

The DMRDP has six major program areas:

- Medical Training and Health Information Services
- Military Infectious Diseases
- Military Operational Medicine
- Combat Casualty Care
- Radiation Health Effects
- Clinical and Rehabilitative Medicine

Each program is managed by a Joint Program Committee (JPC) consisting of tri-service military and non-military medical and programmatic experts and representatives from the Departments of Veterans Affairs and Health and Human Services. These experts provide strategic program management oversight and translate guidance and programmatic goals into actionable R&D.

The OASD(HA) assigned execution management responsibilities to the U.S. Army Medical Research and Materiel Command (USAMRMC) as one of several execution agents to provide strategic and operational management support (see Figure 1, p. 4). USAMRMC assigned operational support responsibility to two primary execution agents, the Office of the Congressionally Directed Medical Research Programs (CDMRP) and the Telemedicine and Advanced Technology Research Center.

Program Execution by the Congressionally Directed Medical Research Programs

The CDMRP execution model utilizes a well-established two-tiered review process, described below, with the ability to provide full life-cycle support to the DMRDP. The CDMRP has a history of providing this type of support since it began in 1992 with a DoD appropriation for breast cancer research. Since then, the CDMRP has grown to encompass multiple targeted programs and has received approximately $7 billion in appropriations through FY12. The CDMRP manages individual research programs with DoD funds allocated via specific guidance from Congress. The CDMRP manages these programs from receipt of funds through the full life cycle of award management with a goal of generating high-impact research products and outcomes. Through FY11, more than 10,000 awards have been made to advance health care solutions via extramural grants, contracts, and cooperative agreements. The two-tiered review process consists of peer review, a criteria-based process where applications are evaluated for their scientific and technical merit by an independent panel of experts including scientists and consumers (individuals or their family members/caregivers afflicted with the subject disease or injury), and programmatic review, where a separate panel constituted by the specific CDMRP research program with different subject area experts evaluates applications for their programmatic relevance and adherence to the vision and mission of that research program.

The programmatic review panel makes funding recommendations to USAMRMC to allocate funds for the panel's respective program. Once awards are made, CDMRP Science Officers employ their expertise to ensure that high-impact research products are rendered from program funds.

In support of the DMRDP, JPCs act as the programmatic review panel and make funding recommendations to the DHP. The CDMRP provides full life-cycle support from program announcement development and solicitation through peer and programmatic reviews and out-year grant management. In FY10, the CDMRP was designated to support DMRDP for execution of two extramural program announcements encompassing basic and applied research overlapping four of six JPC research areas (JPC-2, -5, -6, and -8). The CDMRP was responsible for operational execution of approximately $120 million of $306 million in DMRDP RDT&E funds executed in FY10 (see Figure 2, p. 5). Since FY10, the CDMRP was assigned administrative support and out-year award management for program announcements from JPCs-2, -5, and -8 aimed at basic through translational research in the respective JPC's areas of interest. Final execution of FY11 DMRDP support assignments is ongoing across execution agents.

JPC-2
Military Infectious Diseases Research Program

JPC-5
Military Operational Medicine Research Program

JPC-6
Combat Casualty Care Research Program

JPC-8
Clinical and Rehabilitative Medicine Research Program

Figure 1. USAMRMC Execution Support to the DMRDP Joint Program Committees

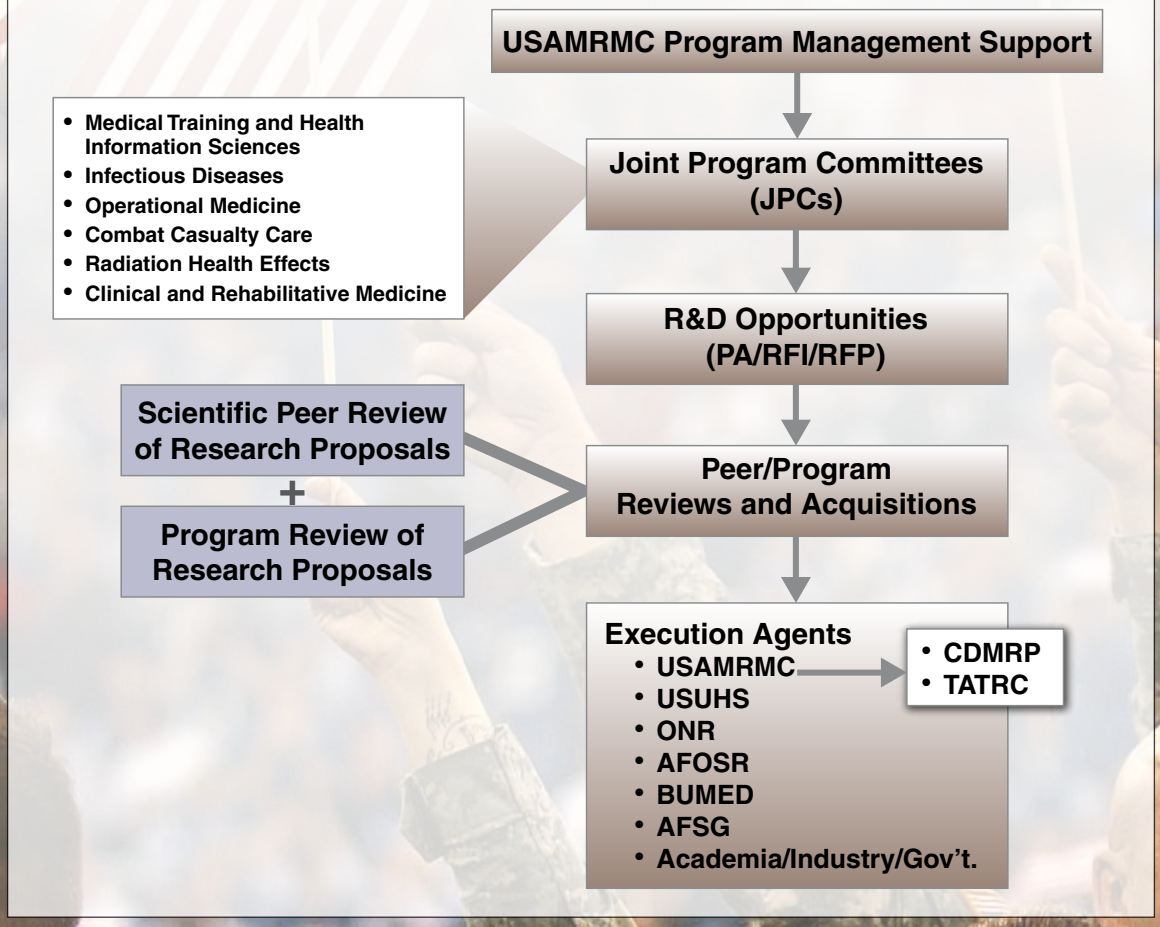
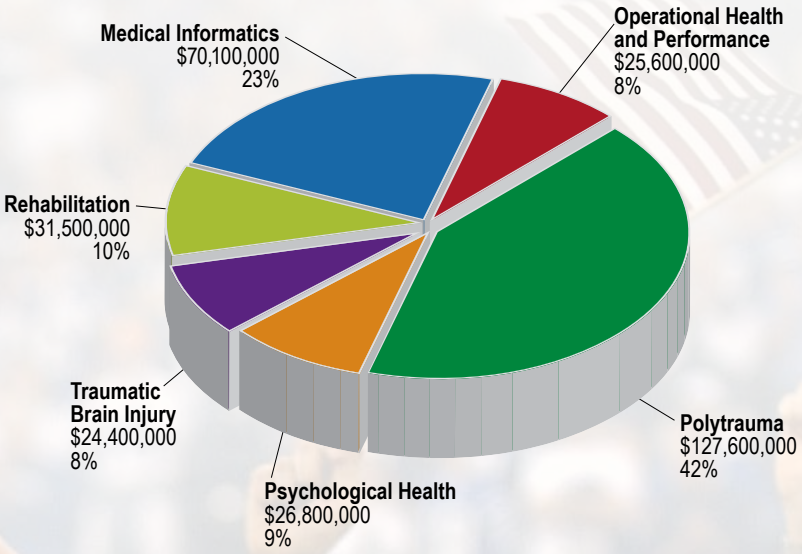
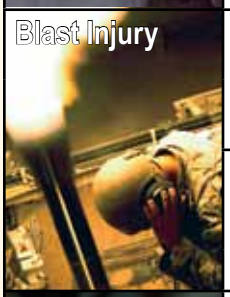


Figure 2. DMRDP FY10 Investment by Project Area



Innovative Approaches to Address the Needs of Service Members, Veterans, and Family Members

The JPCs identify topic areas that represent the most pressing needs on the battlefield and beyond. Program announcements are developed to solicit research proposals to address these topic areas.

Topic Area	Organization	Military Need	Mechanisms	Awards[1]
 Traumatic Brain Injury	Deployment Related Medical Research Program (DRMRP) – JPCs-5,6,8	• Methods to diagnose mild traumatic brain injury (mTBI) that can be used for deployed troops • Epidemiology with emphasis on battle-induced mTBI • Innovative therapies for mTBI	FY08 Advanced Technology/ Therapeutic Development Award	2
			FY08 Hypothesis Development Award	7
	DMRDP – JPC-6	• Mechanisms of TBI • Diagnosis and treatment of TBI • Clinical management of TBI	FY10 Applied Research and Advanced Technology Development Award	7
			FY10 Basic Research Award	1
	DMRDP – JPC-8	• Oculomotor effects of TBI	FY10 Basic Research Award	2
 Blast Injury	DRMRP – JPC-6	• Injury prevention related to blast	FY08 Advanced Technology/ Therapeutic Development Award	1
			FY08 Hypothesis Development Award	1
	DMRDP – JPC-8	• Blast-related ocular injury • Tinnitus	FY10 Applied Research and Advanced Technology Development Award	3
			FY10 Basic Research Award	1
 Polytrauma	DRMRP – JPC-6	• Characterization of oral, maxillofacial, and craniofacial injuries • Novel approaches for repair and treatment of nerve damage • Novel approaches for targeted therapy for hemorrhagic injury	FY08 Hypothesis Development Awards	2
			FY08 Advanced Technology/ Therapeutic Development Award	1
	DMRDP – JPC-8	• Treatment, Restoration and Rehabilitation of Ocular/Visual System Injury • Novel approaches for repair and treatment of nerve damage	FY10 Applied Research and Advanced Technology Development Award	2
			FY10 Basic Research Award	3
			FY12 Clinical Trial Award – Regenerative Medicine, Pain, Sensory System	5
	DMRDP – JPC-6	• Improved evacuation practices • Forward surgical applications	FY10 Applied Research and Advanced Technology Development Award	3

[1] Many of these awards overlap multiple JPCs in their focus area association. The primary association is provided here.

Topic Area	Organization	Military Need	Mechanisms	Awards[1]
 Wound Infection	DRMRP – JPCs-2,6,8	• New treatment protocols, drugs, biologics, and devices to reduce wound-related infections and accelerate wound healing • Methods and technologies for prevention of the formation of bacterial biofilms in wounds	FY08 Hypothesis Development Award	6
			FY08 Advanced Technology/ Therapeutic Development Award	1
			FY08 Clinical Trial Award	1
	DMRDP – JPC-2	• Wound infection prevention and management • Antimicrobial countermeasures • Development of new methods for rapid multi-pathogen/multi-phenotype detection of multidrug-resistant organisms (MDROs) • Development and preclinical testing of novel chemotypes (chemical classes/materials) and/or biologics as potential therapeutics or prophylactics	FY10 Applied Research and Advanced Technology Development Award	8
			FY10 Basic Research Award	9
			FY11 Military Infectious Diseases Clinical Trial Award	2
			FY11 Military Infectious Diseases Applied Research Award	7
			FY11 Military Infectious Diseases Basic Research Award	7
Blood Products & Safety	DRMRP – JPC-6	• Pathogen inactivation of whole blood • Hemorrhage control methods	FY08 Advanced Technology/ Therapeutic Development Award	2
 Psychological Health	DRMRP – JPC-5	• The impact of military life on quality-of-life/ health indices among spouses, partners, caregivers, and co-resident families • Detection, prevention, and etiology of post-traumatic stress disorder (PTSD)	FY08 Advanced Technology/ Therapeutic Development Award	5
			FY08 Clinical Trial Award	3
	DMRDP – JPC-5	• Diagnosis and treatment of PTSD and deployment-related psychological health problems • Military family and community health and resilience	FY10 Applied Research and Advanced Technology Development Award	7
			FY10 Basic Research Award	9
 Rehabilitation	DRMRP – JPCs-6,8	• Novel rehabilitation techniques, including virtual reality, non-surgical treatment of extremity injuries and physical rehabilitation • Characterization of oral, maxillofacial and craniofacial injuries • Prosthetics	FY08 Hypothesis Development Award	7
			FY08 Advanced Technology/ Therapeutic Development Award	2
	DMRDP – JPC-8	• Neuromusculoskeletal injuries • Acute and chronic pain management • Rehabilitation and restoration of sensory systems after traumatic injury	FY10 Applied Research and Advanced Technology Development Award	9
			FY10 Basic Research Award	5
			FY12 Clinical Trial Award - Regenerative Medicine, Pain, Sensory System	6
 Device Development	DRMRP – JPC-6	• Development of U.S. Food and Drug Administration (FDA)-approved field-deployable devices to assess injury parameters	FY08 Advanced Technology/ Therapeutic Development Award	1

[1] Many of these awards overlap multiple JPCs in their focus area association. The primary association is provided here.

A Consumer's Perspective…

The DMRDP's commitment to provide innovative medical solutions for military personnel is embodied in the wounded warriors reintegrated into active duty or civilian society following traumatic injury. They are living examples of technology in action and the direct beneficiaries of R&D funded by the DMRDP.

Wounded Warrior, Heart of a Champion: Melissa Stockwell

On April 13, 2004, 1st Lieutenant Melissa Stockwell's life changed forever. Deployed to Iraq 3 weeks earlier, she was working as a transportation officer leading supply convoys from one point to the next. On that fateful day, Melissa was traveling on a routine convoy through central Baghdad when her Humvee was hit by a roadside bomb. The bomb, and subsequent injuries, resulted in amputation of her left leg above the knee during emergency, lifesaving surgery at the American hospital in Baghdad. She was soon transported home from Iraq for treatment at the Walter Reed Army Medical Center. Melissa spent the next year recovering from infections, regaining her strength, learning to walk with a prosthetic leg, and becoming independent again. A positive, motivated attitude helped her to resume a normal life and to dream of even greater things. Once she began walking with a prosthetic leg, her lifelong passion for sports and the thrill of competition drove her to get back in the game. With the help of the Wounded Warrior Project, Disabled Sports USA, and Achilles, it was not long before she was skiing the mountains of Breckenridge, Colorado, and running in the NYC marathon. "I really learned that losing a leg didn't have to stop me from doing anything I wanted to do with my life. In the year after my injury, I had already done more with one leg than I ever would have imagined doing with two legs."

In April 2005, Melissa medically retired from the U.S. Army, earning a Purple Heart Award and a Bronze Star Medal. She decided to return to school to become a prosthetist, learning how to fit other amputees with artificial limbs. Throughout her recovery, her love of sports never wavered. Soon after school started, she learned about the Paralympics, the international competition for athletes with physical disabilities. This was a venue for her to not only compete on the second largest athletic stage in the world (second only to the Olympics), but one in which she could once again proudly wear the uniform of her country. With the support of her family and friends, her hard work and dedication to practicing endless laps in the pool helped her to achieve her dream of making the 2008 U.S. Paralympic swim team. "Competing in Beijing was one of the most incredible things I have ever done and [I] will take my experiences there with me wherever I go."

After the Beijing Paralympics, Melissa returned home to Chicago to resume her training as a prosthetist and to continue her athletic goals. Soon after she returned, she learned of the CDMRP and took part in her first session as a consumer advocate for the DRMRP. "It was here where I was able to vote on the services and programs that I felt were most important to the returning veterans. I was able to influence where the financial resources would go and what programs the government would support dealing with deployments, prosthetic research, and more. It is my hope that people like me could benefit along with all the other returning wounded soldiers. My experience as a consumer advocate was great and I would highly recommend it. I left with a feeling of satisfaction that I made a difference and hoped that others would reap the rewards of the work we all put in and benefit from the choices we had made."

DMRDP Awards: Research Highlights

Prosthetic Knee-Ankle-Foot System with Biomechatronic Sensing, Control, and Power Generation

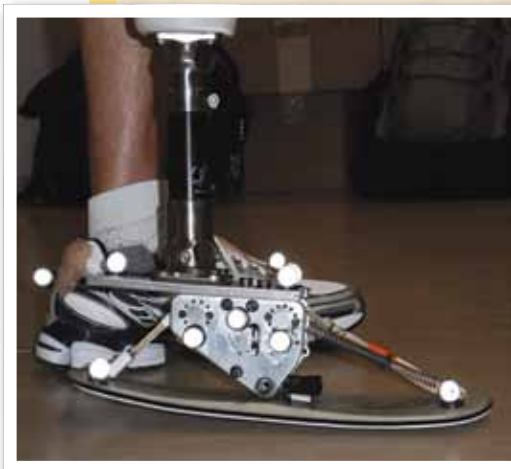
Arthur Kuo, Ph.D. – University of Michigan

Hugh Kerr, Ph.D. – Massachusetts Institute of Technology

Glenn Klute, Ph.D. – Seattle Institute for Biomedical and Clinical Research

The number of veterans living with lower limb amputees is an expanding population in the armed forces and the Department of Veterans Affairs system. Amputees experience reduced comfort, endurance, and mobility, decreasing their ability to return to active duty and to participate in the workforce. Computer-controlled prosthetic devices have improved some aspects of mobility, but the energy expenditure of walking remains much higher for amputees than able-bodied persons. A team of researchers brought together under an FY08 DRMRP Advanced Technology/ Therapeutic Development Award is working to develop new technology to improve mobility with computer-controlled prosthetic knees and ankles that will harvest energy from the user and thus have lower external energy requirements than existing devices.

Dr. Arthur Kuo at the University of Michigan, Dr. Hugh Kerr at the Massachusetts Institute of Technology (MIT), and Dr. Glenn Klute at the Seattle Institute for Biomedical and Clinical Research aim to develop a prosthetic knee-ankle-foot system that actively coordinates the joints using multimodal biomechatronic sensory data to integrate user intent and control. A key innovation in the project is how the knee and ankle-foot prostheses will be computer-controlled but self-powered by harvesting energy from the user. The researchers hypothesize that sufficient energy can be generated from passive knee motion to power a prosthesis with minimal user effort and that elastic energy can be captured from the ankle action to assist with a pushing off motion.



The electromechanics/electronics integration components of prototype prostheses are being developed and fabricated by the Michigan and MIT groups. Knee and foot prototypes are being tested by amputees with encouraging preliminary results. The Seattle group is developing a prosthesis-embedded instrument to measure and record environmental, physiologic, activity, and performance/ diagnostic metrics, to include developing sensing algorithms to detect ambulatory mode, user intent, and varying terrain.

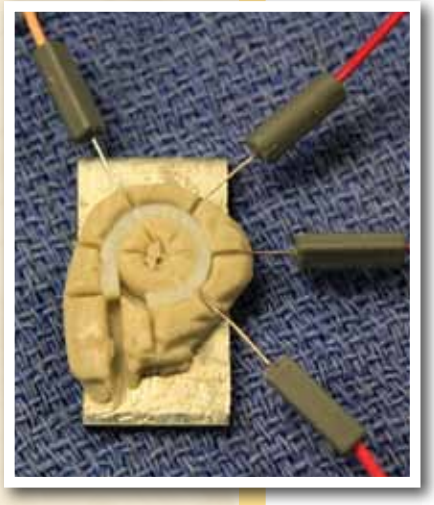
This project has the potential to significantly improve the function of leg prostheses by reducing the energy need from the user and offering improved adjustment to uneven terrain, like stair descent. Furthermore, the project will develop new devices for assessing and quantifying the long-term usage of prostheses in daily living, providing a valuable data resource for future technological advances.

Reconstruction of Facial Cartilage Frameworks Using Electromechanical Reshaping

Brian Wong, M.D., Ph.D., University of California, Irvine

For more than a century, surgeons have envisioned reshaping tissue to correct defects in the face and neck resulting from combat injuries, trauma, burns, or birth defects. Combat-related injuries sometimes require complete reconstruction of the ear or nose, which requires vast amounts of cartilage. Cartilage is a flexible connective tissue with properties of both hard and soft tissues found in the nose, ear, larynx, and trachea. Although ribs harbor massive amounts of cartilage, most of it warps and cannot be used for facial reconstruction using conventional methods. Dr. Wong and colleagues have developed a novel technology referred to as electromechanical reshaping (EMR) to allow surgeons to bend cartilage into the shape they desire by simply inserting platinum-plated needles and then applying electrical current. To provide the necessary information to bring EMR into surgical practice, Dr. Wong received funding from an FY08 Advanced Technology/Therapeutic Development Award to reconstruct ear defects in animals using EMR.

Dr. Wong first studied the anatomy of rabbit rib cages and ears to determine the best rib cartilage for production of a graft and the best site for implantation into the ear. Based on length, thickness, and width measurements as well as a statistical analysis of rib and ear geometry, he identified the best grafting cartilage (sixth rib) and the implant site (base of the ear). To reshape the grafting cartilage, prototype reshaping jigs were designed and built based on geometrical analysis of cartilage in the ear. To produce consistent and uniform thickness grafts, Dr. Wong's team developed and practiced graft extraction and closure from the thoracic donor site in animals. A series of numerical simulations and reshaping experiments were then performed to determine optimal electrode placement geometry, voltage, and application time and the results showed that a low voltage can reshape cartilage grafts within several minutes and without the heat generation.



Dr. Wong concludes that EMR can provide a new means to reshape rib cartilage and existing cartilage tissues that may then be fully exploited to rebuild face and airway structures of both military personnel injured in combat and civilians with injuries or birth defects. Since EMR is a low-risk, needle-based technology, it is amenable to endoscopic methods, potentially converting traditionally open operations used in major airway reconstructive surgery to a minimally invasive procedure. Dr. Wong believes EMR can be rapidly moved into advanced clinical development and could represent a major breakthrough in facial/aural rehabilitative reconstructive surgery. In fact, EMR technology patented in 2008 (under both NIH and DoD support) is already being commercialized by two companies and may have applications in orthopedics and ophthalmology as well.

Exploration of a Novel Persistent Reversal of Pathological Pain

Linda Watkins, Ph.D., University of Colorado, Boulder

Persistent neuropathic pain, resulting from nerve injury or inflammation, affects millions of Americans and is a significant area of concern for those treating our warfighters and veterans. Chronic pain has been shown to be poorly managed by currently available therapeutics and has resulted in staggering medical costs for our economy. Most of the therapeutics for chronic pain management specifically target neurons. However, it is now known that spinal glia (astrocytes and microglia) play an important role in facilitating and maintaining neuropathic pain. Dr. Linda Watkins and her team at the University of Colorado at Boulder hope to find methods to conquer chronic pain and prevent acute pain from becoming chronic by focusing a novel therapeutic on these spinal glial cells. Using a DMRDP FY10 Basic Research Award, Dr. Watkins is investigating a novel, nonopiate, nonaddictive therapeutic, adenosine 2A receptor, A2AR agonists, that target spinal glia cells rather than neurons.

Preliminary data for A2AR agonists show that a single intrathecal (into the cerebrospinal fluid surrounding the spinal cord) dose of A2AR agonists powerfully resolves neuropathic pain for over 4 weeks in an animal model. Dr. Watkins hypothesizes that A2AR agonists create these remarkable effects by causing glia to shift from a proinflammatory state that amplifies pain to an anti-inflammatory state that resolves pain through perseverant release of the anti-inflammatory cytokine interleukin-10 (IL-10). Early work on the project has focused on working with animal models of pain to define the breadth of applicability across models of inflammatory neuropathy, the “window of opportunity” between preventing chronic pain from ever developing if the therapy is delivered near the time of injury or reverse recently established pain to prevent the chronic condition, and the breadth of route administration between intrathecal administration versus oral administration post injury. The team will also look at basic molecular mechanisms underlying the effects observed to inform future drug targeting and development.

This novel approach of shifting spinal glia from a pain-enhancing proinflammatory state to a pain-resolving anti-inflammatory state could lead to a novel and powerful approach for pain control with vast potential to help those in pain.

A Transportable Pathogen Reduction System for Treatment of Whole Blood

Raymond Goodrich, Ph.D., Caridian BCT Biotechnologies, Lakewood, Colorado

During combat, fresh whole blood (FWB) is used to treat life-threatening blood loss resulting from traumatic injuries when screened blood components are unavailable. While FWB may be critical in saving the lives of injured warriors, it is often transfused without any donor screening nor standard viral testing. Additionally, FWB is used without leukoreduction, which introduces a large number of viable white blood cells into severely injured patients, potentially increasing the rate of infections among other serious immunological complications.

Dr. Raymond Goodrich and his research group, recipients of an FY08 DRMRP Advanced Technology/Therapeutic Development Award, aim to develop a portable, disposable device for pathogen reduction in FWB that will minimize the risk of infectious disease transmission as well as potential adverse immunological effects of bypassing leukoreduction. With the award, Dr. Goodrich and his team are developing a prototype for the device (named the Mirasol System for Whole Blood) that uses riboflavin (vitamin B2) and UV light to rapidly inactivate pathogens and leukocytes in whole blood. Validation and optimization studies are being conducted for the device's effectiveness against pathogens including bacteria, viruses, and parasites. Dr. Goodrich plans on assessing the quality and safety of FWB for use in patients following Mirasol System treatment under various storage conditions. When completed, the Mirasol System will undergo operational testing in simulated combat environments.

Episcleral Therapy for IED-Related Ophthalmic Injury

Ricardo Carvalho, M.D./Ph.D., Targeted Therapy Technologies, Inc.

Vision loss from ocular trauma and brain injury caused by improvised explosive devices (IEDs), among other sources, is a pressing concern in current battlefield engagements.

There are currently no therapeutic interventions available for ocular trauma injuries, which include retinal detachment, retinal ganglion cell (RGC), and photoreceptor apoptotic death. The drug brimonidine and preclinical compound EC-4565 have demonstrated retinoprotective efficacy in clinical studies (brimonidine) and animal models (EC-4565). Both drugs modulate retinal ganglion cell loss in several models, and EC-4565 also preserves photoreceptor viability in a transgenic animal model of retinodegeneration. Taken together, these drugs could be neuroprotective to slow or stop vision loss resulting from TBI-related ocular trauma and may also offer synergistic benefits. Dr. Richard Carvalho of Targeted Therapy Technologies, Inc. is using an FY10 DMRDP Applied Research and Advanced Technology Development Award to develop these treatments, which are delivered to the retina via an episcleral device also in development in- and outside this award. The project aims to conduct efficacy studies of these drugs in relevant animal models of retinal damage as well as performing U.S. Food and Drug Administration Investigational New Drug (FDA IND)-enabling studies, which will be followed by the filing of an IND.

This treatment will be able to be delivered on the battlefield by nonspecialized medical personnel with minimal delay before application. The episcleral delivery device, which is placed on the exterior of the eye with surgical glue or suture, enables sustained, measured, highly bioavailable delivery of drugs to the retina without the need for further intervention.

So far in the project, episcleral formulations of both drugs, including a lead formulation for brimonidine suitable for on-site immediate diffusion into the intraocular tissue, have been developed utilizing current Good Manufacturing Practice (cGMP)-compliant components and processes. Therapeutically relevant concentrations of drug formulations have been found to be safe following ocular safety studies. Methodologies for in vitro, ex vivo, and in vivo experiments, including those for maximum tolerated dose, have been developed pursuant to future FDA IND submission. Two new designs of the episcleral devices (50 µL and 100 µL) have been developed and tested using ex vivo explants and are suitable for cGMP manufacture.

The research proposed here could ultimately provide immediate and sustained retinoprotective therapies applicable following IED-induced retinal detachment or other ocular and brain injuries, a pressing need for current and future deployed military personnel.

Toward Development of a Field-Deployable Imaging Device for TBI

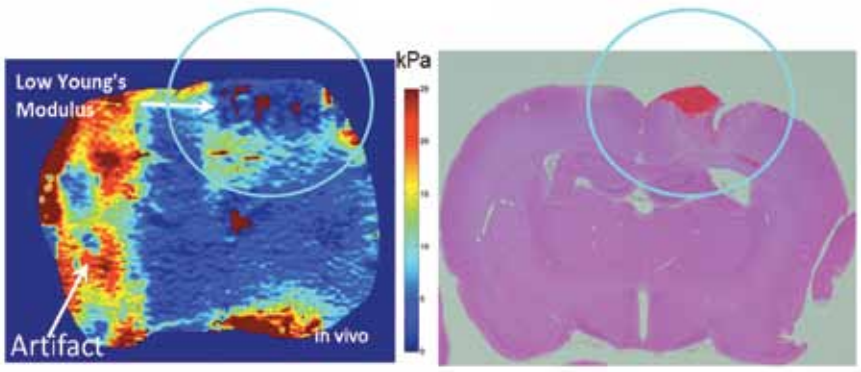
Pierre D. Mourad, Ph.D., University of Washington

In 40% to 62% of surviving soldiers, the cause of head injury was produced by IEDs. These head injuries include extensive edema and contusions (a mix of edema and small-scale hemorrhage), intracranial bleeding, and traumatic axonal injury (TAI). Soldiers who are brain-injured do not receive adequate brain imaging studies until they are flown to rear-echelon medical service centers. This is because MRI is unavailable in or near the theater of war and because of the paucity of operational CT machines at medical centers in Iraq. To assess the extent and location of the injured portion of the brain, neurosurgical care often requires a complete hemicraniectomy due to the lack of adequate neuroimaging systems at or near the battlefield.

Dr. Pierre D. Mourad from the University of Washington's Applied Physics Laboratory and Department of Neurological Surgery received an FY09 Psychological Health and Traumatic Brain Injury Applied Research and Advanced Technology Development Award to develop a field deployable brain imaging system responsive to brain stiffness through the use of ultrasound applied transcranially. The system would rival CT in its clinical usefulness and surpass CT in its ability to distinguish hemorrhage versus edema versus normal brain, and normal versus abnormal white matter. Dr. Mourad and his team will create two ultrasound-based imaging systems based on brain-tissue displacement methods and apply them to relevant animal models of TBI.

Dr. Mourad and a team from the University of Virginia (Drs. James Stone and Robert Salzar) have generated evidence supporting the hypothesis that imaging of brain stiffness using exogenous "palpation" of brain tissue with diagnostic ultrasound can successfully detect changes caused by both ischemic stroke and TBI. These observed changes in brain tissue stiffness after ischemic stroke and TBI are consistent with observations of short-term ipsilateral edema formation and short-term contralateral reduction in blood flow followed by longer-term contralateral edema formation. Dr. Mourad has also generated evidence supporting the hypothesis that endogenous palpation of brain by cerebral blood flow can form the basis of ultrasound images that highlight hemorrhage and edema, as found within the brain of a TBI patient. This work demonstrates strong progress being made toward incorporating ultrasound technology to image TBI with a field-deployable device.

Ultrasound-based stiffness imaging of TBI, in vivo



Microassay Diagnostic Device for Rapid Assessment of Traumatic Brain Injury

Sai Kumar, Ph.D., SFC Fluidics, LLC

Traumatic brain injury (TBI) is considered by many to be the hallmark injury of recent U.S. military conflicts, including Operations Iraqi Freedom and Enduring Freedom. The symptoms of TBI vary among individuals and may not present at the time of injury. There is a growing need for rapid, reliable, and quantified diagnostic tests for TBI that can be used in the field or in the clinic, allowing appropriate treatment and care to be initiated immediately. Dr. Sai Kumar, with funding from an FY08 Advanced Technology/Therapeutic Development Award, is working to develop a portable device that analyzes a panel of established biomarkers that are present in minute quantities of blood for the rapid diagnosis of TBI.

Dr. Kumar and his team at SFC Fluidics began by adapting and optimizing TBI biomarker assays for use in a small, portable instrument (BioSmart®, shown in picture). Aside from this, the team is also developing a field-deployable handheld TBI-triaging device (a model being held by a scientist in the picture), which utilizes a versatile assay platform that enables the detection of multiple TBI biomarkers from a single blood sample. Whole blood samples are introduced into a "prep" module to separate blood cells from plasma. The plasma is then transferred into the assay module composed of specially fabricated microimmunocolumns and microelectrochemical detectors for rapid quantification of early-stage TBI biomarkers. SFC Fluidics' handheld diagnostic device represents the first point-of-care, quantitative, and objective test for TBI and will allow a forward medical triage unit to rapidly and accurately diagnose mild, moderate, and severe TBI at the site of injury. Additionally, Dr. Kumar's team is evaluating the inclusion of a novel biomarker from the University of Texas Health Sciences Center at Houston that predicts the onset of intracranial pressure soon after TBI. The ability to rapidly quantify early-, mid-, and late-stage TBI biomarkers will be useful in monitoring injury progression or resolution following TBI, which in turn may enable patient-specific treatment protocols to be defined over time.

Use of Low-Dose Methamphetamine as a Neuroprotective Agent Following Traumatic Brain Injury

David Poulsen, Ph.D., University of Montana

TBI is an important health concern in both the civilian and military populations. Up to 22% of service members have suffered a TBI while deployed in combat with a significant percentage of these patients having a moderate to severe injury. Currently, there are no effective medications to treat acute TBI, though multiple medications have been tried to date without success. Methamphetamine, a drug approved by the FDA for other medical conditions, has been shown to decrease cellular death and improve neurocognitive outcomes in an ischemic brain injury (stroke) model in animals. Ischemic brain injury and TBI share many common pathophysiological pathways and ongoing studies using methamphetamine in a TBI model have shown significantly decreased neuronal loss and improved neurocognitive outcomes.

Dr. David Poulsen of the University of Montana has used an FY08 DRMRP Advanced Technology/Therapeutic Development Award to continue the investigation of methamphetamine to determine the optimum dose level and post-injury timing for administration of the drug using an animal (rat) model of severe TBI. Escalating dose levels of the drug have been administered and the lowest effective dose has been determined. It has been further established that low-dose methamphetamine administration can be delayed up to 12 hours post injury. This represents the longest therapeutic window for any neuroprotective agent tested to date. Under this dosing regimen, Dr. Poulsen's laboratory has demonstrated that low-dose methamphetamine significantly improves both behavior and cognitive function after severe TBI. In addition, immunohistochemical studies performed under this funding have demonstrated that treatment with low-dose methamphetamine reduces neuronal loss and enhances neurogenesis.

Other animals have undergone an MRI time course analysis. Data from these studies strongly suggest that treatment with low-dose methamphetamine can significantly improve white matter track changes following severe TBI. These changes could explain the observed improvements in behavior and cognitive function associated with methamphetamine treatment after severe TBI.

The results from these studies provide important preclinical data necessary to support approval of human trials. Methamphetamine is already an FDA-approved medication, with an established side effect and safety profile, and these studies have demonstrated that its use improves clinically significant, patient-oriented outcomes. This study has the potential to help expedite the clinical availability of a treatment that could drastically improve the standard of care for this injury and contribute greatly to the evidence-based literature of TBI mechanisms.

Neuroprotective Strategies for Repetitive Mild Traumatic Brain Injury

Andre Obenaus, Ph.D., Loma Linda University, Loma Linda California

Repetitive mild traumatic brain injuries (rmTBIs) are an important medical concern for civilians who participate in active sports and military personnel on active duty because they can result in cumulative damage to brain tissues leading to lingering cognitive, social, and behavioral symptoms. Hyperbaric oxygen therapy (HBOT) has been shown to be neuroprotective in some neurological disorders, but its efficacy in the management of rmTBI is unknown. Dr. Andre Obenaus using support from an FY08 DRMRP Hypothesis Development Award demonstrated that HBOT given either before or after the initial mild injury in a rat model is neuroprotective for subsequent rmTBI. It provides a basis for future investigation into the application of these neuroprotective strategies for active combat personnel and civilians after rmTBI.

Dr. Obenaus developed a rat model of rmTBI by delivering a mild controlled cortical impact to the brain followed by an identical injury at the same site occurring several days after the initial injury. Using magnetic resonance imaging (MRI), he found that animals with incurred rmTBI 3 days apart had increased edema, bleeding, and lesion size in the brain compared to those of incurred rmTBI 7 days apart, suggesting a time-dependent vulnerability of mildly injured brain to the repeated injury. Interestingly, using this animal model, Dr. Obenaus demonstrated that pretreatment with HBOT for 1 hour per day for 3 days was able to reduce the size of edema and bleeding in the brain resulting in improved tissue damage following the second mTBI impact. This protective effect of HBOT pretreatment lasted for a period of 14 days, a final time point in his study. Similar studies evaluating the effect of HBOT given 24 hours after the first mild impact consistently showed that HBOT post treatment was as effective in decreasing edema, bleeding, and lesion size due to the second impact. These findings demonstrate that HBOT when given before or soon after an initial brain injury can enhance tissue tolerance against subsequent injury and improve tissue recovery. These results provide a scientific basis for future investigations into the use of HBOT for prevention and treatment of active combat personnel and civilians at high risk for rmTBI.

Publications:

Huang L, Obenaus A. Hyperbaric oxygen therapy for traumatic brain injury (review). *Medical Gas Research*, 2011; 1:21

Huang L, Coats CS, Mohd-Yusof A, Neglerio K, Yin Y, Assad S, Muellner M, Kamper J, Hartman RE, Donovan V, Oyoyo U, Obenaus A. Tissue vulnerability is increased following repetitive mild traumatic brain injury in the rat. *J. Neurotrauma* (submitted)

Rapid Nucleic Acid Based Screening of HIV, HBV, and HCV from Fresh Whole Blood for Pretransfusion

John Gerdes, Ph.D., Micronics, Inc.

In today's wartime environment, there are pressing needs to accelerate the transition of medical technologies into deployed products that can be utilized in theater. In particular, there exists a need for accurate and timely diagnosis of potential blood donors under emergency conditions when standard donor testing is not available (DoD HA policy memo 10-002). Testing of such potential donors for exposure to infectious pathogens, such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV-1 and HIV-2), requires a deployable and rapid nucleic acid-based solution comparable to current FDA-cleared detection methods used routinely in the standard reference laboratory environment. Typically, emergency combat casualty transfusion efforts require the use of walking blood bank donors who were tested for HBV, HCV, and HIV viral infections prior to deployment. However, the need exists in theater to detect new or recent bloodborne infections post deployment. In addition, in certain situations, injured personnel, including military and civilian, may require blood transfusions from donors who have not been tested previously for infectious pathogens. Thus, there is a need for a fast, sensitive, specific, and cost-effective method of testing donors in theater at the time of donation need.

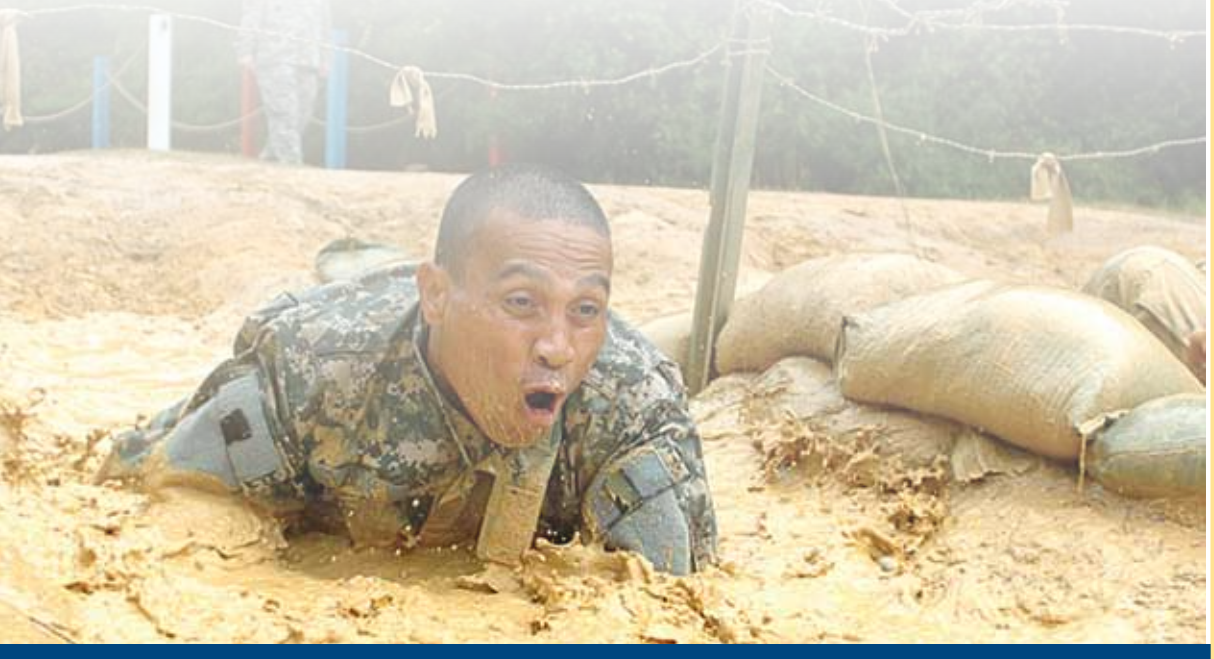
With funding from an FY09 Applied Research and Advanced Technology Development Award, Dr. John Gerdes and colleagues at Micronics, Inc. are developing and verifying a portable instrument and reagent-containing disposable cartridges that will enable rapid detection of deployment-acquired HIV, HBV, and HCV infections in donors using a nucleic acid-based method. Detection of nucleic acids is required as there is a time window during which infectious viruses are circulated in the blood prior to the appearance of antibodies that can be detected at a later time point. Objectives of this project include the development of new assays to detect HBV, HCV, and HIV viral infections and the integration of the assays on Micronics' integrated injection-molded cartridges that will be processed using Micronics' PanNAT™ fluorescent-detection based platform instrument. Once detection of bloodborne pathogens has been confirmed using spiked blood specimens, Micronics will collaborate with Dr. John Scott at the University of Washington-Harborview Medical Center to test anonymous patient specimens for the presence of interfering compounds; optimize specimen handling and processing; characterize the accuracy, precision, and detection limit of the assay; and verify detection of genotypes and clades in infected patients. The final phase of this effort will involve collaboration with Dr. Wei-Mei Ching at the Naval Medical Research Center for a transition plan to military personnel use. This transition will include testing archived military specimens collected globally and conducting mock field site testing of the final platform. The overall effort goal is to move forward into advanced development with clinical trials to support FDA clearance of the diagnostic assays. This project addresses a critical need for a rapid and accurate means to test potential blood donors in theater through the development of a rapid nucleic acid-based test for detection of HIV, HBV, and HCV at time of donor recruitment.

Integrated Detection of Pathogens and Host Biomarkers for Wounds

Crystal Jaing, Ph.D., Lawrence Livermore National Laboratory

The community of microorganisms inhabiting the human body is known as the human microbiome. It is estimated that the microbial cells outnumber human cells in the adult human ten to one. However, characterization of the human microbiome has been understudied and its influences on human health and disease, including wound infection, pathology, and response, remain largely unknown. Moreover, host response mechanisms to wound healing are also an understudied area of investigation but would provide compelling insight into wound treatment. Thus, identification and integration of both pathogenic microbes and immune markers associated with the host response may lead to improved prognosis for wound outcome and more efficacious wound treatment regimens.

Military combat environments pose unique and difficult challenges for the treatment of injured warfighters. Troops are deployed in all areas of the world and wounded personnel can be exposed to numerous pathogens not only in theater but at subsequent point-of-care hospitals and clinics. Dr. Crystal Jaing was funded through an FY10 Basic Research Award to develop new technologies that will produce a complete clinical wound profile to aid in clinical decision making of wounded patients. A specialized, collaborative team was assembled consisting of clinical wound expertise with access to a unique wound sample collection from the Naval Medical Research Center; advanced bioinformatics and pathogen detection expertise from Lawrence Livermore National Laboratory; and proteomic and biomarker research expertise from the University of California, Davis. Tissue and wound samples will be analyzed for the identification of a broad range of microbes using the Lawrence Livermore Microbial Detection Array. Host factors will be identified using a two-dimensional gel electrophoresis system. This expert team and the unique approach of characterizing both pathogen and host profiles in wound healing have the potential to greatly improve the treatment, outcome, and quality of life of wound victims in both military and civilian settings.



Intranasal Peptide Delivery to Reduce Psychological Stress Injury

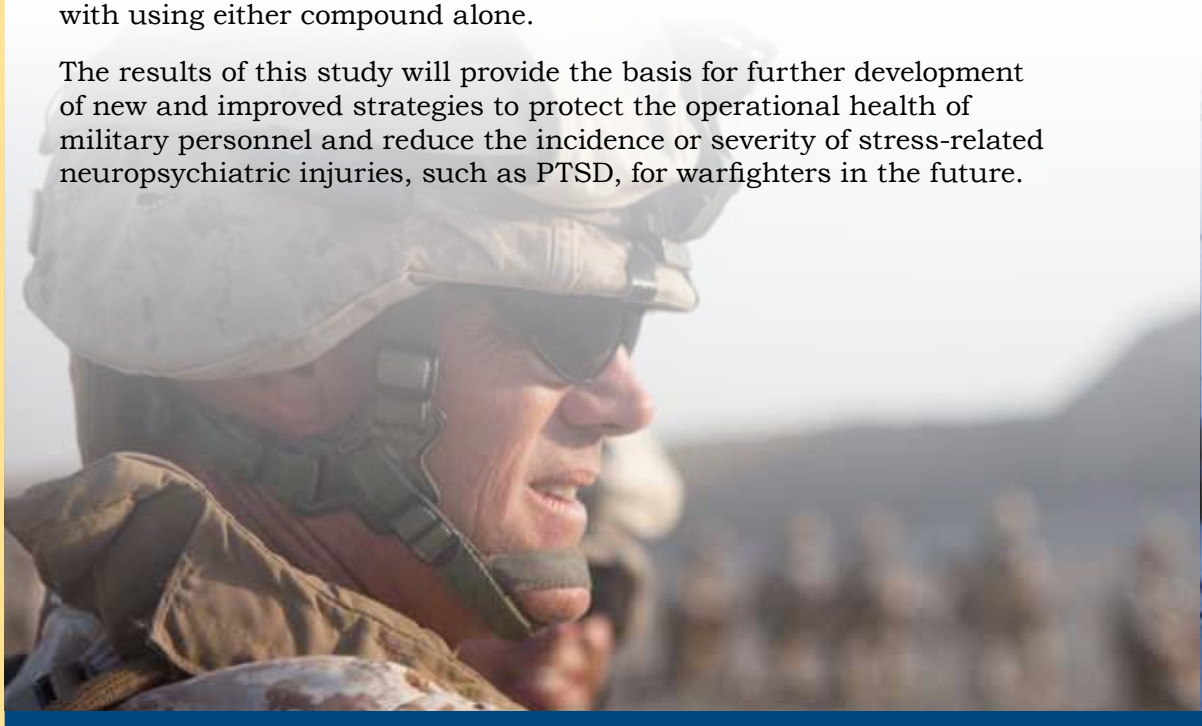
Esther Sabban, Ph.D., New York Medical College

Stress disorders are a very serious consequence of military operations. Following active duty in Iraq or Afghanistan, nearly 20% of military personnel report symptoms of major depression, generalized anxiety, or post-traumatic stress disorder (PTSD). PTSD is a prolonged and devastating disorder triggered by exposure to severe traumatic stress and individuals with PTSD are six times more likely to attempt suicide. There is a vital need for improved medications for this disorder.

Dr. Esther Sabban of the New York Medical College is using an FY10 DMRDP Basic Research Award for one such medication for PTSD. Based on an improved understanding of the underlying changes in brain chemistry occurring with PTSD, Dr. Sabban hypothesizes that delivery of the compounds neuropeptide Y (NPY) and melanocortin receptor (MC4R) antagonist such as AGRP (83-132), alone or combined, to the brain by intranasal administration will lessen the manifestations of PTSD. NPY is a naturally occurring compound and increased levels in the brain are associated with resilience to development of PTSD and less stress triggered anxiety. AGRP (83-132) is an inhibitor of some of the actions of naturally occurring hormones involved with stress.

Dose and intranasal delivery parameters for NPY have been established in an animal model of PTSD, along with baseline behavioral data for stressed animals versus controls. Dr. Sabban will evaluate several regimens for intranasal administration of these compounds to demonstrate their effectiveness to prevent or ameliorate the progression of PTSD-like symptoms. These experiments will examine both pre-event and post-event administration and short- and long-term biochemical, hormonal, and behavioral effects. Initial pretreatment short-term test results showed improved ability of animals to cope with stress. Longer term studies are currently under way. Dr. Sabban will also investigate whether there is a greater benefit for reducing negative responses to stress by combining administration of NPY and an MC4R antagonist compared with using either compound alone.

The results of this study will provide the basis for further development of new and improved strategies to protect the operational health of military personnel and reduce the incidence or severity of stress-related neuropsychiatric injuries, such as PTSD, for warfighters in the future.



Adjuvant Heart Rate Variability Biointerventions for Combat-Related PTSD

J.P. Ginsberg, Ph.D., Dorn Research Institute

Study team (l-r): Kurt Gleichauf, Rebecca Rambharose, Madan Nagpal, Ph.D., J.P. Ginsberg, Ph.D.

Currently, there are few highly effective treatment options for patients suffering from PTSD. In addition, associated deficits in attention and immediate memory remain a serious issue for patients with PTSD. While lowered heart rate variability (the small beat-to-beat changes in heart rate) has been shown to be associated with PTSD, this association has not been well studied. The heart beats at a changing rate and variability in heart rate can affect physical, emotional, and mental well-being. These changes in heart rate are natural and are a sign of health. A therapeutic intervention called heart rate variability biofeedback (HRVB) is a novel technique that has successfully been used to treat patients with various medical and psychiatric conditions. HRVB teaches patients to change the variability and rhythms in heart activity through attention focusing, resonant frequency breathing, imagery, and positive emotion induction.

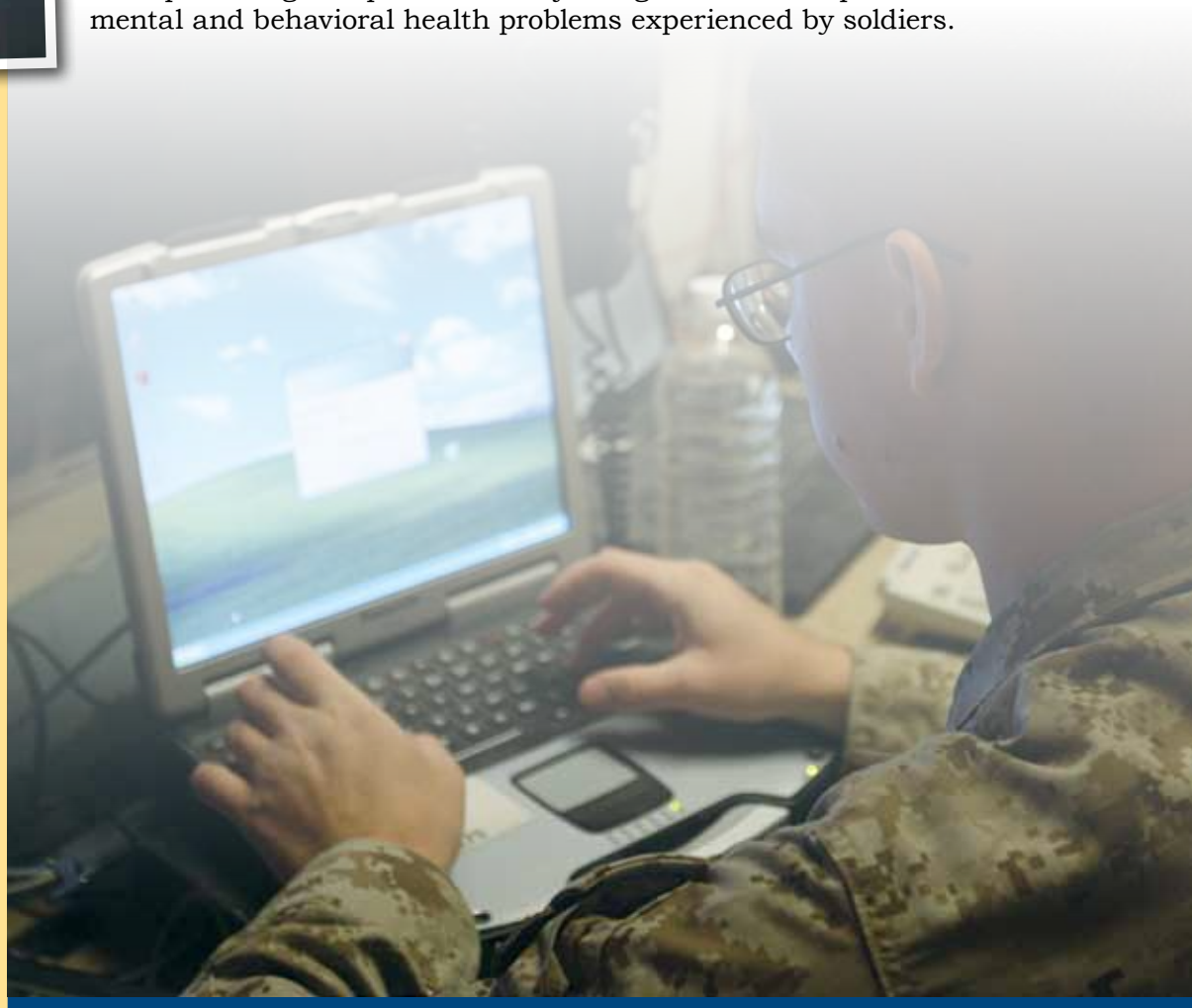
Dr. J.P. Ginsberg and colleagues are investigating the clinical use of HRVB for PTSD-induced deficits in concentration and memory recall in post-combat veterans diagnosed with PTSD. Preliminary data gathered by Dr. Ginsberg showed that HRVB increased coping ability and improved thinking and memory in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans with PTSD. Dr. Ginsberg is extending these preliminary findings in a larger population of OIF/OEF veterans. Patients enrolled in the study will learn the biofeedback techniques with a trained biofeedback practitioner to improve their heart rate variability. Currently, subject enrollment, training, and assessment are ongoing. It is anticipated that this study will reduce or eliminate deleterious physiological and cognitive effects associated with PTSD and ultimately increase functional adjustment to everyday and acute stressors in veterans with PTSD.

Preliminary data taken from all subjects at the time of entry into the study does provide support for the hypothesis that PTSD impairs accuracy of early-stage information processing compared to normative populations. Results of treatment effects of the intervention cannot be reported at this time because study blinding has not been broken.

Reducing Barriers to Help-Seeking for Mental Health Problems

Lydia O'Donnell, Ed.D., Education Development Center, Inc.

Despite increased efforts to support soldiers with mental and behavioral health problems, stigma and discrimination are still associated with seeking help for psychological injuries. The "invisible wounds" borne by soldiers result in mounting burdens and costs to individuals, families, and the military. Co-led by Dr. Lydia O'Donnell and Colonel (Retired) David Litts at the Education Development Center, this study is investigating how different forms of stigma and discrimination impede soldiers' and family members' recognition of and response to mental and behavioral health problems. Three populations—soldiers, family members, and health service providers—will be surveyed at three U.S.-based Army posts. Face-to-face and telephone interviews will be conducted and used with public information to map systems of mental and behavioral health policies, practices, and services. Then, a web-based survey of a random sample of active-duty soldiers (n=6,000), family members (n=1,200) and service providers (n=450) will be conducted to assess responses to vignettes depicting soldiers experiencing post-traumatic stress disorder, mild traumatic brain injury, depression alcohol/substance abuse, and suicidality. The data will be analyzed to identify how different forms of stigma and discrimination may impede help-seeking behaviors. The findings from this action-oriented research will ultimately be used to inform policies and practices to reduce barriers to help-seeking and promote timely recognition and response to the mental and behavioral health problems experienced by soldiers.



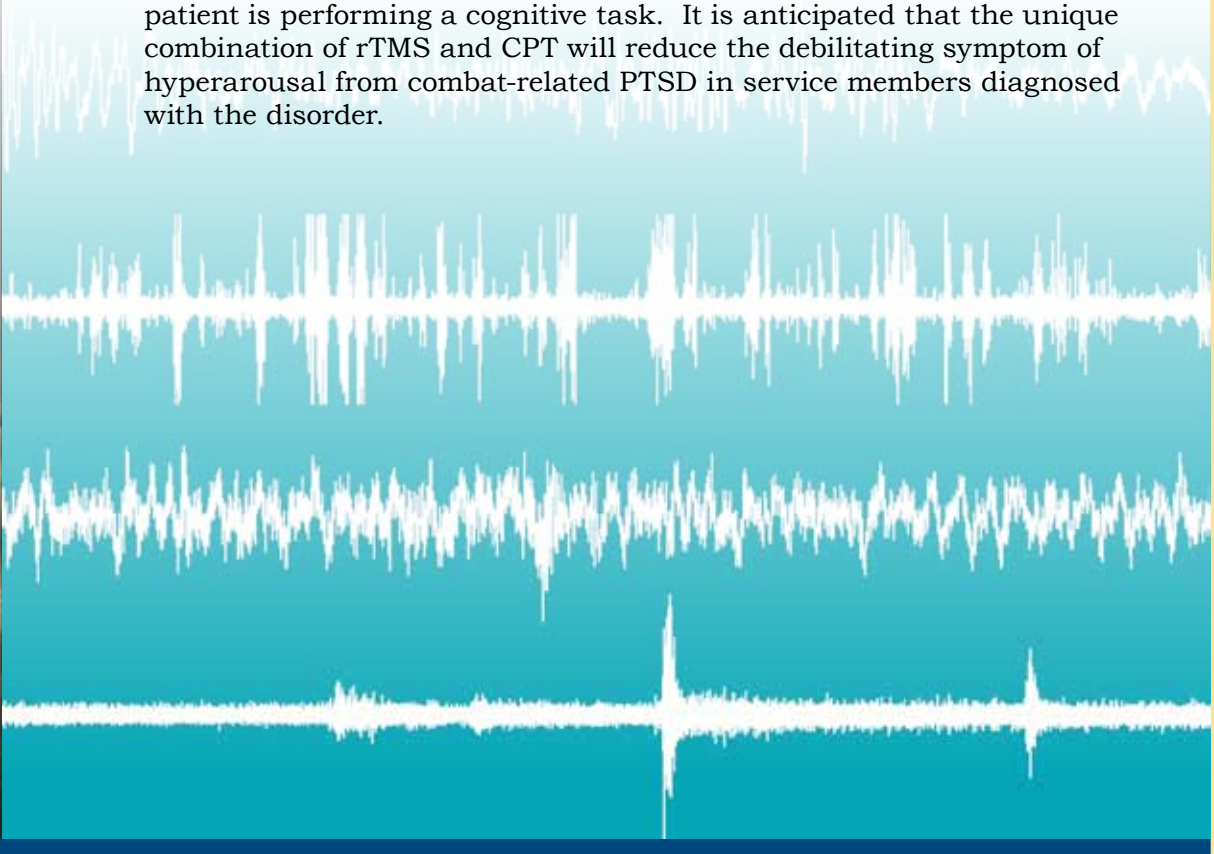
Novel Treatment of Emotional Dysfunction in PTSD

John Hart, Ph.D., University of Texas at Dallas

It is estimated that approximately 18% of veterans returning from Iraq and 11% of veterans returning from Afghanistan experience post-traumatic stress disorder (PTSD). Hyperarousal, an overemotional, out-of-proportion response to a stimulus that would typically induce a mild emotional response, is a debilitating symptom reported by soldiers suffering from PTSD. Despite the prevalence of PTSD in active duty and veteran populations, this condition has proven difficult to manage with current treatment methods.

Dr. John Hart and colleagues at the University of Texas at Dallas are combining two nonpharmacological approaches, repetitive transcranial magnetic stimulation (rTMS) and cognitive processing therapy (CPT), to treat combat-related hyperarousal experienced by veterans of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) who have been diagnosed with PTSD. rTMS is a safe, noninvasive procedure currently being used to treat depression and other neuropsychiatric disorders. This procedure uses a conducting coil that is placed around the patient's scalp, and pulses of alternating electrical current pass through the coil resulting in the production of magnetic pulses. The other modality being used, CPT, is a behavioral-based therapy that helps patients reduce their symptoms related to the traumatic experience.

Approximately 100 OEF/OIF veterans with a diagnosis of PTSD will be randomized to either CPT plus sham rTMS or combined active rTMS with CPT treatment groups. Both groups will receive 12 treatment sessions over 6 weeks. Objective markers of hyperarousal symptoms will be measured, including electrical responsiveness to emotional stimuli as recorded from EEG electrodes as well as changes in neural activity-related blood oxygenation using functional MRI while the patient is performing a cognitive task. It is anticipated that the unique combination of rTMS and CPT will reduce the debilitating symptom of hyperarousal from combat-related PTSD in service members diagnosed with the disorder.



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