

FY20

Science & Technology Efforts & Programs

PREVENTION, MITIGATION, AND TREATMENT OF BLAST INJURIES

REPORT TO THE EXECUTIVE AGENT



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FOREWORD FROM THE DIRECTOR



I joined the DOD Blast Injury Research Coordinating Office (BIRCO) this year, a year like no other in recent memory. Conducting blast injury research is complicated under normal circumstances, and the constraints of the pandemic have made those challenges more formidable. Yet it has allowed me to witness the incredible tenacity and agility of the blast injury research community. Despite the difficulties of this year, blast injury researchers and materiel developers have made significant strides in understanding mechanisms of injury, advancing diagnostic capabilities, investigating new treatment paradigms, and improving quality of life after injury.

I would like to thank our colleagues at the Joint Trauma and Prevention of Injury in Combat (JTAPIC) Program Management Office and the Psychological Health Center of Excellence (PHCoE) for contributing chapters to this year's report (Chapters 5 and 7, respectively). I hope readers will consider how the significant achievements and capabilities from these organizations may assist in other blast injury research and development endeavors.

In FY20, BIRCO hosted the International State-of-the-Science Meeting titled, "Mitigating the Impact of Blast-Related Burn Injury." With this in mind, I have invited LTC Julie Rizzo to join me in introducing this Report. She has served our Warfighters for seven years as a burn/trauma surgeon, through multiple combat deployments, and has operated on hundreds of severely burned and traumatically injured Soldiers, including many victims of blast injury. As Chief of the Burn Study Branch at the U.S. Army Institute of Surgical Research (USAISR) and Director of the U.S. Army Burn Flight Team, she engages in both patient care and some of the DOD's most advanced and combat-relevant research into care of burn- and blast-injured Service members. Contributions to her essay were made by one of her predecessors at USAISR, Dr. Ian Driscoll, a former Army surgeon with subspecialty training in burn surgery, now an Associate Professor of Surgery at the University of Florida College of Medicine.

I am confident that readers will better appreciate the advances detailed in this Report considering LTC Rizzo's insights and recollections, and that we will remember them as we dedicate ourselves in service to easing the burdens of the Warfighter. I look forward to engaging with the research and development community to advance the mission of preventing, mitigating, and treating blast injuries.

Colonel David H. Dennison, MD

Director, DOD Blast Injury Research Coordinating Office
U.S. Army Medical Research and Development Command

Blast injury is just different. Blast is not simply trauma plus burn—it's far worse. Blast casualties present the most complex cascade of challenges from point of injury through the remainder of long-term recovery. Patients, families, caregivers, and clinicians all experience the devastating changes a blast injury produces. In other words, once a blast patient, always a blast patient, who needs clinicians dedicated to blast injury care and a dedicated blast injury research initiative.

I think about blast injury care in terms of acute, plateau, and long-term phases, which correlates with BIRCO's descriptions of acute treatment and reset. In each phase, a distinct set of blast-related issues requires careful consideration. Even the most experienced combat surgeons and research scientists must live outside of their comfort zones when these patients and challenges present themselves. Collaborating among many disciplines, sharing experiences, and building upon previous blast research efforts are activities essential to identifying knowledge gaps and to caring for these most gravely injured patients.

Central to the acute phase of injury is a heavily contaminated wound resulting from extremely high-energy forces that devastate any human tissue and profoundly distort anatomy. Damage control resuscitation, as well as aggressive early and frequent debridements, have proven paramount to the patient's survival. A hospital must be able to accommodate extensive operations every day, with the necessary equipment, trained personnel, blood product availability, and flexibility to change the plan intraoperatively based on injury pattern, contamination, and the patient's physiology. Many times, in the operating room, the most experienced surgeons find themselves asking, "What was this supposed to be, anatomically?" while holding a piece of muscle, tendon, vessel, or bone. Blast forces make limb salvage versus amputation an even more difficult choice. If amputation is performed (often to finalize a process nearly completed by the injury itself), prosthetic planning for the residual limb needs to begin at the first operation, when the wound is still contaminated and far from definitive closure. Wound contamination after blast injury is the worst encountered, with a rapidly increasing incidence of multi-drug resistant organisms. Wound decontamination techniques, including pulsatile jet lavage, antimicrobial impregnated dressings, and a variety of antiseptic irrigation solutions continue to evolve based on previous study findings.

Blast-injured patients, particularly those injured in dismounted activities, have an increased risk of invasive fungal infections, a complication of contaminated wounds that greatly increases mortality. The Joint Trauma System's latest Clinical Practice Guideline addresses this risk through an extremely aggressive debridement strategy, early and liberal use of broad-spectrum anti-fungal agents, and wound biopsies. The key technical factors needed for a pathologist to quickly and accurately identify invasion of fungus into viable tissue, particularly blood vessels, still require study. The difference between fungal colonization or invasion could mean the difference between a superficial debridement and a proximal amputation that renders an already severely injured patient completely disabled.

Preventing acute neuropathic pain is a necessity and requires multi-modal therapy. Blast patients report neuropathic pain as the most distressing and disruptive feature in their recovery. We have found success with a cocktail of amitriptyline, dronabinol, and high-dose gabapentin, but this treatment strategy requires prospective study. Radiofrequency ablation of involved nerves must be considered much earlier compared to other traumatically injured patients. Finally, targeted muscle

reinnervation is increasingly being recognized as a great technique to prevent neuropathic pain—I like to think of it as giving the nerve a new job by implanting it into a new muscle. Blast injury research will continue to advance these techniques as well as to discover new modalities to prevent and treat pain.

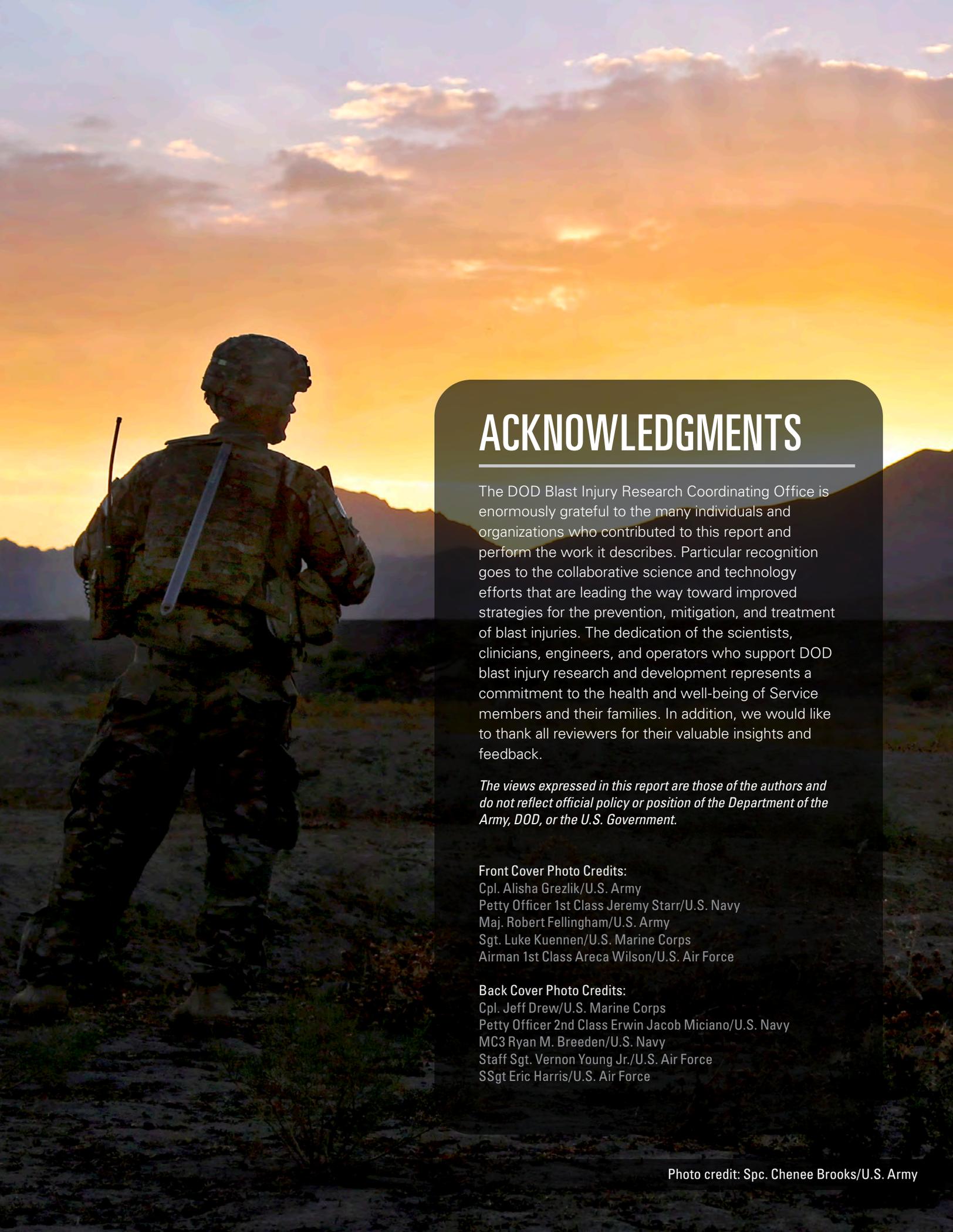
In response to contingency operations over the last 19 years, modern military medicine has excelled in blast research. The expected survival of a blast patient is much higher than anyone would have imagined decades ago. The consequence of this longevity is the need to address the plateau and reset phases. The plateau phase occurs after patients have survived acute hospitalization but are not yet ready for the extensive reconstruction necessary to compensate for missing anatomy. This phase is where patients and families are adjusting to their “new normal” of living with disabilities and physiologic consequences. Recurrent infections are always a concern, even at sites not injured in the initial blast. Wound complications, especially at amputation sites, are a persistent problem that needs to be addressed expeditiously in order to limit immobilization. Prosthetics are a constant work-in-progress, and the early involvement of an experienced prosthetics team is essential for success. The technology of prosthetics is simply awe-inspiring and will continue to be a crown jewel of success for the blast research community as they restore the function of missing anatomy far beyond most patients’ and providers’ wildest dreams.

Perineal blast injuries deserve special mention, as these carry a vast array of acute and chronic complications. Bowel and bladder function can be an enigma in terms of why some patients retain control and why some never regain it. Thankfully, there are many military-experienced providers that have developed a bag of tricks to give patients their best chance for full function. Sexual function is a concern that understandably occupies the minds of young Service members after blast injury. Laboratory values and other standard evaluation modalities often aren’t of great utility until many months have passed. Expectation management and frequent counseling are needed for many patients and families regarding this topic, which often remains a point of contention and disappointment even in the most-recovered patients. Ongoing work with rehabilitation services is necessary to address the complex array of concerns present among blast survivors, including physical, occupational, and cognitive rehabilitation. Psychological treatment also facilitates recovery from blast-related psychological disorders and adjustment to disability.

Moving forward, multidisciplinary collaboration, sharing experiences, and building upon previous blast research are essential to the best care for these gravely injured patients. Blast injury research must continue with full support and dedication to advance the science and delivery of care for blast-related injuries. Future blast research must address our knowledge gaps to help us continue to save lives and to preserve the quality of life among these survivors. The list of needs is long. The list of successes is long, too. The reason why we do what we do walks into our clinic on prosthetic limbs with their family in tow.

Lieutenant Colonel Julie A. Rizzo, MD

Burn/Trauma Surgeon
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The views expressed in this report are those of the authors and do not reflect official policy or position of the Department of the Army, DOD, or the U.S. Government.

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EXECUTIVE SUMMARY

This report highlights the activities and accomplishments of the Blast Injury Research Coordinating Office (BIRCO) and the blast injury research community during FY20. Their work throughout this year, especially amid the significant challenges of the COVID-19 pandemic, demonstrated DOD's continued drive to advance blast injury research to protect and heal those who serve.

Blast injury includes the entire spectrum of injuries that can result from an explosion or, potentially, from heavy weapons firing in training or in theater. Blast injuries can be caused by the interaction of a blast wave with the body; impact from objects propelled by the blast or from displacement of the body; heat and toxic or radiological substances released from the explosion; or wound infection after injury. Those exposed to blast often sustain more than one injury, making their treatment highly complex. Even relatively mild symptoms of blast injuries (e.g., tinnitus, dizziness, disorientation) can have major effects on operational readiness and quality of life. To address these challenges, DOD invests significant resources in medical and nonmedical research on the prevention, mitigation, and treatment of blast injuries.

Congress passed legislation in 2006 to address critical gaps associated with blast injury research. Section 256 of Public Law 109-163, the FY06 National Defense Authorization Act (NDAA), directed the Office of the Secretary of Defense to designate an Executive Agent (EA) to coordinate DOD medical research efforts and programs relating to the prevention, mitigation, and treatment of blast injuries. In response to this direction, DOD Directive 6025.21E, Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, formally established the DOD Blast Injury Research Program and designated the Secretary of the Army as the DOD EA. In 2017, EA authority was delegated to the Commander, U.S. Army Medical Research and Development Command (USAMRDC).



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[Chapter 1](#) reviews the responsibilities and functions assigned to the EA and other key DOD components for coordinating and managing blast injury research and provides an overview of DOD blast injury research management, advisory groups, and stakeholder collaboration efforts.

In 2007, BIRCO was established at USAMRDC under a charter signed by the Commander, U.S. Army Medical Command, to assist in fulfilling EA responsibilities and functions. BIRCO continues to support the EA by coordinating blast injury research to ensure that critical knowledge gaps are addressed, unnecessary duplication of effort is avoided, and fielding of prevention and treatment strategies is accelerated through collaboration and information sharing.

In FY20, BIRCO engaged in the following key initiatives and engagements to support these coordination efforts, outlined in Chapters 2, 3, 4, and 6 of this report.

- **Leading a line of inquiry on weapon systems for the Section 734 Blast Overpressure Study (BOS).** The goal of Section 734 BOS is to address the requirements in Section 734 of the FY18 NDAA, and in subsequent related legislation, by improving DOD's understanding of the impact of blast pressure exposure from weapon systems to the Service member's brain and auditory health and informing policy for risk mitigation, unit readiness, and health care decisions. BIRCO is the office of primary responsibility for one of the five lines of inquiry, LOI 2: Weapon Systems, which aims to assess and review the safety precautions surrounding heavy weapons in training to account for emerging research on blast exposure, and the effects of such exposure on cognitive performance of Service members. In FY20, the LOI 2 team initiated and led the Blast Overpressure Injury Threshold Review to summarize existing and currently used low-level blast overpressure exposure injury thresholds for preventing blast-related brain and auditory injury. The LOI 2 team also established the foundation to integrate a Blast Overpressure Tool into the Range Manager ToolKit—an existing suite of virtual tools that assist Unit Commanders and range safety officials in promoting safety during weapons training. Read more about BIRCO's efforts for the Section 734 BOS, and summaries of other BIRCO activities during FY20, in [Chapter 2](#).
- **Chairing the U.S.-India Collaboration on Blast and Blunt TBI to a successful conclusion.** FY20 was the final year for the U.S.-India project agreement, "Experimental and Computational Studies of Blast and

Blunt Traumatic Brain Injury." BIRCO chaired the U.S. component of this group, part of a senior bilateral forum between the U.S. and the Indian Ministry of Defence. Notable accomplishments include establishing blast and blunt injury dose-response curves in animal models, developing a replicable blast rodent model, and new discoveries on the brain's responses to blast exposure. Studies such as these help build a better understanding of the mechanisms of injury in TBI, which is critical to accelerating the development and transition of blast injury prevention and treatment strategies. Read more about the research and accomplishments from this U.S.-India collaboration in [Chapter 6](#).

- **Directing the Military Health System (MHS) Blast Injury Prevention Standards Recommendation (BIPSR) Process.** To support the EA's responsibility of recommending blast injury prevention standards, BIRCO developed the MHS BIPSR Process—DOD's first unbiased, stakeholder-driven critical assessment methodology for recommending biomedically valid blast injury prevention standards. These standards support weapon system health hazard assessments, combat platform occupant survivability assessments, and protection system development and performance testing. In FY20, BIRCO facilitated a thorough evaluation of 14 candidate auditory injury prevention standards by a panel of subject matter experts. The next steps are to review the results of these evaluations, develop a draft recommendation, and hold a consensus-building meeting with stakeholders from DOD, academia, and industry. Read more about the MHS BIPSR Process in [Chapter 3](#).



Photo credit: Master Sgt. Matt Hecht/U.S. Air National Guard

- **Sponsoring the Ninth International State-of-the-Science Meeting.** In March 2020, BIRCO sponsored the Ninth International State-of-the-Science Meeting on blast-related injuries, “Mitigating the Impact of Blast-Related Burn Injuries: From Prolonged Field Care to Rehabilitation and Resilience.” Based on the presentations and discussions during the meeting, an expert panel made four recommendations for blast-related burn injury research that covered injury classification and data collection methods, training for prolonged field care of burn injuries, strengthening of rehabilitation practices, and theater-based research on burn management. These recommendations and more proceedings from the meeting, including summaries of a literature review and working group discussions, are included in [Chapter 4](#).
- **Guiding the DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats.** BIRCO established this working group in 2017 to promote cohesion among the many modeling and simulation efforts that seek to improve Warfighter protection and survivability from blast injury. In FY20, the working group drafted a strategic plan that provides actionable, impactful guidance and recommendations for developing a DOD Computational Human Body Modeling Framework. This Framework will support model selection for scenario development, scenario execution, guidelines and best practices for inter-model communication, guidelines and best practices for inputs and outputs, and analyses of results. Read more about the efforts of the working group, and summaries of other BIRCO activities during FY20, in [Chapter 2](#).

As part of the EA's mission is to promote information sharing and facilitate collaboration, BIRCO welcomes contributions to this report from the blast injury research and development community. The Joint Trauma Analysis and Prevention of Injury in Combat Program Management Office contributed [Chapter 5](#), which highlights their recent achievements in collecting, integrating, analyzing, and storing operations, intelligence, materiel, and medical data to inform solutions that prevent or mitigate injury during the full range of military operations. The Psychological Health Center of Excellence provided [Chapter 7](#), in which they discuss their recent work in facilitating evidence-based research and clinical practices across the continuum of care to enhance the psychological health of the military community. Finally, BIRCO collated 130 submissions of accomplishments from other DOD organizations and partners representing the research, development, and test and evaluation communities in [Chapter 8](#). Notable highlights of the many significant accomplishments from DOD-funded blast injury research include the following:

- Several research groups, including those from Applied Research Associates, Uniformed Services University of the Health Sciences (USU), Walter Reed Army Institute of Research, Naval Medical Research Center, University of Virginia, and Naval Health Research Center, are investigating the effects of repetitive exposure to low-level blast that may occur throughout a Service member's training and career. These studies include, but are not limited to, the development of algorithms to interpret blast exposure data from body-mounted blast gauges, cognitive performance testing, biomarker identification, neuroimaging, and evaluation of hearing loss. Researchers are examining data collected at acute and chronic time points, from experiments conducted with animals and humans, and using prospective and retrospective methods. The results from this broad body of work addressing repetitive exposure to low-level blast will promote Service member safety in combat and during heavy weapons training ([pages 143-151, 181, and 215](#)).
- Researchers associated with the DOD-VA Extremity Trauma and Amputation Center of Excellence (EACE) at Joint Base San Antonio and VA Puget Sound identified several critical factors that influence a Service member's decision to return to duty after severe lower extremity trauma: family support, career trajectory, and institutional and policy support. A better understanding of this decision-making process could reduce barriers in returning to duty after blast injury and improve force readiness ([page 206](#)).
- Scientists from multiple institutions have contributed to a body of work supported by the Office of Naval Research to better understand mechanisms of injury for TBI. Integrated efforts combining material physics theory, computational approaches, and experimental approaches studied the formation and collapse of microbubbles (i.e., cavitation) in the fluid surrounding brain tissue. A better understanding of TBI injury mechanisms will help inform the development of improved personal protective equipment ([pages 125-139](#)).
- Researchers at the University of Michigan developed engineered skeletal muscle units and demonstrated their ability to restore muscle mass and force production in a large animal model of volumetric muscle loss (VML) ([page 226](#)). This work contributes to the regenerative medicine capabilities in development to improve outcomes after this devastating injury. In related work, researchers with EACE and USU are studying ways to promote greater efficacy of regenerative medicine therapies for VML ([page 195](#)).



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- The U.S. Army Medical Materiel Development Activity (USAMMDA), the University of California San Francisco, and the Transforming Research and Clinical Knowledge for TBI Network (TRACK-TBI NET) evaluated generic drugs for their potential use in phase 2 clinical trials to treat moderate TBI. There are currently no FDA-approved drugs for TBI treatment, despite dozens of clinical trials. Generic drugs, which are already approved by the FDA for non-TBI indications, offer the lowest risk and fastest regulatory pathway for TBI drug development. An effective drug to treat TBI could influence meaningful management of TBI and return to duty ([page 197](#)).

The report concludes with a presentation of the future plans for BIRCO and the blast injury research community ([Chapter 9](#)). BIRCO will continue critical initiatives like the Section 734

BOS, MHS BIPSR Process, and the DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats. Additional FY21 efforts include forming and chairing two NATO Human Factors and Medicine Panel groups and sponsoring the tenth International State-of-the-Science Meeting, “Understanding the Computational Modeling of the Human Body’s Responses to Blast-Related Injury.” The blast injury research community will continue their ongoing work and launch new efforts in areas such as TBI diagnostics; numerous ongoing clinical trials and longitudinal studies to improve outcomes after blast injury; and continued pursuit of regenerative medicine therapies for injuries like VML, peripheral nerve injury, and burns. Together, this community will continue to ensure that advances in blast injury research help better protect and heal Service members.

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CHAPTER 1: INTRODUCTION

Blast injuries are complex physical traumas resulting from explosion and potentially from firing weapons in training or in theater. Weapons with a blast component were responsible for 82 percent of U.S. Service members killed in action (KIA) and 86 percent wounded in action (WIA) in Iraq and Afghanistan between December 2001 and September 2017. During this time, for each KIA there were over 8 WIA, and of those wounded, five percent suffered traumatic extremity loss (Joint Trauma Analysis and Prevention of Injury in Combat [JTAPIC], 2017). Those exposed to blast often sustain more than one injury, making their treatment highly complex. In addition, preliminary evidence suggests that repetitive, low-level blast exposure due to occupational training (e.g., breaching) or heavy munitions firing may cause transient physical changes or psychological symptoms. Together, these data underscore the need for the DOD’s unwavering commitment to research and development of strategies to prevent, mitigate, and treat blast injuries sustained in combat or training.

Civilians are also affected by explosions from acts of terror and industrial accidents. On August 4, 2020, a massive chemical explosion in Beirut killed over 200 people and wounded approximately 5,000. Several bombings killed more than 250 people and injured more than 400 across Sri Lanka on Easter Sunday in 2019. An explosive detonated during the morning rush on September 17, 2017 at the Parsons Green station of the London Underground injured more than 30 people. On the evening of May 22, 2017, a suicide bomber detonated explosives as teenage fans were leaving a concert at the Manchester Arena in the United Kingdom. The attack killed 23 people and injured 800. On April 15, 2013, three people were killed and 264 were wounded when homemade pressure-cooker explosives were detonated during the Boston Marathon. Clearly, the DOD’s research and development investments in mitigating and treating blast injuries will benefit civilians as well.

In 2006, Congress passed legislation to address critical gaps associated with blast injury research. In Section 256 of Public Law 109-163, National

Defense Authorization Act (NDAA) for FY06, Congress directed the Office of the Secretary of Defense to designate an Executive Agent (EA) to coordinate DOD medical research efforts and programs relating to the prevention, mitigation, and treatment of blast injuries. In response to this direction, DOD Directive (DODD) 6025.21E, “Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries,” formally established the DOD Blast Injury Research Program on July 5, 2006 (see [Appendix C: DODD 6025.21E](#)).

DODD 6025.21E designates the Secretary of the Army (SECARMY) as the DOD EA. SECARMY delegated authority and assigned responsibility to execute EA responsibilities directly to the Surgeon General of the U.S. Army. The Surgeon General of the U.S. Army delegated this authority to the Commander, U.S. Army Medical Research and Development Command (USAMRDC) (Figure 1-1).

FIGURE 1-1: Assignment of EA authority



* During FY18, the Under Secretary of Defense for Acquisition, Technology and Logistics (USD(AT&L)) was split into two offices: the Under Secretary of Defense for Acquisition and Sustainment (USD(A&S)) and the Under Secretary of Defense for Research and Engineering (USD(R&E)). Oversight of the EA was retained by USD(R&E).

The DOD Blast Injury Research Coordinating Office (BIRCO), established and chartered at USAMRDC in 2007, supports the EA by coordinating DOD-sponsored biomedical research programs aimed at preventing, mitigating, and treating blast-related injuries; identifies knowledge gaps and shapes research programs accordingly; promotes information sharing among the operational, intelligence, medical, and materiel development communities; and facilitates collaborative research among DOD laboratories and the laboratories of other federal agencies, academia, and industry (Figure 1-2) to leverage resources and take full advantage of the body of knowledge that resides both within and outside of the DOD to accelerate the delivery of blast injury prevention and treatment strategies to Service members.

Responsibilities and Functions

DODD 6025.21E assigns key DOD components specific responsibilities to coordinate and manage the medical research efforts and DOD programs related to the prevention, mitigation, and treatment of blast injuries.

For a more detailed description, please see [Appendix C: DODD 6025.21E](#).

- **The USD(R&E)** oversees the functions of the DOD EA; establishes procedures to ensure new technology developed under the DODD is effectively transitioned, integrated into systems, and transferred to DOD components; chairs the Armed Services Biomedical Research, Evaluation, and Management (ASBREM) Community of Interest (CoI), now called the Biomedical CoI; and serves as the final approving authority for DOD blast injury research programs.
- **The Assistant Secretary of Defense for Health Affairs (ASD(HA))** assists in requirements development; assesses and coordinates relevant research efforts to resolve capability gaps; approves Military Health System (MHS) blast injury prevention, mitigation, and treatment standards; appoints representatives to DOD EA coordination boards and committees; and ensures that MHS information systems capabilities support the EA.



FIGURE 1-2: Breadth of BIRCO’s coordinating responsibilities

Joint Improvised Threat Defeat Organization (JIDO); Joint Intermediate Force Capabilities Office (JIFCO); Technical Support Working Group (TSWG); North Atlantic Treaty Organization (NATO); Uniformed Services University of the Health Sciences (USU); United States Special Operations Command (USSOCOM); Defense Advanced Research Projects Agency (DARPA).

- **The SECARMY** was designated as the DOD EA for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries. In 2017, the Surgeon General of the U.S. Army designated this authority to the Commander, USAMRDC.
- **The Commander, USAMRDC**, as the delegated EA, coordinates and manages DOD blast injury research efforts and programs by:
 - a. Maintaining a DOD technology base for medical research related to blast injuries
 - b. Performing programming and budgeting actions for all blast injury research based on analysis and prioritization of DOD component needs
 - c. Providing medical recommendations on MHS blast injury prevention, mitigation, and treatment standards
 - d. Ensuring that blast injury research information is shared
- **The Secretary of the Navy and the Secretary of the Air Force** assist in requirements development and coordinate all blast injury research efforts and requirements through the EA.
- **The President of the Uniformed Services University of the Health Sciences (USU)** ensures education relating to blast injury prevention, mitigation, and treatment is included in the USU medical education curriculum and programs. The USU President coordinates all blast injury research efforts and requirements through the EA and appoints representatives to any coordination boards or committees related to blast injury research.
- **The Chairman of the Joint Chiefs of Staff** coordinates all blast injury efforts and requirements through the EA, appoints a senior member to the ASBREM Col (now called the Biomedical Col), and appoints representatives to any other coordination boards or committees related to blast injury research.



Photo credit: Volker Ramspott/U.S. Army

- **The Commander, U.S. Special Operations Command (USSOCOM)** establishes procedures for the coordination of Defense Major Force Program II activities with those of the EA, forwards the Command’s approved blast injury research requirements to the DOD EA, and appoints representatives to the ASBREM Col, (now called the Biomedical Col) and any other coordination boards or committees related to blast injury research.
- **The Joint Improvised Explosive Devices Defeat Organization (now the Joint Improvised Threat Defeat Organization under the Defense Threat Reduction Agency)** supported the development, maintenance, and use of a joint database on the efficacy of in-theater personal protective equipment (PPE) and vehicular equipment designed to protect against blast injury by helping to establish the JTAPIC Program at USAMRDC. The JTAPIC Program fulfills the intent of a “joint database” by providing a process that enables data sharing and analysis across communities. Continuing responsibilities include identifying related operational and research needs, coordinating research efforts to resolve capability gaps, and appointing representatives to the ASBREM Col and any other coordination boards or committees related to blast injury research.

TABLE 1-1: Taxonomy of Injuries from Explosive Devices

Injury Type	Description
<p>Primary Blast Injuries:</p> <ul style="list-style-type: none"> • Blast lung • Ear drum rupture and middle ear damage • Abdominal hemorrhage and perforation • Eye rupture • Non-impact induced mild TBI 	<p>Primary blast injuries result from the high pressures created by a blast. These high pressures, known as blast overpressure, can crush the body and cause internal injuries. Primary blast injuries are the only injury classification that is unique to blast.</p> 
<p>Secondary Blast Injuries:</p> <ul style="list-style-type: none"> • Penetrating ballistic (fragmentation or blunt injuries) • Eye penetration • Mild to severe brain injury 	<p>Secondary blast injuries result when strong blast winds behind the pressure front propel fragments and debris against the body and cause blunt and penetrating injuries.</p> 
<p>Tertiary Blast Injuries:</p> <ul style="list-style-type: none"> • Fracture and traumatic amputation • Closed and open brain injury • Blunt injuries • Crush injuries 	<p>Tertiary blast injuries result from strong winds and pressure gradients that can accelerate the body and cause the same types of blunt force injuries that would occur in a car crash, fall, or building collapse.</p> 
<p>Quaternary Blast Injuries:</p> <ul style="list-style-type: none"> • Burns • Injury or incapacitation from inhaled toxic fire gases 	<p>Quaternary blast injuries are the result of other explosive products (such as heat and light) and exposure to toxic substances from fuels, metals, and gases that can cause burns, blindness, and inhalation injuries.</p> 
<p>Quinary Blast Injuries:</p> <ul style="list-style-type: none"> • Illnesses, injuries, or diseases caused by chemical, biological, or radioactive substances 	<p>Quinary blast injuries refer to the clinical consequences of post-detonation environmental contaminants, including chemical, biological, and radioactive substances (e.g., dirty bombs).</p> 

from DODD 6025.21E

DOD Framework for Characterizing Blast Injuries

The EA plays a key role in coordinating research and development for the entire spectrum of blast injury that can result from exposure to explosive weapons. The DOD adopted the “Taxonomy of Injuries from Explosive Devices,” as defined in DODD 6025.21E, to provide a common framework for characterizing the full spectrum of blast injuries. This taxonomy assigns blast injuries to five categories—primary, secondary, tertiary, quaternary, and quinary (Table 1-1). Blast injuries referred to in this report may include any injury, or multiple injuries, from these five categories.

Blast Injury Research Program Areas

Blast injury research works to close knowledge gaps in the prevention, mitigation, and treatment of blast injuries. To address the gaps and capability requirements for the full spectrum of blast injuries, current research efforts must actively pursue new tools and understanding in each of three research areas: Injury Prevention, Acute Treatment, and Reset (Figure 1-3).

Injury Prevention

Injury prevention mitigates and reduces the risk of sustaining blast injuries. This research program area provides medically based design guidelines and performance standards for individual and combat platform occupant protection systems; comprehensive injury surveillance systems that link injury, operational, and protection system performance data; tools to identify individual susceptibility to injury; and training to prevent or mitigate injuries.

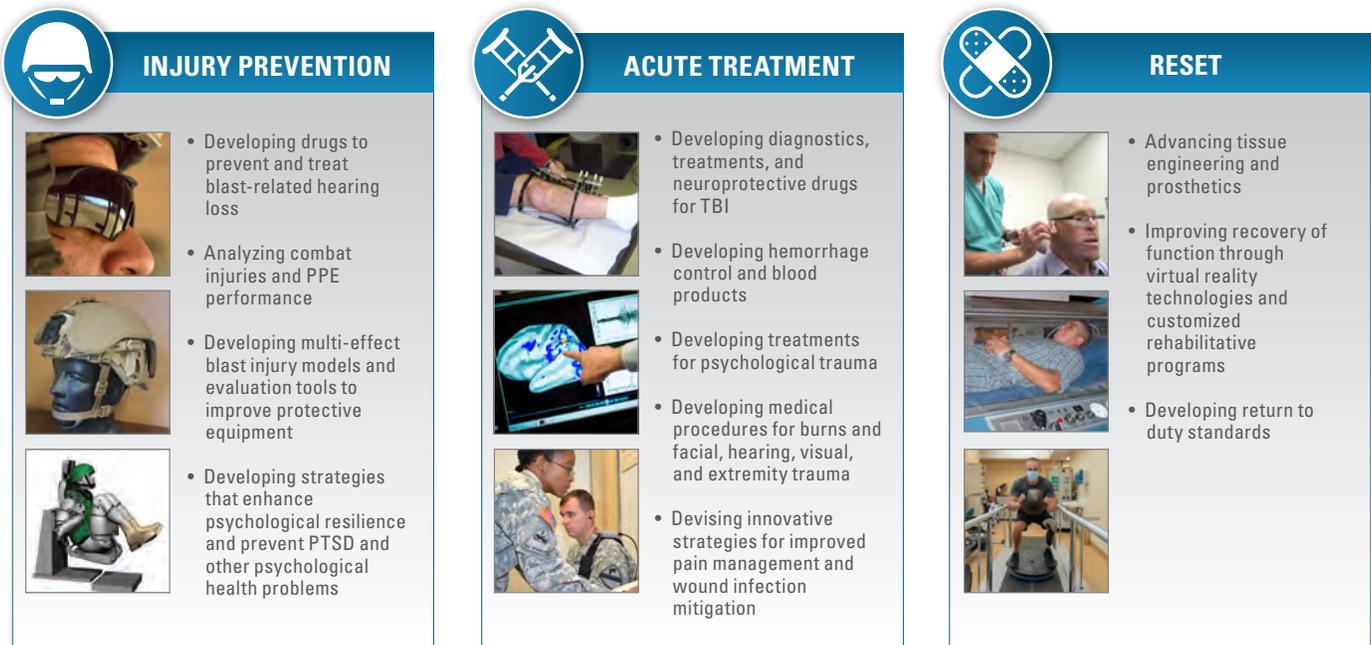


FIGURE 1-3: Blast injury research program areas

Post-traumatic stress disorder (PTSD); traumatic brain injury (TBI). Photo credits: Column 1—U.S. Marine Corps, U.S. Naval Research Laboratory, U.S. Army; Column 2—U.S. Army Medical Command, U.S. Army Medical Research and Development Command, U.S. Army; Column 3—U.S. Air Force, Defense Advanced Research Projects Agency, Naval Medical Center San Diego.

Acute Treatment

Research and development in the area of **acute treatment** is intended to improve survivability and mitigate long-term disability for Service members suffering from the full spectrum of injuries following blast events. The acute treatment research program area explores development and implementation of new blast injury management strategies, to include diagnostic tools, interventions, and clinical guidelines to save lives and improve outcomes following hemorrhage, TBI, burn, extremity injury, and sensory systems injury, as well as complex polytrauma involving blast. This research program area will lead to a greater understanding of the capabilities and limitations of current technologies, as well as new tools and validated methods for blast injury mitigation in the prehospital setting.

Reset

Research and development in the area of **reset** aims to mitigate disability by providing a biomedically based performance assessment for return-to-duty and redeployment following injury; rebuilding full performance capabilities in redeployed individuals; and restoring function and ability to seriously injured

Service members with prosthetic devices. Reset acknowledges a concept that extends beyond rehabilitation to include all activities necessary to return injured Service members to duty or to productive civilian lives.

Coordination of Blast Injury Research and Development Activities

The DOD follows a requirements-driven approach to blast injury research and development, with the goals of preventing injuries, treating injuries, and resetting after injury. In pursuit of these goals, the DOD has established numerous research management, advisory groups, and stakeholder collaboration efforts that address various aspects of blast injury research. Promoting and maintaining effective coordination among these groups is essential to achieving gains in injury prevention, acute treatment, and reset after injury.

DOD Component Services and Agency Research and Development Programs

Each of the Services and the Defense Advanced Research Projects Agency (DARPA) have blast injury research programs primarily funded through the President's Budget. These programs sponsor research internally, within DOD laboratories and clinical centers, and externally through academic and industry partnerships. DOD blast injury research focus areas include injury surveillance, combat casualty care, military operational medicine, and clinical and rehabilitative medicine.

Defense Health Agency Research and Development Directorate

Established in FY14 by the Office of the ASD(HA), the Defense Health Agency (DHA) Research and Development Directorate (DHA J-9) oversees medical research, development, test, and evaluation (RDT&E) programs related to the health care needs of Service members. DHA J-9 manages the RDT&E funds of the Defense Health Program. Joint Program Committees (JPC), which consist of DOD and non-DOD technical experts, make funding recommendations for research and manage the research programs under DHA J-9 in diverse military medical program areas, including those that directly address blast injuries (see Table 1-2). These collaborative research

TABLE 1-2: Joint Program Committees (Defense Health Agency, n.d.)

JPC	DHA J-9 Program Areas
JPC-1	Medical Simulation and Information Sciences
JPC-2	Military Infectious Diseases
JPC-5	Military Operational Medicine
JPC-6	Combat Casualty Care
JPC-7	Radiation Health Effects
JPC-8*	Clinical and Rehabilitative Medicine

*During FY20, JPC-8 was dissolved and its research portfolios integrated with JPC-5 and JPC-6

programs rely on expertise and capabilities from across the Services, U.S. Department of Veterans Affairs (VA), U.S. Department of Health and Human Services, academic centers, industry partners, and other scientific and technical communities.

Congressionally Directed Medical Research Programs

The Congressionally Directed Medical Research Programs (CDMRP) is a global funding organization managing targeted biomedical research programs in cancer research, military medical research, and other disease- and injury-specific research areas. CDMRP represents a unique partnership among Congress, the military, and the American public that invests congressionally directed dollars (not a part of the presidential budget appropriation) to fund groundbreaking, high-impact research awards. CDMRP works collaboratively within the DOD, and other members of the federal (e.g., NIH and VA) and non-federal medical research community, as well as with consumer advocates, to focus its investment in meritorious research that synergistically targets critical gaps, including several in areas highly relevant to blast injury research. [Appendix D: Supplemental Tables](#) lists CDMRP research programs supporting blast injury research.

Centers of Excellence

In response to congressional requirements within the FY08 NDAA, the DOD established several clinical Centers of Excellence (CoE). These centers seek to improve clinical care capabilities using new and updated clinical practice guidelines and policy recommendations, to understand injury and outcome trends, and to inform research sponsors about the needs and requirements of the clinical communities. As a part of their mission, a number of CoEs address blast injury research, including Defense and Veterans Center for Integrative Pain Management, DOD-VA Extremity Trauma and Amputation Center of Excellence, National Intrepid Center of Excellence (NICoE), and those that are now part of DHA J-9: DOD-VA Vision Center of Excellence, Hearing Center of Excellence (HCE), Psychological Health Center of Excellence (PHCoE), and TBI Center of Excellence.



Photo credit: Cpl. Sarah Marshall/U.S. Marine Corps

Research Forums, Consortia, and Programs Supporting Blast Injury Research

Numerous ongoing collaborative efforts (e.g., working groups, consortia, research programs) are also investigating blast injuries and associated health outcomes. These efforts include the development of new blast injury protective or preventive measures, the development of new treatments for blast injury, and improvements in rehabilitation. Table 1-3 contains examples of collaborative research efforts that involve the DOD and are related to blast injury research.

DOD Component Services and Agency Product Development Programs

The goal of DOD-funded blast injury research is the transition of research outcomes to fielded solutions for Service members. Product development is the

process of selecting, maturing, and testing safe, effective, and sustainable medical capabilities to meet military needs. It includes the evaluation of potential solutions to medical capability gaps, guiding medical products through U.S. Food and Drug Administration (FDA) approval or licensing, and supporting the fielding and sustainment of the final product. The U.S. Army Medical Materiel Development Activity (USAMMDA) at USAMRDC is the DOD's medical product development activity. USAMMDA conducts product development through four project management offices: Warfighter Brain Health; Warfighter Expeditionary Medicine and Treatment; Warfighter Health, Performance, and Evacuation; and Warfighter Protection and Acute Care.

Preview of this Report

The following chapters highlight efforts by BIRCO and the blast injury research community to advance the DOD's ability to prevent, mitigate, and treat blast injury:

- [Chapter 2](#) describes BIRCO's strategic approach and key activities during FY20 to facilitate collaboration, identify blast injury research knowledge gaps, disseminate blast injury research information, shape research programs to address knowledge gaps, and promote information sharing and partnerships.
- [Chapter 3](#) focuses on how BIRCO is advancing the MHS Blast Injury Prevention Standards Recommendations Process.
- [Chapter 4](#) presents the findings and recommendations resulting from the International State-of-the-Science Meeting, "Mitigating the Impact of Blast-Related Burn Injuries: From Prolonged Field Care to Rehabilitation and Resilience."
- [Chapter 5](#) describes JTAPIC, a DOD program that supports the EA by collecting, integrating, analyzing, and storing operations, intelligence, materiel, and medical data to inform solutions that prevent or mitigate injury during the full range of military operations. This chapter was contributed by JTAPIC.
- [Chapter 6](#) reviews the research outcomes from a strategic partnership between the U.S. and India on experimental and computational studies of blast and blunt TBI.
- [Chapter 7](#) provides an overview of the PHCoE and their mission to facilitate evidence-based research and clinical practices across the continuum of care to enhance the psychological health of the military community. This chapter was contributed by PHCoE.
- [Chapter 8](#) presents the latest accomplishments in blast injury RDT&E supported by the DOD. These accomplishments include scientific advancements, improvements in standards of care, and the development of products to prevent, diagnose, and treat blast injuries.
- [Chapter 9](#) is a discussion of the way forward for BIRCO and the blast injury research community.



Photo credit: Senior Airman Brittany Y. Bateman/U.S. Air Force

TABLE 1-3: Examples of DOD research forums, consortia, and programs supporting blast injury research

DOD Entity	Blast-Related Efforts
<p>Acute Effects of Neurotrauma Consortium</p>	<p>The Acute Effects of Neurotrauma Consortium (AENC) focuses on research into early diagnosis and treatment of TBI. The AENC is an activity of Phelps County Regional Medical Center in partnership with the Leonard Wood Institute, through which university partners study TBI protection, identification, and treatment. (The AENC is separate and distinct from the Long-Term Impact of Military-Relevant Brain Injury Consortium—Chronic Effects of Neurotrauma Consortium [LIMBIC—CENC].)</p>
<p>Armed Forces Institute of Regenerative Medicine</p>	<p>The multi-disciplinary Armed Forces Institute of Regenerative Medicine collaborates across numerous agencies to accelerate the development of diagnostic products and therapies for severely wounded Service members in need of reconstructive treatments. The goals of the program are to fund basic through translational regenerative medicine research and to position promising technologies and therapeutic and restorative practices for clinical trials.</p>
<p>Center for Neuroscience and Regenerative Medicine</p>	<p>The Center for Neuroscience and Regenerative Medicine (CNRM) is a federal military TBI research program organized as a partnership between USU and the National Institutes of Health (NIH). The CNRM was established by congressional action (Public Law 110-252) as an intramural federal TBI research program focused on the study of blast injury to the brain and post-traumatic stress in Warfighters. The CNRM consists of more than 20 senior scientific investigators and 50 staff, a robust in-house clinical trials unit, and three clinical support cores. The CNRM has funded a total of 135 research projects and has enrolled over 9,000 research participants, 63% of whom are Service members enrolled at nationwide military treatment facilities. The CNRM research programs emphasize research with high relevance to military populations, particularly Service members cared for at the Walter Reed National Military Medical Center and those exposed to blast events.</p>
<p>Collaborative Auditory Vestibular Research Network</p>	<p>The Collaborative Auditory Vestibular Research Network (CAVRN) is composed of strategically aligned research laboratories, medical treatment facilities, nonprofit and foundation counterparts, industry and academic partners, international bodies, and other government CoEs. It was established and is maintained by the Hearing Center of Excellence. CAVRN holds annual meetings to collaborate on areas of hearing and balance issues that Service members and Veterans face as a result of their military service. This growing research network works to advance the community’s understanding, spur innovation, encourage interdisciplinary collaboration, and overcome system barriers that may otherwise challenge research.</p>
<p>The Consortium to Alleviate PTSD</p>	<p>The Consortium to Alleviate PTSD (CAP) is a joint VA and DOD effort to understand and treat PTSD and related conditions in active-duty Service members and Veterans. The primary CAP objectives are to focus on the advancement of treatment strategies for PTSD and to identify and confirm clinically relevant biomarkers as diagnostic and prognostic indicators of PTSD and comorbid disorders. The CAP has completed several of the largest clinical trials of PTSD in DOD history.</p>
<p>DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats</p>	<p>The goal of the DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats is to shape, focus, and coordinate efforts to enable the computational modeling and simulation of human lethality, injury, and impairment resulting from the entire spectrum of blast-related threats. The Working Group includes representatives from DOD organizations and other government agencies.</p>

DOD Entity	Blast-Related Efforts
Federal Interagency Traumatic Brain Injury Research Informatics System	<p>The Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System was initiated as a collaborative effort supported by the USAMRDC Combat Casualty Care Research Program and the National Institute of Neurological Disorders and Stroke at the NIH as a secure, centralized informatics system developed to accelerate research in support of improved diagnosis and treatment for Service members and civilians who have sustained a TBI. De-identified data from DOD- and NIH-funded clinical TBI studies are required to be uploaded into FITBIR. Benefits include accelerating the testing of new hypotheses, allowing multi-study data aggregation to increase the statistical power of a study, providing existing comparator data for new studies, and identifying patterns not easily extracted from a single study.</p>
Interagency Explosives Terrorism Risk Assessment Working Group	<p>The Interagency Explosives Terrorism Risk Assessment Working Group was created by the Department of Homeland Security to review progress on the Homeland Explosives Consequence Assessment Tool (HExCAT). The HExCAT is an end-to-end risk assessment tool that includes information from the intelligence community and law enforcement to characterize threat, vulnerability, and interdiction; consequence modeling to calculate the possible range of lethal and sub-lethal injuries; the medical response to an event; and the impact of various security and mitigation strategies.</p>
Linking Investigations in Trauma and Emergency Services	<p>Linking Investigations in Trauma and Emergency Services (LITES) is a clinical research network established by the USAMRDC Combat Casualty Care Research Program in 2016 to sustain and continue the hard-earned advances in military trauma research from the 15+ years of conflict in Iraq and Afghanistan. LITES leverages civilian trauma systems and medical centers to answer trauma and treatment questions to facilitate the narrowing of high-priority gaps in the care of severely injured patients. LITES is not a singular research study. Through the task order generation process, independent research studies or analyses can be performed. Each LITES task order is unique, and sites are selected for participation based on the objectives of the specific task order and the site's readiness to participate. Additional information about the current network participants and active task orders can be found here: www.litesnetwork.org</p>
Long-Term Impact of Military-Relevant Brain Injury Consortium—Chronic Effects of Neurotrauma Consortium	<p>LIMBIC–CENC is a joint DOD and VA funding effort addressing the long-term consequences of mild TBI in Service members and Veterans. It continues and expands on the efforts of the original CENC and aligns to initiatives under the National Research Action Plan for Improving Access to Mental Health Services for Veterans, Service members, and Families. The LIMBIC–CENC Coordinating Center is located at Virginia Commonwealth University and executes six studies and three integrated research cores across academic, VA, and DOD research sites. LIMBIC–CENC studies include data and participants with blast exposure history.</p>
Major Extremity Trauma and Rehabilitation Consortium	<p>The Major Extremity Trauma and Rehabilitation Consortium (METRC) consists of a network of clinical centers and one coordinating center that work together with the DOD and other sponsoring agencies to conduct multicenter clinical research studies relevant to the treatment and outcomes of traumatic orthopaedic injuries. The overall goal of METRC is to produce the evidence needed to establish treatment guidelines for the optimal care of the wounded warrior and ultimately to improve the clinical, functional, and quality of life outcomes of both Service members and civilians who sustain high-energy trauma to the extremities.</p>

DOD Entity	Blast-Related Efforts
<p>The National Collegiate Athletic Association - DOD Grand Alliance: Concussion Assessment, Research, and Education Consortium</p>	<p>The National Collegiate Athletic Association (NCAA)-DOD Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium is a joint DOD and NCAA research effort dedicated to studying concussion to better understand the development of injury and trajectory of recovery utilizing a multisite, longitudinal investigation of concussive and repetitive head impacts. The CARE Consortium’s clinical study also allows for more advanced research projects, such as testing impact sensor technologies, studying potential biomarkers, and evaluating concussion with advanced neuroimaging. In their first award, focused on the acute effects of concussion, the CARE Consortium enrolled over 37,000 student athletes and Service academy Cadets and Midshipmen at 30 sites. In their second award, focused on the cumulative and persistent intermediate effects of concussion, the Consortium has brought enrollment to over 50,000 participants. The CARE Consortium will allow scientists to develop evidence-based approaches to understanding the risks, management, and possible treatment strategies for concussion.</p>
<p>Pharmaceutical Intervention for Hearing Loss Working Group</p>	<p>The Pharmaceutical Intervention for Hearing Loss Working Group is a working group coordinated by the Hearing Center of Excellence that develops strategies for standardized analysis of potential systemic and local therapies for hearing loss prevention and rescue.</p>
<p>Section 734 Blast Overpressure Study</p>	<p>The Section 734 Blast Overpressure Study (BOS) is addressing requirements in the National Defense Authorization Acts for fiscal years 2018 (Section 734), 2019 (Section 253), and 2020 (Sections 717 and 742) for a “Longitudinal Medical Study on Blast Pressure Exposure of Members of the Armed Forces.” The goal of the Section 734 BOS is to improve the DOD’s understanding of the impact of blast pressure exposure from weapon systems to the Service member’s brain and auditory health, and better inform policy for risk mitigation, unit readiness, and health care decisions.</p>
<p>South Texas Research Organizational Network Guiding Studies on Trauma and Resilience</p>	<p>South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR) is a DOD-funded, multidisciplinary, and multi-institutional research consortium that develops and evaluates interventions for the detection, prevention, diagnosis, and treatment of combat-related PTSD and related conditions in active-duty Service members and recently discharged Veterans. There are currently 18 ongoing studies supported by STRONG STAR established infrastructure.</p>
<p>TBI Endpoints Development Initiative</p>	<p>The TBI Endpoints Development Initiative is a collaborative, multidisciplinary team which seeks to advance and validate endpoints that can be used as U.S. Food and Drug Administration (FDA)-qualified outcomes, such as Clinical Outcome Assessments and blood-based and neuroimaging biomarkers, in support of TBI clinical trials.</p>
<p>U.S.-India Project Agreement on Experimental and Computational Studies of Blast and Blunt TBI</p>	<p>The U.S.-India Project Agreement on Experimental and Computational Studies of Blast and Blunt TBI seeks to develop and to validate a blast injury animal model for mild TBI using imaging techniques and histological procedures, as well as assessing changes in behavior and cognition; to develop, validate, and cross-validate a computational model for blast and blunt injury; to develop anatomically accurate head/brain models for blast/brain injuries from clinical and experimental data; and to compare the blast and blunt data to develop a scaling ratio. For more information, see Chapter 6 of this report.</p>
<p>USU/NIH Traumatic Brain Injury Research Consortium</p>	<p>The USU/NIH Traumatic Brain Injury Research Consortium is an alliance among the various TBI research activities within USU. Its mission is to ensure research throughout the university is coordinated, streamlined, and visible.</p>

02



Photo credit: Cpl. Dylan Chagnon/U.S. Marine Corps

CHAPTER 2:

DOD BLAST INJURY RESEARCH COORDINATING OFFICE

The DOD Blast Injury Research Coordinating Office (BIRCO) supports the DOD Executive Agent (EA) by coordinating blast injury research inside and outside of DOD, nationally and internationally, to support the delivery of timely and effective blast injury prevention, mitigation, and treatment solutions for Service members. BIRCO's activities help identify and address knowledge gaps, disseminate information, and minimize duplication of effort. BIRCO promotes collaboration among researchers across DOD, other federal agencies, academia, industry, and international partners to solve complex challenges related to blast injury. Taking full advantage of the body of knowledge and expertise that resides both within and beyond DOD, BIRCO advances blast injury research to protect and to heal those who serve.

Coordination is a necessary function of DOD blast injury research because of the immensely complex nature of blast injury. Across DOD, dedicated researchers with deep domain expertise pursue technologically advanced and highly specialized solutions to individual challenges, advancing, for example, tactical measures for rapid medical evacuation, treatment guidance for infection control among blast victims, diagnostic tools for brain function, or therapeutics for severe burns. Coordination enables DOD to place these efforts within the broad landscape of blast injury research, thus empowering leaders to direct additional resources to mission-critical efforts and to identify trade-offs among them. Coordination also enables researchers to share insights and experiences across disparate lines of effort and to identify complex dependencies. BIRCO's activities are chosen to encourage and to support these synergies.

i Acronyms and references used in this chapter are included in Appendices A and B.



MISSION

To assist in fulfilling the DOD Executive Agency responsibilities and functions related to medical research for the prevention, mitigation, and treatment of blast injuries in accordance with DODD 6025.21E by:



- Coordinating and managing relevant DOD medical research efforts and programs
- Identifying blast injury knowledge gaps
- Shaping medical research programs to fill identified gaps
- Facilitating collaboration among diverse communities within and outside of the DOD
- Widely disseminating blast injury research information

VISION

To establish and maintain a fully coordinated DOD Blast Injury Research Program, as envisioned by Congress and directed by the Secretary of Defense, that delivers timely and effective blast injury prevention, mitigation, and treatment strategies to our Service members today and in the future.

**Advancing Blast Injury Research to
Protect and Heal Those Who Serve**

BIRCO's Operational Approach

To enable and maintain a ready force that prepares for and responds to new threats with agility and speed within multi-domain operations, it is critical to better understand blast effects on Service members and develop improved strategies to protect against, mitigate, and treat blast injuries. Service members may face new blast-related challenges in the hyperkinetic environment as they overcome enemy area denial and swiftly maneuver to achieve operational objectives. They may need prolonged medical care for blast injuries in resource-constrained settings such as dense urban environments and under austere conditions. They must also be protected from adverse outcomes that may result from occupational exposure to blast events as they train to be ready for the future fight.

BIRCO's Operational Approach (Figure 2-1) supports the blast injury research community in meeting these challenges. BIRCO envisions a fully coordinated DOD blast injury research program that delivers timely and effective injury prevention, mitigation, and treatment strategies to Service

members operating in a multi-domain environment today and in the future.

To reach this future state, BIRCO operates through five lines of effort:

1. Identify knowledge gaps
2. Shape research programs to fill knowledge gaps
3. Promote information sharing and partnership
4. Facilitate collaboration within and outside the DOD
5. Disseminate blast injury research information

BIRCO chooses its initiatives and engagements to support these lines of effort and aid researchers across DOD, other federal agencies, academia, industry, and international partners in solving complex challenges related to blast injury. Figure 2-2 presents the alignment of key BIRCO initiatives and engagements to these lines of effort. The remainder of this chapter describes BIRCO's efforts to advance these key initiatives and other activities during FY20.

FIGURE 2-1: BIRCO's Operational Approach

National Defense Authorization Act for Fiscal Year 2006 (FY06 NDAA); DOD Directive (DODD); Secretary of Defense (SECDEF); Secretary of the Army (SECARMY); U.S. Army Medical Research and Development Command (USAMRDC).



FIGURE 2-2: BIRCO’s key initiatives and engagements aligned to strategic lines of effort
 Military Health System (MHS); Small Business Innovation Research (SBIR); Small Business Technology Transfer (STTR); traumatic brain injury (TBI).



BIRCO’s Key Initiatives in FY20

Section 734 Blast Overpressure Study

BIRCO is a member of the DOD team responding to National Defense Authorization Act for Fiscal Year 2018 (FY18 NDAA) Section 734, which mandates that the Secretary of Defense conduct a “Longitudinal Medical Study on Blast Pressure Exposure of Members of the Armed Forces.” FY19 NDAA Section 253 and FY20 NDAA Sections 717 and 742 expand on the FY18 mandate. The collective efforts to address these requirements compose the Section 734 Blast Overpressure Study (BOS). They are also a component of DOD’s overarching

“Comprehensive Strategy and Action Plan for Warfighter Brain Health.” The goal of the Section 734 BOS is to improve DOD’s understanding of the impact of blast pressure exposure from weapon systems on Service members’ brain and auditory health and to better inform policy for risk mitigation, unit readiness, and health care decisions.

The Office of the Assistant Secretary of Defense for Health Affairs leads the effort. The program structure comprises five Lines of Inquiry (LOI): Surveillance, Weapon Systems, Exposure Environment, Blast Characterization, and Health & Performance. Each LOI is led by an Office of Primary Responsibility (OPR).



Photo credit: Lance Cpl. Israel Chincio/U.S. Marine Corps

BIRCO is the OPR for LOI 2: Weapon Systems. In this role, BIRCO’s objectives are to 1) coordinate, collate, and analyze information on blast pressure resulting from high kinetic weapons and events and 2) inform strategies to account for emerging research on the effects of blast pressure exposure on health and performance.

In FY20, the LOI 2 team initiated and led the Blast Overpressure Injury Threshold Review. This endeavor is a cross-LOI effort to summarize current low-level blast overpressure exposure injury thresholds for preventing brain and auditory injury.

The Blast Overpressure Injury Threshold Review describes how occupational blast overpressure exposure from weapon systems is measured, factors that contribute to how those measurements are collected, and initiatives to formalize the monitoring, recording, and analysis of blast exposures. It discusses current DOD blast exposure guidelines and standards to promote an understanding of how exposure thresholds for auditory and lung injury originated and covers

BIRCO’s ongoing implementation of the MHS Blast Injury Prevention Standards Recommendation (BIPSR) Process for auditory blast injury. The Review summarizes computational, preclinical, and human studies that seek to better understand the mechanisms of injury and adverse outcomes after single and cumulative exposures to blast overpressure. It also presents limitations of the available data and identifies efforts that may close critical knowledge gaps in determining injury thresholds. The final version of the Review is in progress and is anticipated in FY21.

Another focus of the LOI 2 team in FY20 was establishing the foundation to integrate a Blast Overpressure (BOP) Tool into the Range Manager ToolKit (RMTK)—an existing suite of virtual tools that assist Unit Commanders and range safety officials in promoting safety during weapons training. The RMTK BOP Tool will provide a new capability of predicting the blast overpressure exposure of Service members using, or near, selected weapon systems. This information can guide decisions regarding training practices and injury risk tolerance, such as firing lane

distances and allowable number of rounds. Initial development of the RMTK BOP Tool was performed under a Defense Health Program-funded Small Business Innovation Research (SBIR) project, managed by BIRCO. This effort is also discussed in the [Managing SBIRs and Small Business Technology Transfers \(STTR\)](#) section of this chapter.

Moving forward, the LOI 2 team plans to form a working group in collaboration with the DOD Training and Doctrine Command (TRADOC), the U.S. Army Combined Arms Center, the U.S. Marine Corps, and other RMTK working groups (which include representation from all the Services) to support the coordination and execution of a prototype RMTK BOP Tool that focuses on a priority subset of weapon systems identified by the Services. After achieving a successful prototype, the next step will be to validate the tool under operational conditions. These field validation studies involve collecting data, such as high resolution blast wave forms, positioning of individuals relative to the blast source, atmospheric conditions, and characteristics of surrounding reflective surfaces, to generate simulations of blast wave propagation and blast pressure loading on individuals. A validated RMTK BOP Tool will lead to an improved understanding of Service member blast exposure and will inform safer protocols for repeated blast exposure in training.

MHS Blast Injury Prevention Standards Recommendation Process

BIRCO established the MHS BIPSR Process to fulfill the EA's responsibility to provide medical recommendations for blast injury prevention, mitigation, and treatment standards. The MHS BIPSR Process is DOD's first unbiased, inclusive, stakeholder-driven process to identify and assess the suitability and applicability of existing candidate standards and to recommend standards that meet DOD Stakeholder needs with a suitable level of validity, rigor, precision, and confidence.

In FY20, BIRCO continued to direct the BIPSR Processes for auditory blast injuries and dermal burns. A panel of subject matter experts (SME) thoroughly evaluated 14 candidate auditory injury prevention standards for their usability and to identify instances of high variability between them. The next steps are to review the results of these evaluations and eventually hold a consensus-building meeting with stakeholders from DOD, academia, and industry. For the dermal burns BIPSR Process, a call for participation led to interest throughout DOD in participating in this effort. Impacts from the COVID-19 pandemic delayed convening of a kickoff meeting until FY21.

Read more about the BIPSR Process, including more detailed information on the auditory blast injury and dermal burns efforts, in [Chapter 3](#).

International Collaborations

Advancements in blast injury prevention and treatment for Service members require close collaboration among researchers, clinicians, engineers, and other stakeholders domestically and internationally. BIRCO participates in several collaborative efforts of global scope and interest, which leverage the best talent and technology the world has to offer for the protection of Service members from blast injury. These activities include leading NATO-sponsored efforts to more precisely direct mitigation strategies for blast injury and participating in broad-ranging collaborations with other nations to pool scientific and technical expertise. Through BIRCO's collaborative international engagements, the U.S. shares and gains knowledge and insights on blast injury research with many other nations, improving our Service members' resilience against blast injury.

BIRCO has chaired Research Task Groups (RTGs) through the NATO Science and Technology Organization Collaboration Support Office's Human Factors and Medicine (HFM) Panel, including HFM-234 RTG and HFM-270 RTG. The NATO

HFM-234 RTG was tasked with establishing a framework for a new interdisciplinary research area focusing on the environmental toxicology of blast exposure. To meet this goal, collaborators developed a dictionary of blast injury terms; along with guidelines for conducting epidemiological studies, reproducing blast exposure in the laboratory, and using animal models in blast injury research. These products are the first international guidelines for conducting blast injury research and were published as a series of articles in *BMJ Military Health*.

The HFM-270 RTG produced a framework for the development of a comprehensive, threat-to-outcome computational modeling capability that can support an agile and streamlined approach to designing, testing, and fielding blast protection equipment. A final technical report is in preparation that comprises an extensive literature review of existing computational models, thorough list of modeling gaps, robust repository of information on existing modeling capabilities, and comprehensive dictionary of modeling and simulation terms.

Building on the HFM-270 work, BIRCO will chair a new RTG, “Validation of Modeling and Simulation Methodologies for Human Lethality, Injury, and Impairment from Blast-Related Threats,” which aims to start in FY21. The objective of this RTG, HFM-341, is to develop standardized methodologies and criteria to validate computational models and the simulation approaches established in the HFM-270 for the entire spectrum of blast-related injuries to mounted and dismounted personnel. The outcome will be an approach and criteria to validate component computational models and simulation techniques.

In addition, BIRCO will co-chair, with the U.S. Army Military Operational Medicine Research Program, the newly formed NATO HFM-Exploratory Team-192, “Blast Exposure Monitoring in Military

Previous NATO Activities Related to Blast Injury

- HFM-090: Test Methodology for Protection of Vehicle Occupants against Anti-Vehicular Landmine Effects
- HFM-175: Medically Unexplained Physical Symptoms in Military Health
- HFM-193: mTBI in a Military Operational Setting
- HFM-207 Symposium: A Survey of Blast Injury Across the Full Landscape of Military Science
- HFM-234: Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods, and Standards
- HFM-270: Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-Related Threats

Training and Operations.” The primary purpose of this exploratory team is to understand Service member occupational health hazards resulting from repetitive use of weapon systems and explosives during their military career. The secondary purpose is to recommend further exploration of strategies to prevent, mitigate unnecessary exposures, and sustain Service members’ brain health and performance. Outcomes from this effort will include both documentation of known and unknown relationships among blast exposure, brain health, and performance; and strategies used by NATO members to mitigate unnecessary blast exposures and brain health degradation.

The second International Forum on Blast Injury Countermeasures (IFBIC) was planned for May 2020 but was postponed until 2021 due to the COVID-19 pandemic. IFBIC started as the Japan-U.S. Technical Information Exchange Forum on Blast Injury, through which BIRCO has been collaborating with the National Defense Medical College of the Japan Self-Defense Forces since 2016. The second IFBIC in 2021 will be the fifth



Photo credit: 1st Lt. Matthew Groff/U.S. Army

meeting of the Japan-U.S. Technical Information Exchange Forum on Blast Injury. BIRCO organized the first IFBIC in 2019 after BIRCO and the National Defense Medical College of the Japan Self-Defense Forces agreed to open their ongoing information exchange forum to other nations.

BIRCO was the U.S. project lead for a collaborative effort between several DOD and academic labs and the Indian Ministry of Defence that concluded during FY20. This project, titled, “Experimental and Computational Studies of Blast and Blunt Traumatic Brain Injury (TBI),” was part of a bilateral forum between the U.S. and the Indian Ministry of Defence. The overall purpose of this effort was to better understand the mechanisms of blast and blunt TBI. It was a prolific collaboration, resulting in publication of dozens of peer-reviewed scientific articles (cited in Chapter 6). Notable accomplishments include establishing blast and blunt injury dose-response curves in animal models, developing identical shock tubes at two locations to replicate blast-related injury data

across laboratories, and new discoveries on the brain’s responses to blast exposure. Studies such as these build toward a better understanding of the mechanisms of injury in TBI, which is critical knowledge for accelerating the development and transition of blast injury prevention and treatment strategies.

Read more about the research and accomplishments from this U.S.-India collaboration in [Chapter 6](#).

International State-of-the-Science Meeting Series

BIRCO established the annual International State-of-the-Science (SoS) Meeting series in 2009 as a unique and enduring capability that leverages the expertise of outstanding scientists, engineers, and clinicians to identify knowledge gaps and to inform future research needed to close the gaps in the prevention, mitigation, and treatment of blast injury. Foundational components of each meeting

include a comprehensive background literature review to inform the meeting, panel discussions, presentations by researchers, and working groups chaired by expert panelists who assess the state of the science and make recommendations regarding policy and future research directions.

In March 2020, BIRCO sponsored the Ninth International SoS Meeting on blast-related injuries, which was hosted by the RAND Corporation. The topic of this meeting was, “Mitigating the Impact of Blast-Related Burn Injuries: From Prolonged Field Care to Rehabilitation and Resilience.” This meeting brought together 90 stakeholders from across DOD, other federal laboratories, academia, and industry, including both domestic and international participants.

Based on working group discussions, an expert panel prioritized knowledge gaps and made the following recommendations for blast-related burn injury research (Hoch et al., 2020):

1. Revisit injury classification and data collection methods to develop agreed-upon definitions for blast-related burn injuries that can be broadly disseminated
2. Develop improved training and guidance to support burn injury management in prolonged field care settings
3. Strengthen rehabilitation practices to enhance continuity of care and emphasize a return to full function
4. Conduct additional research on burn management in theater

A detailed discussion of these recommendations and other components of the meeting is provided in [Chapter 4](#).

The literature review and meeting proceedings for all International SoS Meetings, including the knowledge gaps and recommendations from the Expert Panels, are available on the BIRCO website (<https://blastinjuryresearch.amedd.army.mil/index.cfm/sos>).

Report to Congress on Research to Enhance Protection from Blast Injuries

BIRCO led the development of a report to Congress on the Army’s activities to improve protection from blast injuries. FY19 NDAA Section 226 required the Secretary of the Army, in consultation with the Director of Operational Test and Evaluation, to carry out activities to develop and assess the effectiveness of personal protective equipment (PPE) that provides enhanced protection against blast injuries. The law also required a report on these activities conducted during 2019.

BIRCO worked with research and development organizations across the Army to prepare the report. Overall, the report demonstrated how the critical collaboration between medical and non-medical communities within and outside DOD drives advancements in protecting Service members from blast injuries.

DOD Brain Health Research Coordination

Engagement with and coordination among DOD’s brain health research community is part of the scope of BIRCO’s role in fulfilling the EA’s responsibilities. The DOD Brain Health Research Coordinator (BHRC) at BIRCO works on behalf of the EA to promote, support, and coordinate research to yield solutions that improve Service members’ brain health in training, in combat, and at home.

BIRCO contributed to DOD’s “Comprehensive Strategy and Action Plan for Warfighter Brain Health (CSWBH)” effort, including participating in the related Capabilities-Based Assessment meetings to identify requirements and gaps in DOD’s ability to monitor, optimize, restore and support Warfighter brain health. The CSWBH was directed by the Deputy Secretary of Defense on October 1, 2018, to unify and improve efforts across DOD related to Warfighter brain health and countering TBI. BIRCO’s engagement in the



Photo credit: Sgt. Teddy Wade/U.S. Army

CSWBH effort supports the EA's responsibilities to identify knowledge gaps at the intersection of blast injury and brain health and shape research to fill those gaps through doctrine, organization, training, materiel, leadership and education, personnel, facilities, and policy (DOTMLPF-P) solutions. BIRCO's initiatives described elsewhere in this chapter further support DOD brain health research coordination, including the Section 734 BOS effort, U.S.-India collaboration on blast and blunt TBI studies, report to congress on research to enhance protection from blast injuries, and involvement in DOD research planning and evaluation processes.

Four additional examples demonstrate BIRCO's work in the brain health research community during FY20. The BHRC was the DOD Co-Principal Investigator of the "Long-term Impact of Military-relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium." Studies conducted

through this joint DOD and VA effort aim to address the long-term consequences of mild TBI in Service members and Veterans. The BHRC was also the appointed DOD ex officio member of the National Institute of Neurological Disorders and Stroke (NINDS) National Advisory Neurological Disorders and Stroke Council, which recommends support for grant applications, provides recommendations on policies and procedures affecting extramural research, and advises on program planning and concept clearance for NINDS initiatives. The BHRC also participated in the MHS TBI Advisory Committee, and presented at Brain Injury Awareness Day on Capitol Hill, which included discussing the path forward for TBI research, prevention, and recovery with the various technology, scientific, congressional, and advocacy groups in attendance.

DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats

BIRCO established the DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats (CMWG) in 2017 to promote coordination among the many modeling and simulation efforts that seek to improve protection and survivability from blast injury. The CMWG includes representatives from 28 DOD organizations and from other government agencies including the National Institutes of Health, the National Science Foundation, the National Aeronautics and Space Administration, the Federal Bureau of Investigation, the Federal Aviation Administration, Department of Veterans Affairs, Department of Homeland Security, and the National Highway Traffic Safety Administration.

The objective of the CMWG is to shape, focus, and coordinate efforts to enable an integrated and comprehensive capability for the computational modeling and simulation of human lethality, injury, and impairment resulting from the entire spectrum of blast-related threats and

environments, from initial point of interaction with the blast hazard to return-to-routine.

This new modeling capability will make it possible to rapidly develop and assess the impact of innovative personal and combat platform occupant protection concepts in a virtual environment, accelerate the development of effective treatment strategies, and predict health outcomes and disabilities. Valid predictive models will reduce the number of expensive and time-consuming dynamic tests by identifying only the specific cases that require additional experimental verification. As Service members encounter novel threats in future combat scenarios, this capability will allow DOD to quickly and adeptly address those threats. Reductions in resources required for Live Fire Test and Evaluation is also an expected outcome.

The modeling capability, as envisioned by the CMWG members, is sufficiently broad in scope to allow computational modeling and simulation from the time of exposure to the blast hazard through return-to-routine and is depicted in Figure 2-3. The blue block on the left of the schematic, *Until homeostasis is reached*, represents and focuses

FIGURE 2-3: Scope of modeling capability from blast threat to return-to-routine

The modeling capability is represented by everything within the dotted lines and has two modules: 1) Until homeostasis is reached and 2) Recovery and/or further degeneration.

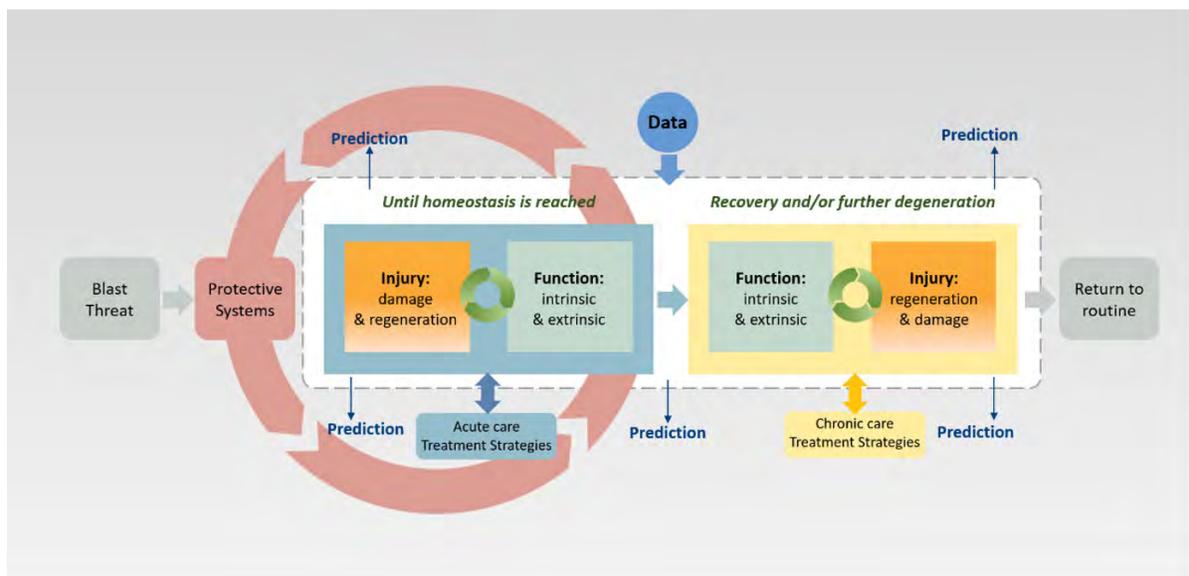




Photo credit: Sgt. Jesus Sepulveda Torres/U.S. Marine Corps

on the human condition from the point of injury until clinical homeostasis is reached; the yellow block, *Recovery and/or further degeneration*, represents and focuses on the human condition from the point of homeostasis through the rehabilitative process (until either rehabilitation is no longer needed or is stopped because it is not expected to yield an increase in function).

To achieve an integrated modeling capability, a DOD Computational Human Body Modeling Framework is envisioned that will support model selection for scenario development, scenario execution, guidelines and best practices for inter-model communication, guidelines and best practices for inputs and outputs, and analyses of results. Over the course of several meetings and follow-on discussions, the CMWG is developing a strategic plan to provide actionable, impactful guidance and recommendations for developing the Framework. A white paper on the technical challenges associated with development of the Framework has also been produced.

The strategic plan includes definitions of key terms in the modeling capability taxonomy, and it sets near-, mid-, and long-term strategies to develop, grow, and sustain the Framework, which will guide successful implementation of the modeling capability. Focusing on the near-term, the strategic plan details goals, objectives, and performance indicators that will drive the first five years of activity for the Framework. The central themes of the near-term strategy are promoting a shared vision of the modeling capability among stakeholders, increasing stakeholder access to models and data sources, and producing results that influence Warfighter lethality and return-to-duty practices.

In addition to the strategic plan, the CMWG developed a prototype Human Body Computational Modeling Registry to provide a centralized location for information about computational models so that users can easily obtain key information about the models and the developers or owners of those models. Information on models developed within

DOD, academia, and industry was captured using a Modeling Questionnaire developed by the CMWG and is included in the Modeling Registry. Model information is organized and searchable by criteria such as body region, use case, blast taxonomy, validation and verification, required data, and simulation type.

The CMWG also developed a prototype Blast Lethality, Injury, and Impairment Data Sources Registry to house information about data sources that inform human body computational models. As with the Modeling Registry, the CMWG developed a Data Sources Questionnaire to capture pertinent information about each data source. Collected information is organized and searchable within the Data Sources Registry by criteria such as use case, persons from whom the data were collected, timeframe of data collection, blast threat, spatial resolution, and standardized data format. The Data Sources Registry also includes information on how to access data.

In FY21, BIRCO plans to finalize the strategic plan, continue to add new information to the Modeling and Data Sources Registries, identify potential owners for the registries in perpetuity, and nurture and grow engagement in and commitment to the Framework through established and novel pathways.

The actions of the CMWG have garnered interest from high-level stakeholders outside DOD regarding the critical role that improved, validated mathematical models in coordination with data science and analytics can play in accelerating injury prevention, mitigation, and treatment strategies. In May and September 2020, BIRCO, on behalf of the CMWG, provided an invited briefing on the goals and activities of the CMWG to the Director and members of the Board of Mathematical Sciences and Analytics for the National Academies of Sciences, Engineering, and Medicine; and their colleagues from several academic institutions. The CMWG

and the National Academies plan to continue engaging to further their mutual goals.

Annual Report to the Executive Agent

BIRCO's annual report to the EA covers research and development efforts and programs focused on the prevention, mitigation, and treatment of blast injuries. Intended to inform senior DOD policy-makers, researchers, and public audiences, the annual report to the EA highlights blast injury research accomplishments across DOD that address the full spectrum of blast injuries. These reports are available on the BIRCO website (https://blastinjuryresearch.amedd.army.mil/index.cfm/annual_reports).

Every annual report features significant achievements submitted by the blast injury research community. This survey of blast injury prevention, treatment, and reset accomplishments broadly showcases research and development advancements to inform the EA and the blast injury research community of the state of the field. Research and development accomplishments from FY20 are presented in [Chapter 8](#) of this report.

In addition to providing accomplishments from the blast injury research community and substantial updates on BIRCO's activities, the annual reports include contributed chapters from stakeholder organizations. For example, the FY19 Report to the EA featured chapters from the U.S. Army Public Health Center and the National Intrepid Center of Excellence. This year, the report presents contributions from the Joint Trauma Analysis and Prevention of Injury in Combat on their program with EA responsibility to collect, integrate, analyze, and store operations, intelligence, materiel, and medical data to inform solutions that prevent or mitigate injury during the full range of military operations ([Chapter 5](#)). The report also presents contributions from the Psychological Health



Photo credit: Master Sgt. Matt Hecht/U.S. Air Force

Center of Excellence on their mission to facilitate evidence-based research and clinical practices across the continuum of care to enhance the psychological health of the military community ([Chapter 7](#)).

Managing SBIRs and STTRs

BIRCO actively shapes blast injury research through DOD SBIR and STTR programs. These programs harness the innovative talents and entrepreneurial energies of our nation's small technology companies to solve research challenges. BIRCO develops candidate topics for Phase I solicitations in the U.S. Army or Defense Health Agency SBIR and STTR programs and manages successful proposals funded for these topics. BIRCO managed three SBIR/STTR projects during FY20.

The first project was the design and development of a prototype computational modeling framework that consists of improved computational biology tools and whole body and brain injury models for simulations of blast injury and repetitive loading events. Called the CoBi-blast Injury Simulation framework, this anatomically consistent computational model of how the human body responds to injurious scenarios could provide a pathway to better understand blast injuries, interpret experimental data, and develop improved protective armor, diagnostics, and medical treatment procedures. Through coordination with TRADOC and the U.S. Marine Corps, the CoBi-blast Injury Simulation framework is being considered for integration in the RMTK as the RMTK BOP Tool. This new capability could assist installation range management authorities, Service members, unit commanders, and instructors involved in weapon systems training,

testing, and combat to make informed decisions on risk assessments. This effort is also discussed in the [Section 734 Blast Overpressure Study](#) section of this chapter.

The second project focused on the design and development of a “Warfighter Health Avatar” simulation platform, which consists of physiology-based modeling of a Warfighter body. This personal, predictive, preventive, and participatory capability could enable definite assessment of health status, physical and physiological performance, and injury trajectory by the user and medical personnel using mobile computing platforms.

Finally, the third, and ongoing, project is developing a biomechanically accurate rat model surrogate that can precisely measure the loading conditions experienced from a blast wave. This capability will allow correlation and cross-validation of research outcomes from different studies. Primary research can then be validated in the context of existing science, and actionable information can more efficiently be provided to medical researchers, protective equipment developers, and clinical personnel.

Historical Blast Bio-Effects Research Data Archive

Through the Historical Blast Bio-effects Research Data Recovery Project, BIRCO recovered, digitized, and has made available online, 50 years of research data on the biological effects of blast from DOD research conducted at Kirtland Air Force Base, New Mexico. This effort allows program managers, researchers, and decision-makers to use existing knowledge to address current and future blast injury problems. Applying lessons learned to current research and product development efforts prevents wasteful duplication of effort and allows DOD to focus scarce blast injury research resources on other critical knowledge gaps.

The DOD Historical Blast Bio-effects Research Data Archive is available for use by DOD and other government-sponsored researchers and can be accessed through the website <https://historical.blastinjuryresearch.amedd.army.mil/>.

Involvement in DOD Research Planning and Evaluation Processes

BIRCO helps to shape blast injury research programs by participating in research program planning, management, and advisory committees. Being an active participant in the blast injury research community ensures that key blast injury knowledge gaps are addressed, encourages collaborative research efforts, and identifies potentially duplicative research.

BIRCO’s continued engagement with the Joint Program Committees (JPC) and other organizations that manage research portfolios ensures that high-priority blast injury research issues are addressed in future medical research investments. In FY20, BIRCO brought perspectives gained from its research collaboration function to In-Progress Reviews and Review & Analysis meetings for 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, and Congressionally Directed Medical Research Programs. These meetings provide a high-level summary of the key areas of each program’s medical research investment and highlighted the importance of coordination and collaboration with researchers from other federal agencies, academia, and industry. They also underscore the remaining knowledge gaps, requirements, and challenges facing each research area.

Conclusion

Blast injuries include the entire spectrum of injuries that can result from exposure to an explosion. They are highly complex, involving multiple types of injuries and multiple body systems at once. Only a coordinated research effort involving DOD, other federal agencies, academia, industry, and international partners can solve our toughest blast injury research challenges.

Established and chartered in 2007 to support the DOD Executive Agent for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, BIRCO has structured an operational approach to move DOD toward a fully coordinated blast injury research program that delivers timely and effective injury prevention, mitigation, and treatment strategies to our Service members operating in a multi-domain environment today and in the future. Figure 2-4 summarizes recent accomplishments that have resulted from BIRCO's initiatives and engagements as presented throughout this chapter. See [Chapter 9](#) for a preview of BIRCO's activities in FY21 and beyond.

FIGURE 2-4: A summary of recent accomplishments from some of BIRCO's initiatives discussed in this chapter



Photo credits: Pfc Rashene Mincy/U.S. Army, Lance Cpl. Harrison Rakhshani/U.S. Marine Corps, Petty Officer 3rd Class James Hong/U.S. Navy.

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Photo credit: LCpl. Darien Bjorndal/U.S. Marine Corps

CHAPTER 3:

MHS BLAST INJURY PREVENTION STANDARDS RECOMMENDATION PROCESS

D ODD 6025.21E assigns to the DOD Executive Agent (EA) for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries the responsibility to “provide medical recommendations with regard to blast injury prevention, mitigation, and treatment standards to be approved by the Assistant Secretary of Defense for Health Affairs (ASD(HA)).” The term “Military Health System (MHS) Blast Injury Prevention Standard” is defined as a “biomedically-valid description of the physiologically- or biomechanically-based injury and performance response of a human to blast insults.” The standards can range from simple dose-response curves and injury thresholds that address single components of blast insults, such as peak force, to complex algorithms and computational models that address multiple components of blast insults, such as force-time history. Candidate standards include injury thresholds, human injury probability curves, and injury prediction tools needed to generate the information for informed trade-off and risk acceptance decisions by appropriate decision makers in the Research, Development, Test, and Evaluation (RDT&E), medical, and operational Stakeholder communities across the DOD Components. These standards support weapon

system Health Hazard Assessments, combat platform occupant survivability assessments, and protection system development and performance testing (Figure 3-1).

Designed to address the above requirement, the MHS Blast Injury Prevention Standards Recommendation (BIPSR) Process is the DOD’s first unbiased, inclusive, stakeholder-driven process designed to identify and assess the suitability and applicability of existing candidate standards and to recommend standards that meet DOD Stakeholder needs with a suitable level of validity, rigor, precision, and confidence.

The BIPSR Process has two major objectives. The first is to identify existing biomedically-valid candidate standards for immediate use by the DOD. The second is to inform the research community of gaps where no suitable candidate standards exist. The BIPSR Process is not a research program and is not used to develop new candidate standards. The BIPSR Process also does not attempt to impose acceptability or survivability requirements on the Stakeholder communities; rather, it seeks to ensure that the DOD uses the best available, scientifically sound, and biomedically-valid standards that will protect our Service members from blast injuries.



FIGURE 3-1: Blast injury prevention standards framework



i Acronyms and references used in this chapter are included in Appendices A and B.

The BIPSR Process

The BIPSR Process is designed to identify and objectively evaluate the details of available blast injury prevention standards to determine their suitability for use by the DOD in health hazard and survivability assessments, as well as in protection system development. The BIPSR Process can be tailored for a specific mechanism of injury, resulting in an objective set of recommendations that can serve as the basis of a medical standard. The BIPSR Process is designed to identify and critically evaluate blast injury prevention candidate standards and to recommend those that would best serve as MHS Blast Injury Prevention Standards to inform the DOD medical, test and evaluation (T&E), materiel development, and operational communities.

Core elements of the BIPSR Process include:

- **BIPSR Process Stakeholders Committee:**
A committee that defines the problem statement and scenarios to be assessed, identifies gaps in the current standard set, drives implementation, and participates in all major decisions throughout all phases of the BIPSR Process.
 - **Focused Stakeholder Committee:**
A subset of BIPSR Process Stakeholders with expertise related to a particular Blast Injury Type. They review existing capabilities through a literature survey using relevant keywords, identify subject matter experts (SME), identify existing candidate standards, define intended uses, and identify gaps.
- **SME Panel:** A broad-based, non-advocacy panel whose members are drawn from industry, academia, and government. The SMEs have experience in the domain of interest, development of the candidate standard product (e.g., dose-response curve, computational model), T&E, clinical medicine, and independent verification and validation.

- **Stakeholder-Driven Consensus-Building Meeting:** A forum for Stakeholders, the SME Panel, users, analysts, and candidate standard developers to discuss the DOD's intended uses, gain context and scope for the evaluation, and facilitate individual interviews with developers to gain a detailed understanding of candidate standard capabilities and/or profiles.

The BIPSR Process is initiated by a literature review that serves two purposes: identify existing capabilities and standards pertinent to the injury under evaluation, and compile a list of appropriate experts who may serve on the SME Panel that performs the evaluations. Once a list of candidate standards has been defined, the iterative nature of the BIPSR Process builds layers of information about the capabilities of each candidate under consideration.

The SME Panel conducts the initial evaluations, giving balanced, objective, and knowledgeable advice on the candidate standard's suitability for the DOD's intended uses based on the available information.

The list of candidate standards is narrowed based on an evaluation against a set of defined criteria. Information generated through the evaluation process serves as the basis for a meeting that provides a forum for Stakeholders (users, analysts, and developers) to build consensus, share information, and discuss the applicability of a candidate standard to the DOD's intended use—potentially narrowing the list of candidates that move forward in the evaluation process. In some cases (e.g., for computational models), the candidate standards undergo a detailed examination through a test process focused on Stakeholder-defined test scenarios. Once the test cases have been run, the results are assessed using statistical tools. In the final step of the BIPSR Process, the non-advocacy SME Panel and BIPSR Process support team conduct final evaluations, develop standards recommendations for

discussion with the Stakeholders and community at the Consensus Building Meeting, and prepare process improvement recommendations.

Collaboration opportunities are integrated across the BIPSR Process. As depicted in Figure 3-2, the BIPSR Process consists of six fundamental subprocesses supporting the overarching seventh.

Each phase in the BIPSR Process is designed to leverage the information from the previous phases, which builds layers of information about the viability of the candidate standards. As a result, the later subprocesses (V and VI) do not necessarily occur in sequence but are iterated as necessary to produce sufficient information to support the recommendations. Table 3-1 contains a high-level description of various activities that take place in the subprocesses that make up the BIPSR Process.

The timeline associated with the implementation of the BIPSR Process is driven by the number of candidate standards identified, the complexity of the candidate standards, and the complexity of the injury type. The BIPSR Process can be tailored to support compressed, quick-turnaround implementation that meets the need and critical nature of specific Blast Injury Types.

The identification and prioritization of the injury mechanisms fall outside the scope of the BIPSR Process and are the responsibility of the DOD Blast Injury Research Coordinating Office (BIRCO) and BIPSR Process Stakeholders. The BIPSR Process identifies, but does not resolve, capability gaps in the current standards. These gaps are shared with the DOD medical and non-medical science and technology communities.

BIRCO developed the BIPSR Process via a series of BIPSR Process Stakeholders meetings and obtained Armed Services Biomedical Research Evaluation and Management Committee approval.

The Johns Hopkins University Applied Physics Laboratory, a University-Affiliated Research Center and DOD trusted agent, supported BIRCO through the piloting of the BIPSR Process with an evaluation and analysis of toxic gas inhalation as an exemplar. Currently, the MITRE Corporation, a DOD trusted agent that operates a federally funded research and development center, supports BIRCO in the execution of the BIPSR Process by working closely with BIPSR Process Stakeholders and SMEs in the blast community.

FIGURE 3-2: BIPSR Process pillars

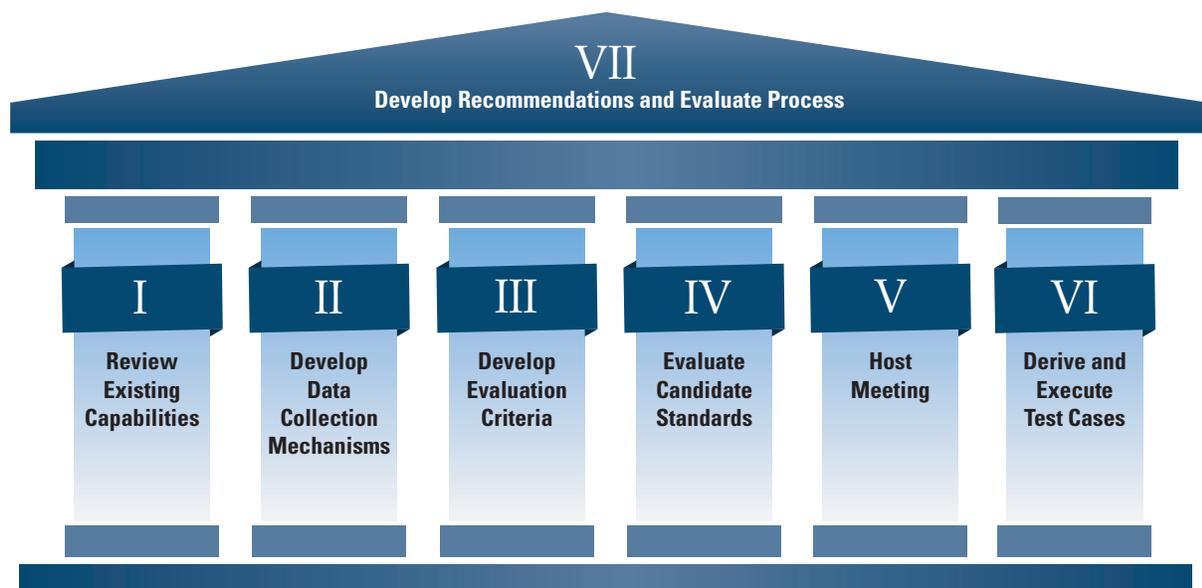


TABLE 3-1: BIPSR Process pillar activities

No.	Pillar	Activities
I	Review Existing Capabilities	<ul style="list-style-type: none"> Engage Stakeholders and identify relevant standards for the injury criteria through a systematic literature survey Establish a broad-based, independent review panel Poll the community by issuing a Request for Information (RFI)
II	Develop Data Collection Mechanisms	<ul style="list-style-type: none"> Develop standardized evaluation and information templates Conduct frequent panel meetings to establish review criteria
III	Develop Evaluation Criteria	<ul style="list-style-type: none"> Define scenarios and evaluation metrics Hold a Consensus-Building meeting
IV	Evaluate Candidate Standards	<ul style="list-style-type: none"> Conduct an interactive set of evaluations with the SME Panel and developers
V	Host Meeting	<ul style="list-style-type: none"> Hold a Consensus-Building meeting for Stakeholders to share information
VI	Derive and Execute Test Cases	<ul style="list-style-type: none"> Involve users and Stakeholders in the development of scenario-based test cases and execute the tests for the identified candidate standards (where applicable)
VII	Develop Recommendations and Evaluate Process	<ul style="list-style-type: none"> Produce a report that recommends standards for consideration as the basis for MHS Blast Injury Prevention Standards Recommend improvements to the BIPSR Process

BIPSR Process Improvements

To expedite the timeline required for the evaluation of a MHS BIPSR Process Blast Injury Type, BIRCO developed the BIPSR Process simulation model using the business process modeling notation standard. This standard modeling methodology graphically represents the BIPSR Process activities and facilitates quantitative and qualitative analysis via simulation.

As BIPSR Process milestones are reached with each Blast Injury Type under evaluation, and through feedback from the Stakeholders, modifications and improvements to the BIPSR Process are considered and evaluated for implementation.

In addition, the development and implementation of a web-based collaboration environment known as interactive BIPSR (iBIPSR) was initiated to enhance information sharing in real time and to further reduce the timeframe to complete the BIPSR Process for each of the remaining MHS BIPSR Process Blast Injury Types.

iBIPSR Capability

The iBIPSR capability has foundations in collaborative semantic web technology, an information synthesis technology well-suited for large, collaborative, multi-user information sharing and decision-making efforts. The iBIPSR site is an online forum developed to enhance information sharing among blast injury experts. The standard wiki format has been enhanced with user-friendly user interfaces, built-in help capability, and an internal feedback mechanism to allow users to report inconsistencies and suggest enhancements.

iBIPSR relies on commercial off-the-shelf (COTS) software and MITRE-developed extensions. The site now follows the COTS upgrade cycle to remain current and improve the security posture.

iBIPSR supports BIRCO's mission in support of the EA to leverage existing knowledge and foster collaboration among academia, industry, international partners, and government organizations by providing a platform for continuous participation throughout the BIPSR Process, ensuring the collected wisdom resides on iBIPSR.

As shown in Figure 3-3, the iBIPSR capability supports a variety of users engaged in planned collaborative interactions between and among BIPSR Process Stakeholders, SMEs, BIRCO, and the MITRE team.

Additionally, the iBIPSR capability offers transparency by capturing and managing Stakeholder organizations' knowledge gaps and needs to facilitate understanding through near-real-time communication among participants. The MITRE team has developed the iBIPSR capability using best practices, established standards, and user input. iBIPSR will continue to evolve through user input to ensure it meets the knowledge-sharing goals of the mission.

Power of iBIPSR

The iBIPSR capability represents a novel way to shorten the timeline of the BIPSR Process without sacrificing decision quality. Following

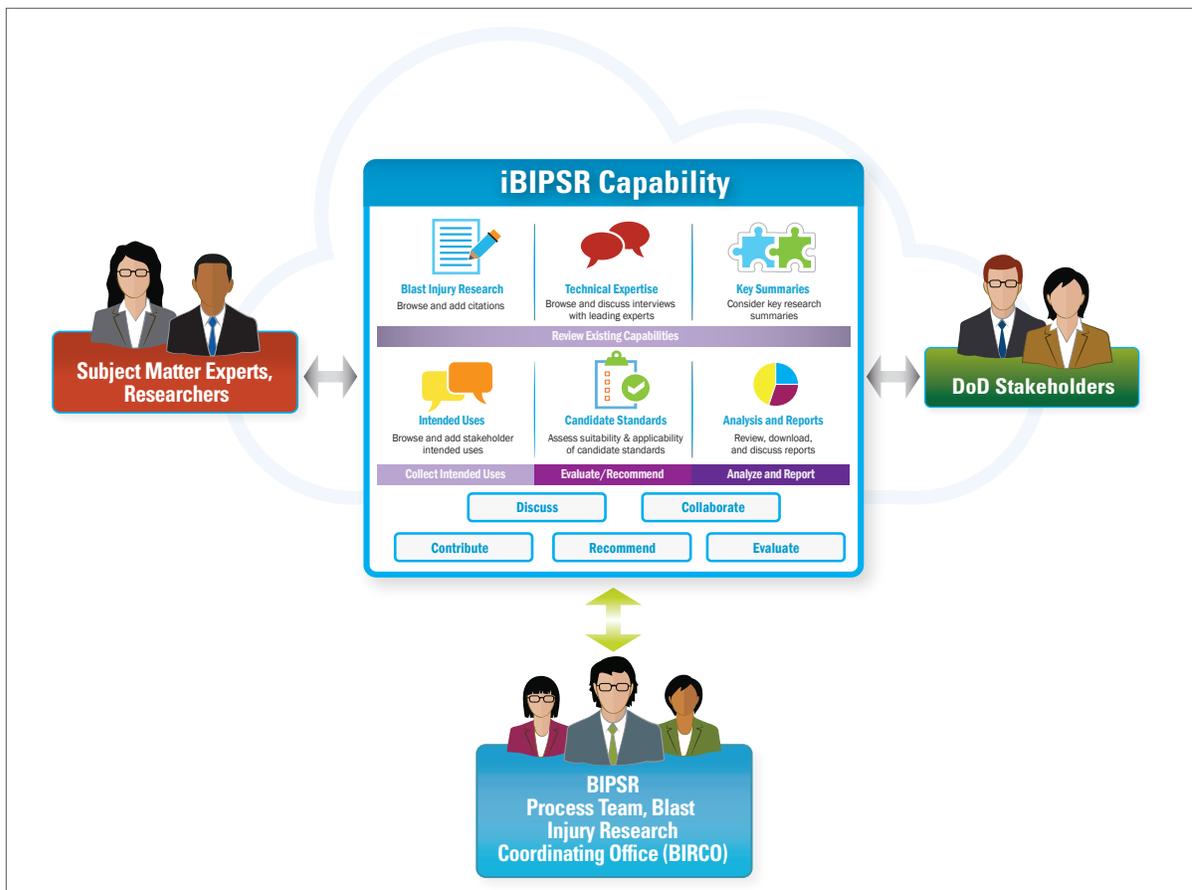
initial enrollment of the Auditory Focused Stakeholders, the iBIPSR capability has been improved by expanding the user base and dynamically incorporating user feedback to develop and improve site features. Ultimately, BIRCO anticipates that all BIPSR Process Stakeholders and designated SMEs will use the iBIPSR capability.

The Power of the iBIPSR Site

The iBIPSR site is well-suited to large, collaborative, multi-user information sharing and decision-making:

- Leverages existing knowledge
- Utilizes technology to foster continuous collaboration
- Removes obstacles to participation (e.g., travel and scheduling)
- Allows for broad engagement in the process with access to information used in all stages of the BIPSR Process

FIGURE 3-3: BIPSR Process supported by the iBIPSR site



MHS BIPSR Process Blast Injury Type Prioritization

Through a series of initial BIPSR Process Stakeholder Meetings hosted by BIRCO, BIPSR Process Stakeholders categorized a total of 14 MHS BIPSR Process Blast Injury Types based on specific body regions (Figure 3-4). This represented a shift from an older classification of injury types that referred to individual organs and bones (as described in a 1989 report from the Walter Reed Army Institute of Research).

To initially identify the needs of the DOD, the BIPSR Process team applied a mathematical methodology, using Stakeholder inputs, to establish a priority ranking of the Blast Injury Types that determined the initial order for executing the BIPSR Process. This Blast Injury Type prioritization methodology assessed and rated each MHS BIPSR Process Blast Injury Type against six Evaluation Factors that were developed by the BIPSR Process Stakeholders and are defined in Table 3-2. As of FY20, the Lower Extremity, Spine and Back, and Upper Extremity Blast Injury Types are complete, and the BIPSR

Process is underway for the Auditory and Dermal Burns Blast Injury Types.

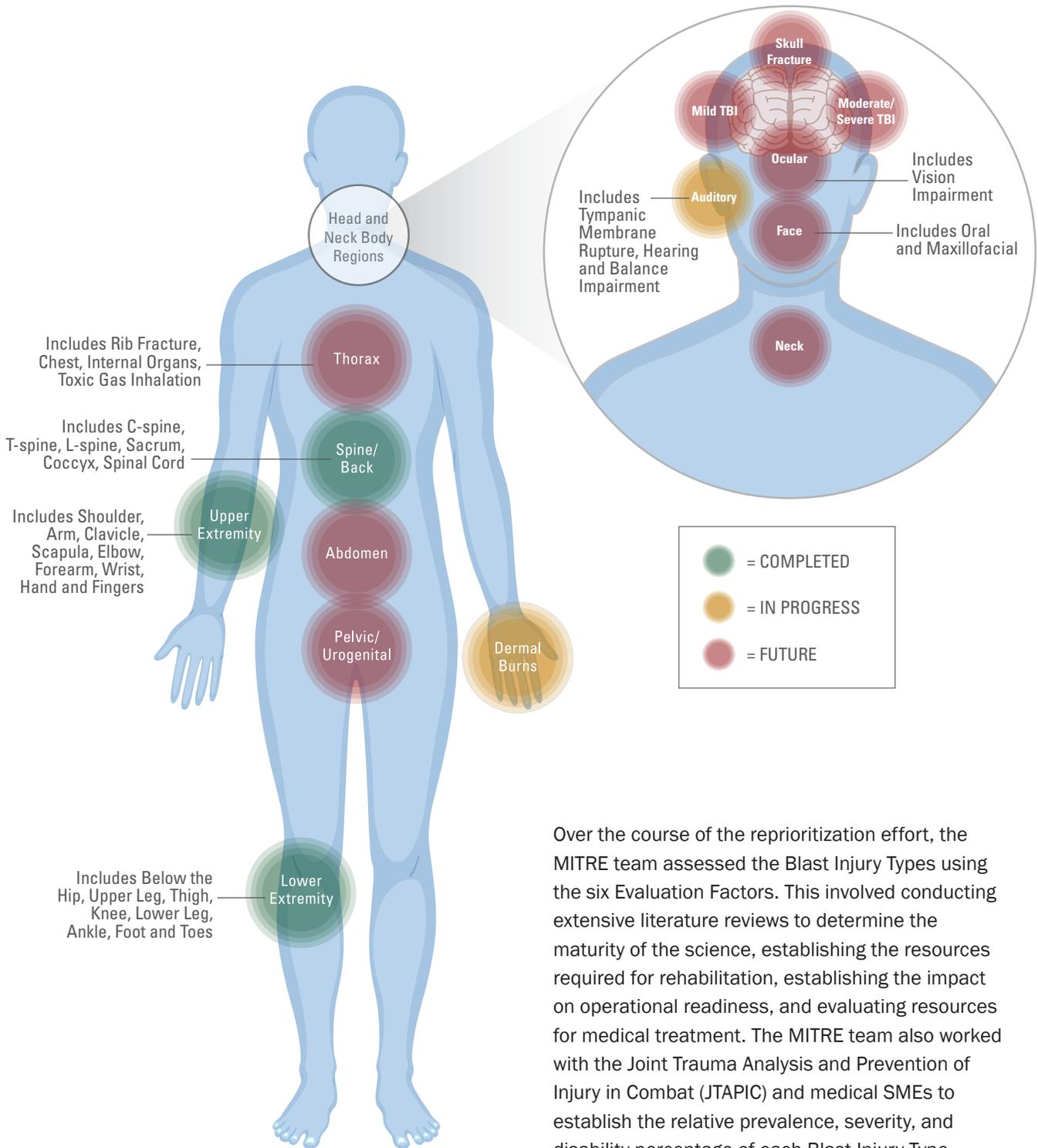
To ensure the current needs of the operational environment and the DOD are being met, BIRCO has performed a reprioritization effort for the remaining nine MHS BIPSR Process Blast Injury Types: Ocular, Face, Neck, Thorax, Abdomen, Pelvic/Urogenital, Skull Fracture, mild traumatic brain injury (mTBI), and Moderate/Severe TBI. The reprioritization effort applied an established mathematical analysis technique, multi-attribute utility theory (MAUT), a widely used, widely accepted methodology for guiding tradeoffs among multiple objectives.

This reprioritization effort again assessed the remaining MHS BIPSR Process Blast Injury Types against the six BIPSR Process Evaluation Factors that had been developed and used in the initial prioritization effort (Table 3-2). The Evaluation Factors and scoring scales used in the MAUT methodology provide a framework for capturing subjective assessments to support an objective and unbiased decision-making process.

TABLE 3-2: BIPSR Process evaluation factors

Evaluation Factor	Description
Impact on Operational Readiness	The time for a Service member to return to duty.
Blast Injury Prevalence Rate	The number of cases of a given Blast Injury Type expressed as a percentage of the total number of blast injuries.
Treatment Resources	Roles of medical treatment, which are the distribution of medical resources and capabilities to provide Service member's medical care.
Maturity of the Science	Determined by the existence of established standards (e.g., Military Standard (MIL-STD)-1474E Noise limits design criteria) or, in the absence of established standards, by the degree to which biomedically-valid injury mechanisms have been published in the peer-reviewed scientific literature, or by the development and application of assessment methodologies based on the established injury mechanisms to assess injury risks.
Rehabilitation Resources	Resources required to support a Service member's rehabilitation beyond immediate treatment resources and may include therapy, pharmaceuticals, or devices needed to reset for quality of life.
Disability Percentage	Designated percentage assigned to an injury type when calculating disability benefits.

FIGURE 3-4: Categorization of MHS BIPSR Process blast injury types by body region



Over the course of the reprioritization effort, the MITRE team assessed the Blast Injury Types using the six Evaluation Factors. This involved conducting extensive literature reviews to determine the maturity of the science, establishing the resources required for rehabilitation, establishing the impact on operational readiness, and evaluating resources for medical treatment. The MITRE team also worked with the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) and medical SMEs to establish the relative prevalence, severity, and disability percentage of each Blast Injury Type.

BIPSR Process Stakeholders provided inputs to the reprioritization process to ensure that the results reflect current DOD priorities.

In the final step of the exercise, a score was calculated, using the MAUT methodology, for each Blast Injury Type, resulting in a new rank order.

BIRCO shared the results of the reprioritization exercise at the BIPSR Process Stakeholder Committee Meeting #6 on December 11, 2018. Table 3-3 shows the new recommended order for initiating future MHS BIPSR Process Blast Injury Types.

TABLE 3-3: Recommended order for initiating future blast injury types

Blast Injury Type	New Rank Order
Skull fracture	1
Pelvic/urogenital	2
Moderate/severe TBI	3
Thorax	4
Abdomen	5
Mild TBI	6
Face	7
Neck	8
Ocular	9

Update on Implementation of the BIPSR Process

BIPSR Process for the Auditory Blast Injury Type

The BIPSR Process for the Auditory Blast Injury Type is in progress, and is being used as an exemplar to prove the iBIPSR capability. As part of the initial steps of the BIPSR Process, the MITRE team completed the Existing Capabilities Review of the Auditory Blast Injury Type: performing an in-depth literature survey, posting an RFI on the Federal Business Opportunities (FedBizOpps) website, and interviewing SMEs from industry, academia, and government agencies. BIRCO also

established the Auditory Focused Stakeholder Committee, comprising 14 members representing the Army, Navy, Air Force, Marine Corps, Department of Veterans Affairs, and the materiel development, operational, T&E, and medical communities of interest. The Auditory Focused Stakeholder Committee members drive all major decisions for the BIPSR Process Auditory Blast Injury Type.

Summary of Work Before FY20

During the Auditory Focused Stakeholder Committee Meeting in FY16, participants concurred with the MITRE team’s recommendation to continue the BIPSR Process for the Auditory Blast Injury Type by convening a SME Panel of auditory experts to independently evaluate the existing blast-related auditory injury prevention capabilities.

BIRCO subsequently supported the assembly of the BIPSR Process Auditory SME Panel whose members are drawn from industry, academia, and government. Aligned with the BIPSR Process, these SMEs have experience in the domain of interest, development of the candidate standard product (e.g., dose-response curve, computational model), T&E, clinical medicine, and independent verification and validation.

The first meeting of the BIPSR Process Auditory SME Panel took place September 19–20, 2017. During this meeting, the MITRE team introduced the SME Panel to the BIPSR Process, iBIPSR, and the findings to date. After this introduction, the MITRE team worked with the SME Panel to revise the Intended Uses of a Candidate Standard (which were provided by the Stakeholders) and Evaluation Criteria in preparation for the independent Candidate Standards evaluation.

The second meeting of the BIPSR Process Auditory SME Panel was held on February 27, 2018. During Meeting #2, the MITRE team reviewed the Candidate Standard Evaluation Methodology, and the SME Panel discussed and updated the



Photo credit: Pvt. Jared N. Gehmann/U.S. Army

Evaluation Factors. At the end of the meeting, the MITRE team provided information about the next steps in the BIPSR Process, including finalizing the Evaluation Factors.

During SME Panel Meeting #3, held on July 31–August 1, 2018, the Panel reviewed its activities to-date; the Evaluation Methodology and Findings, Evaluation Criteria, and Candidate Standards; and finalized the evaluation materials. The SME Panel discussed topics influencing the relative importance of different Evaluation Factors and discussed information that would be needed about the Candidate Standards in order to complete the evaluation. The SME Panel established the weights and scoring levels that would be used to evaluate the Candidate Standards.

The fourth meeting of the SME Panel was held November 27–28, 2018 and was followed by a series of six teleconference calls. Discussion during these meetings included detailed reviews of Candidate Standard information collected from

the literature and in coordination with Candidate Standard Developers/Champions, Test Cases, and datasets.

The SME Panel reviewed information for 14 Candidate Standards and identified clarifying questions for the Candidate Standard Developers/Champions. Candidate Standard Developers/Champions provided written responses to the SME Panel that were discussed at the following SME Panel teleconference meeting. The culminating result of these meetings was the completion of the Candidate Standard Information Documents on August 9, 2019.

Discussion of datasets and Test Cases resulted in the development of a list of datasets and the SME Panel Usability Assessment Activity to investigate Candidate Standard usability and identify instances of high variability between Candidate Standards, which could be used to prioritize future research.

Developments in FY20

Early in FY20, the SME Panel reviewed and assessed comprehensive information on identified Candidate MHS Auditory Blast Injury Prevention Standards. They also reviewed existing datasets, identified knowledge gaps in existing auditory blast injury data, considered approaches for the upcoming evaluation of candidate standards, and discussed the development of a T&E plan to ensure the validity and biofidelity of the models.

In support of the SME Panel's evaluation, the MITRE team completed the development of the Usability Assessment process for the Auditory Blast Injury Type in October 2019. The goals of this assessment were to investigate Candidate Standard usability and identify instances of high variability between Candidate Standards, which could be used to prioritize future research.

The SME Panelists and Candidate Standard Developers/Champions completed the Usability Assessment in December 2019. Participants used the Candidate Standards to calculate the allowable number of rounds for five deidentified waveforms. MITRE analyzed the results, then presented findings and discussed the outcomes at a SME Panel meeting on March 13, 2020. This included discussion of the potential causes of variability in responses between SME Panelists; consensus allowed the BIPSR Process to progress.

The SME Panel then initiated the next steps of their independent evaluation of each Candidate Standard using the Evaluation Factors they had developed. Over three meetings during April and May 2020, the SME Panel completed a structured evaluation of the Candidate Standards. They discussed topics such as how limitations with collected waveforms (e.g., artifacts) affect the accuracy of Candidate Standards. BIRCO then initiated collation and analysis of the Candidate Standard information and the SME Panel contributions.

Automatic Waveform Anomaly Real-Time Detector (AWARD)

BIRCO supported development of prototype software to detect anomalies that can result from issues with auditory data collection systems and flag waveforms to be further examined. The approach was developed in MATLAB for easiest transition to research and data acquisition communities. SME Panelists provided feedback on this capability and BIRCO plans to expand on the tool, including testing and verification, in FY21.

Next Steps for the Auditory Blast Injury Type

In FY21, BIRCO plans to complete the initial analysis and share initial findings with the SME Panel, including interpretation of results to support auditory blast injury prevention; share these findings with the BIPSR Process Stakeholders; and host a Consensus-Building Meeting with Stakeholders, academia, and industry according to the BIPSR Process.

After the SME Panel finalizes their evaluation of the Candidate Standards using the Evaluation Factors and the Candidate Standard Information template, MITRE will apply MAUT to analyze the information. The SME panel will review the initial results and discuss detailed findings from the Candidate Standard evaluation. Following these steps, the SME Panel will develop a draft recommendation. In the final steps of the BIPSR Process, BIRCO will host a Consensus-Building meeting with Stakeholders, Candidate Standard Developers/Champions, and government SMEs to share findings and allow for discussion and further investigation of the recommended actions. Final recommendations will be shared with DOD Leadership in a report.



Photo credit: Spc. Justin Stafford/U.S. Army

BIPSR Process for Dermal Burns Blast Injury Type

The BIPSR Process for the Dermal Burns Blast Injury Type has been initiated per the recommendation of the BIPSR Process Stakeholders, and the Existing Capabilities Review is in progress. Early activities included a literature review and identification of potential SMEs for interviews.

In early FY20, a call for participation of Dermal Burns BIPSR Process Stakeholders led to interest from throughout DOD. Impacts from the COVID-19 pandemic delayed establishing the full Stakeholder group and convening a kickoff meeting until FY21.

Next Steps for Dermal Burns Blast Injury Type

According to the BIPSR Process, SME interviews will be coordinated to ensure a thorough understanding of the current state of the science. DOD Stakeholders will be invited to formally convene the Dermal Burns Focused Stakeholder Committee, which will drive the activities and decisions of the BIPSR Process. Once convened, the Focused Stakeholders will issue an RFI relating

to potential injury prediction/simulation standards to ensure a broad canvassing of the community. Interviews with Focused Stakeholders following the first Stakeholder Committee Meeting, currently planned for FY21, will generate Intended Uses for an MHS Blast Injury Prevention Standard for Dermal Burns. An analysis of the Intended Uses against identified Candidate Standards will inform the next steps in the BIPSR Process for Dermal Burns.

Way Forward

Ultimately, the knowledge gaps revealed and the recommendations developed through the BIPSR Process will enable DOD to apply MHS Blast Injury Prevention Standards that support weapon system Health Hazard Assessments, combat platform occupant survivability assessments, and protection system development and performance testing. The science and technology knowledge gaps identified for MHS BIPSR Process Blast Injury Types will be shared with the medical research community to inform the development of future MHS Blast Injury Prevention Standards.

04



Photo credit: Master Sgt. Corenthia Fennell/U.S. Air Force

CHAPTER 4:

**INTERNATIONAL
STATE-OF-THE-SCIENCE
MEETING SERIES**

In 2009, the DOD Blast Injury Research Coordinating Office (BIRCO) established the International State-of-the-Science (SoS) Meeting Series. Since the inaugural meeting, the International SoS Meeting Series has been a forum for knowledge sharing, collaboration, and communication across the blast injury research community. The meetings stand as a unique and enduring capability that leverages the expertise of outstanding scientists, engineers, and clinicians to identify knowledge gaps and inform future research needed to close the gaps in the prevention, mitigation, and treatment of blast injury. Participants in the SoS Meetings include representatives from the DOD (including the medical, operational, and materiel communities), other U.S. government agencies, academia, industry, and international communities. Figure 4-1 displays past SoS Meeting topics.

The key objectives of the SoS Meetings are to determine what is known and unknown regarding focused blast injury topics and formulate recommendations for medical research and other actions that will close knowledge gaps and enable delivery of timely and effective blast injury prevention, mitigation, and treatment strategies to Service members.

BIRCO, with support from RAND Corporation, hosted the Ninth International SoS Meeting, “Mitigating the Impact of Blast-Related Burn Injury: From Prolonged Field Care to Rehabilitation and Resilience” in March 2020. A detailed presentation of this meeting and the recommendations that followed is presented after a general overview of the SoS Meeting format.

FIGURE 4-1: Topics of previous SoS Meetings



i Acronyms and references used in this chapter are included in Appendices A and B.

Meeting Format

The SoS Meetings follow a unique format that has proven successful across a variety of blast injury topics, with critical events happening during pre-meeting, meeting, and post-meeting phases (Figure 4-2). During the pre-meeting phase, DOD stakeholders identify a blast injury topic. Then, a Planning Committee is assembled to refine and shape the meeting by setting meeting objectives, overseeing a literature review that is conducted to inform the meeting, selecting scientific presentations and posters, and identifying an Expert Panel. During the meeting, keynote and topic speakers lay out the scope of the challenges in plenary sessions. These sessions are followed by a series of presentations and a poster session to review the state of the science across multiple topic areas. Participants then break out into Working Groups chaired by Expert Panel members, where discussions are driven by questions previously developed by the Planning Committee. During the post-meeting phase, the Expert Panel distills Working Group findings and formulates specific, actionable recommendations. A final proceedings report highlights the key findings and recommendations resulting from the meeting.

The Planning Committee

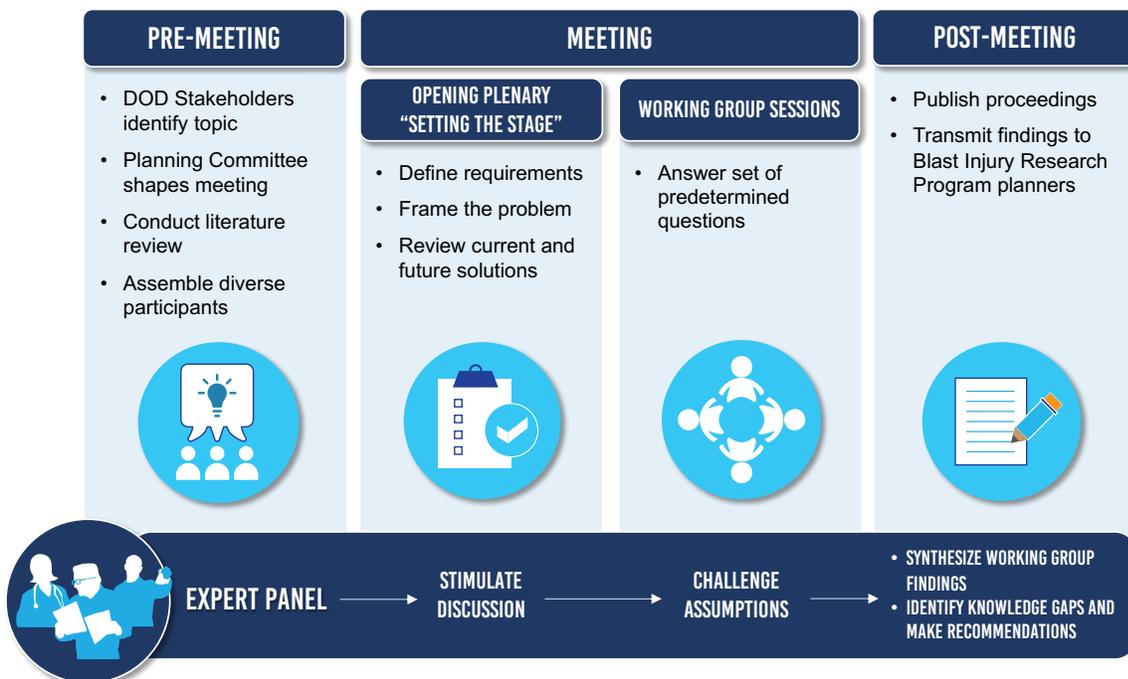
The Planning Committee is essential to the success of the SoS Meeting. After the meeting topic is defined, a Planning Committee of relevant experts is assembled. The Planning Committee includes subject matter experts (SME), research program managers, clinicians, and policy experts chosen from DOD, other federal agencies, academia, and industry, who examine the topic from diverse perspectives. The Planning Committee meets regularly to shape the focus of the meeting and develop the following meeting elements:

Meeting Title: After DOD stakeholders select the topic, the Planning Committee works to focus and refine the meeting title.

Meeting Objectives: The Planning Committee develops meeting objectives that set the tone, direction, and goals for the meeting.

Literature Review: Before each meeting, the Planning Committee commissions an extensive literature review that is distributed to all participants prior to the meeting to familiarize them with the current state of knowledge on

FIGURE 4-2: Overview of the SoS Meeting process



the identified blast injury topic. The Planning Committee shapes the literature review by providing input and guidance at key steps prior to literature review completion.

Working Group Questions: The Planning Committee develops a set of questions to guide Working Group sessions during the meeting.

Expert Panel: The Planning Committee nominates and selects an Expert Panel made up of five or six SMEs, who have key responsibilities during and after each meeting. This Panel comprises distinguished scientists, engineers, clinicians, and military experts who are leaders in their fields and are recognized authorities on the meeting topic.

Meeting Presenters: The Planning Committee shapes the plenary sessions by identifying potential keynote speakers and topic presenters.

Abstract Selection: The Planning Committee reviews and scores abstracts submitted for the meeting. This process is used to determine which abstracts will be accepted for a poster or oral scientific presentation.

Meeting Participants: The Planning Committee helps promote each meeting and ensures involvement from military and other stakeholder communities (e.g., medical, operational, and materiel development), and diverse SMEs from the DOD, other federal agencies, academia, industry, and international partners.

The Expert Panel

During the meeting presentations, the multidisciplinary Expert Panel is charged with challenging assumptions and stimulating thoughtful discussion. Following the presentations, meeting participants are divided into Working Groups, each comprising individuals with diverse expertise, led by an Expert Panel member. Over two days, Working Groups engage in deliberations to answer a set of questions developed by the

Planning Committee. The findings and insights from these sessions are documented and are the basis for formulating specific, actionable recommendations.

Following the conclusion of the meeting, the Expert Panel convenes in a closed session to identify major themes that emerged during the meeting, synthesize the relevant findings, identify knowledge gaps, and make recommendations. This process considers the major discussion points and key ideas that recurred throughout the literature review, meeting presentations, poster sessions, and Working Groups.

The proceedings and recommendations from the meeting are documented in a report that is disseminated to all blast injury research stakeholders and is made publicly available on the BIRCO website at <https://blastinjuryresearch.amedd.army.mil/index.cfm/sos>.

Ninth International SoS Meeting: “Mitigating the Impact of Blast-Related Burn Injuries: From Prolonged Field Care to Rehabilitation and Resilience”

To identify knowledge gaps in the prevention, mitigation, and treatment of blast-related burn injury, and inform future research needed to close those gaps, BIRCO held the Ninth International SoS Meeting on March 3–5, 2020, at the RAND Corporation in Arlington, Virginia.

Blast-related burns sustained by Service members in combat can be devastating, tend to be more severe than burns sustained in civilian environments, and are among the most complex types of injuries to treat. Approximately 5–20 percent of combat casualties in conventional warfare include burn injuries (Cancio et al., 2005). Blast events are a significant source of burn injuries; for example, explosions accounted for 87 percent of burn injuries at a combat support hospital in Iraq (Laird et al., 2012).

Acute treatment of burn injuries is a complex endeavor. Burns cause a severe inflammatory and hypermetabolic state that can lead to multi-organ failure. Blast-related burns may be at an elevated risk of infection due to contamination with dirt and debris from the blast site. Immediate evacuation from theater may not always be possible and casualties may need to be managed in a prolonged field care environment, which presents challenges unique to the military.

Severe burn injuries overcome the body's own regenerative abilities, presenting the need for extensive reconstructive procedures and leading to extended rehabilitation timelines. Scarring from burn injury can be disfiguring and may limit function of the affected area, which can negatively impact mental health and quality of life.

Literature Review

To inform the meeting, the RAND Corporation conducted a comprehensive review of peer-reviewed scientific literature and DOD grey literature (e.g., technical reports) published from 2008 to 2019 on burn injury following a blast event. The review covered basic and applied clinical research on the biophysical mechanisms of blast-related burn injuries and complications, burn injury prevalence, and aspects of acute and long-term burn care. This literature review is available through the link in the call out box. Literature reviews for past SoS Meetings are available on BIRCO's website at: <https://blastinjuryresearch.amedd.army.mil/index.cfm/sos>.

Studies included in the literature review were categorized as basic (foundational, etiologic, and descriptive epidemiological) or applied (clinical, health services, and policy) research areas. A majority of the basic research consisted of epidemiological studies, while applied research addressed a full spectrum of relevant topics: injury prevention, screening and assessment, treatment and follow-up, health services, and military policy.

This introduction and the *Literature Review* section were adapted from the literature review conducted by the RAND Corporation for the Ninth International SoS Meeting (Engel et al., 2020).

The literature review is available at:
www.rand.org/pubs/research_reports/RRA807-1

Epidemiological research suggests that, although the prevalence of blast-related burn injuries is lower than that of some other combat-related injuries, these injuries are nevertheless a common feature of serious combat injury and present a level of complexity that merits greater research attention from both clinical and operational perspectives. Among those evacuated from theater for burn injury, about one-third did not return to duty, depending on the total body surface area (TBSA) burned and inhalation injury (Chapman et al., 2008). Infection is perhaps the most common and serious blast-burn complication and cause of death, and it is potentially more common after combat blast-related burns than non-combat-related burns.

Foundational and etiologic research primarily addressed the physics of blast injury and the biophysiological mechanisms of blast-related burn injuries and ensuing complications. Several studies discussed mathematical models and controlled blast experiments to predict burn-injury severity under a variety of conditions (Antanovskii & Remennikov, 2010; Shuker, 2010). Shorter distance from the blast and enclosed (versus open) spaces resulted in increased burn injury severity. Other factors, such as type of explosive materials and individual risk factors, were discussed less often and might represent important areas for future research.

Etiologic studies of the relationship between blast-related burns and concomitant blast-related injuries, including penetrating wounds,



Photo credit: Jose Rodriguez/U.S. Air Force

blast-related burns among Service members. Multiple authors noted the difficulty of preventing injuries in combat situations while maintaining the flexibility and efficiency necessary for Service members to perform their duties. The results of informational interventions to prevent burn injuries have been mixed (Hedman et al., 2008; Kauvar et al., 2009). Lastly, the literature reviewers inspected articles that assessed effectiveness of diagnostic and severity assessment tools in military contexts. They found evidence that existing methods for measuring TBSA, for example, produce highly variable results (Martin et al., 2014). The impact on clinical outcomes is unclear and should be assessed. Other studies of follow-up care included studies relating to nutritional support, physiotherapy, and family involvement in recovery after burn injury. More research is needed that addresses the long-term needs of patients with blast-related burns.

infection, anemia, and hypertension, have identified various mechanisms by which these injuries can complicate treatment and subsequent outcomes. Future research should address the biophysical relationships between blast-related burns and co-occurring injuries, including polytrauma type and severity. Additional research should focus on the mechanisms behind and clinical complications of blast-burn exposure.

Most treatment research on blast-related burns addressed acute care, early surgical wound care, and longer-term maintenance care. There were fewer studies addressing follow-up care (research addressing the length and durability of treatment, long-term consequences of treatment, rehabilitation, and relapse prevention). Efforts to improve the quality of care for burns are underresearched. Several studies have outlined innovations related to pain management and reduced risk of infection, both of which are areas that require further study.

In terms of prevention and screening, there were relatively few research projects that were concerned with developing new material and devices to prevent

Finally, despite the limited body of research on military policy and health services, articles from these categories provided various insights, which were primarily concerned with cost, care-coordination efforts and guidelines, and flow charts developed to aid in care delivery. In terms of cost, the research indicated that inpatient ward fees, therapeutic treatment fees, and medication fees were the biggest cost drivers. With regard to care coordination, authors emphasized the importance of multidisciplinary and multi-organizational collaboration in triage and transportation of military or civilian burn patients. Finally, studies in which researchers examined the effectiveness of, and user compliance with, burn-resuscitation guidelines and use of burn flow sheets had mixed results. However, system-wide standardization was shown to improve outcomes for severely burned patients.

A unique aspect of health service delivery for burns incurred in the military context involves the potential need for prolonged field care. Therefore, strategic thinking and specific planning are necessary to develop, practice, and refine potential strategies to care for burns in prolonged field care settings.

Recommendations from the Literature Review

The literature review study team issued four recommendations to support the Expert Panelists in facilitation of Working Groups during the SoS Meeting. Their recommendations were to:

1. Invest in research areas where the epidemiology indicates a greater need for improvement in clinical care and service delivery.
2. Review how guidelines are developed, how often they are updated, and how the guidelines integrate new evidence.
3. Expand training on, and test new models of, prolonged field care for blast-related burn injuries.
4. Develop enhanced care coordination and triage strategies for civilian burn patients receiving care in military treatment facilities.

Meeting Summary and Working Group Discussions

Ninety SMEs from across the DOD, other federal laboratories, academia, and industry participated in the SoS Meeting, including representation from 10 countries. The agenda consisted of an invited keynote presentation, topic presentations on key background science and policy, selected scientific presentations, a poster session, concurrent Working Group sessions, and Expert Panel member briefings that summarized discussions during the Working Group sessions. Following the meeting, the Expert Panel reviewed meeting data and formulated recommendations.

On the second and third days of the meeting, participants were divided into five Working Groups that were each chaired by an Expert Panel member. The Working Groups used the expertise of their members, findings from the literature review, and information from the meeting keynote,

topical presentations, and emerging scientific presentations to address four questions:

1. What is the true scale and prevalence of blast-related burn injuries? What research is needed to better characterize the magnitude of this problem?
2. What skills, capabilities, and equipment are needed to better manage blast-related burns in the prolonged field care setting?
3. What are the most promising preventive and/or rehabilitative interventions for patients with blast-related burn injuries? What research is needed to understand their effectiveness and limitations?
4. What are the most important gaps pertaining to blast-related burn injuries?

Working Group discussions, summarized in the meeting proceedings, were used to inform the recommendations developed by the Expert Panel.

Expert Panel Recommendations

The Expert Panel combined findings from the literature review, meeting presentations, and Working Group discussions into four key recommendations to improve the prevention, mitigation, and treatment of blast-related burn injuries. The following recommendations (Table 4-1) are an excerpt from the meeting proceedings published by the RAND Corporation (Hoch et al., 2020).

The Expert Panel recommendations are from the Proceedings Report for the Ninth International SoS Meeting prepared by the RAND Corporation.

The Proceedings Report is available at:
https://www.rand.org/pubs/conf_proceedings/CFA807-2.html

TABLE 4-1: Expert Panel recommendations

Expert Panel Recommendations	
<p>Recommendation 1</p>	<p>Revisit injury classification and data collection methods to develop agreed-upon definitions for blast-related burn injuries that can be broadly disseminated.</p> <p>The long-relied-upon injury severity score is not accurate enough to capture the implications of blast-related burn injuries. Successful polytrauma diagnosis and treatment requires partnerships across medical specialties, from emergency medicine through rehabilitation, yet existing systems do not enable information sharing across the continuum of care, or between the DOD, the VA, and civilian health care systems. Furthermore, existing injury registries limit the ability to understand differences in interventions and outcomes. A critical gap is the near-absence of completed prospective, longitudinal studies with follow-up longer than one year.</p> <p>The many aspects of burn injury, including TBSA, method of injury, location of injury, polytrauma, and rehabilitation needs should be incorporated into data repositories. Once parameters are defined, existing data collection methods should be evaluated, and the ideal methods to facilitate comparison and collaboration with civilian trauma communities should be codified into clinical practice guidelines.</p>
<p>Recommendation 2</p>	<p>Development of improved training and guidance to support burn injury management in prolonged field care settings.</p> <p>Focusing on accelerating the pathway from knowledge acquisition to new-and-improved training of forward Service members is crucial to meet the needs of current and future conflicts. A set of agreed-upon knowledge, skills, and abilities should be incorporated into revised training curricula for field medics, clinicians, and Service members trained in buddy care. More specifically, to decrease morbidity and mortality, medics need to be able to prevent burn wound conversion, avert infections, and manage common comorbidities such as fluid loss, organ damage, and other afflictions associated with blasts. Once Service members are evacuated, military and civilian trauma units must have both the capacity and training necessary to provide higher levels of care.</p>
<p>Recommendation 3</p>	<p>Strengthen rehabilitation practices to enhance continuity of care and emphasize a return to full function.</p> <p>The most underdeveloped area of empirical research reviewed was rehabilitative approaches for blast-injured patients with severe burn injuries. Physical, occupational, and psychosocial rehabilitation should begin as soon as possible after injury and should be viewed as a lifelong task to reduce pain, improve range of motion, and strengthen both the physical and psychological ability to resume daily life. Technology-assisted rehabilitation programs can enhance inpatient programs, improve compliance with daily regimens, and have positive impacts on resilience. Best practices for the various transitions from point-of-care through rehabilitation should be developed and widely disseminated to civilian, military, and VA facilities.</p>
<p>Recommendation 4</p>	<p>Conduct additional research on burn management in theater.</p> <p>Experts noted that many treatments and products employed in the field are decades old. Although promising new products and approaches have been identified, further testing involving computational models, animal models, and clinical trials are needed. Future research should include investigation of topical products to arrest burn conversion, theranostics to diagnose and treat injuries, non-intravenous resuscitation strategies, and basic research on immune response, biomarkers, metabolic impacts, and anabolic agents. Product development should focus on portability, durability, and stability in theater as well as flexibility in terms of application for multiple wounds. Computer and large-animal models should be used to test treatments of burn injury caused by the next generation of weapons.</p>



Photo credit: Staff Sgt. Lindsey Kibler/U.S. Army

Meeting Proceedings

Proceedings from the International SoS Meeting, “Mitigating the Impact of Blast-Related Burn Injury: From Prolonged Field Care to Rehabilitation and Resilience” were developed and published by the RAND Corporation (Hoch et al., 2020). The proceedings include summaries of keynote, topic, and scientific presentations; a synthesis of Working Group discussions; and additional detail on Expert Panel recommendations. The literature reviews and proceedings from all International SoS Meetings are available on BIRCO’s website: <https://blastinjuryresearch.amedd.army.mil/index.cfm/sos>.

Looking Forward

The next International SoS Meeting will be held August 10-12, 2021. As with previous meetings, it will include plenary sessions with keynote, topic, and scientific presentations; a poster session; and Working Groups led by Expert Panel members. Afterwards, the Expert Panel will meet to synthesize the meeting findings and develop research recommendations.

The topic of the 2021 meeting is “Understanding the Computational Modeling of the Human Body’s Responses to Blast-Related Injury.”

The literature review and meeting proceedings will be distributed to key stakeholders and made publicly available.



Photo credit: Petty Officer 2nd Class Ted Green/U.S. Navy

05



Photo credit: U.S. Army

CHAPTER 5:

JOINT TRAUMA ANALYSIS AND PREVENTION OF INJURY IN COMBAT

Invited chapter contributed by JTAPIC

The Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) program was established at the U.S. Army Medical Research and Development Command in July 2006 to assist in fulfilling portions of the Executive Agent responsibilities under DOD Directive 6025.21E, “Medical Research for Prevention, Mitigation and Treatment of Blast Injuries.” (See [Appendix C: DODD 6025.21E](#).) Prior to the establishment of the JTAPIC program, military organizations focused on improving Warfighter survivability individually rather than collaboratively. The medical community focused on battlefield medicine and increasing Warfighter survivability by using the best medical and treatment modalities available. Meanwhile, protective equipment developers focused on performance specifications and the development of process improvements—but under testing conditions, because few articles were returned for analysis from killed in action (KIA) or wounded in action (WIA) events. When an article was returned, analysts lacked full knowledge of the operational context—what happened to the Warfighter and what he or she was doing at the time of injury—or the injuries sustained. When vehicle improvements were fielded in Operation Iraqi Freedom, for example, there was no formal process to provide vehicle developers with relevant, contextualized, medical information on combat injuries that could allow them to understand how well vehicles protected the occupants. Conversely, the medical community lacked a formal process for providing medical injury data, associated with combat operations, to nonmedical users, such as combatant commanders, materiel developers, and requirements developers.

To streamline and enhance joint service information sharing and collaboration for the analysis and prevention of injuries in combat, the JTAPIC program was established as a joint “matrix” partnership (Table 5-1) in fall 2006 and was formalized in 2012. JTAPIC funds medical, materiel, operations, and intelligence subject



matter experts (SME) embedded in 11 separate and geographically dispersed partner organizations (Figure 5-1). Approximately 64 percent of JTAPIC partner organizations are nonmedical and 54 percent are not Army. The JTAPIC Program Management Office (PMO) manages and coordinates partner support and service to the JTAPIC mission.

FIGURE 5-1: JTAPIC partner organizations



As shown in Figure 5-2, the JTAPIC program’s Operational Concept is to provide actionable analysis of medical, intelligence, operational, and materiel information (the cause and effects) to improve the understanding of threat vulnerabilities and to enable the development of improved tactics, techniques, and procedures (TTP), along with materiel solutions that will prevent or mitigate traumatic injuries.

TABLE 5-1: JTAPIC partner organizations and their associated charter responsibilities

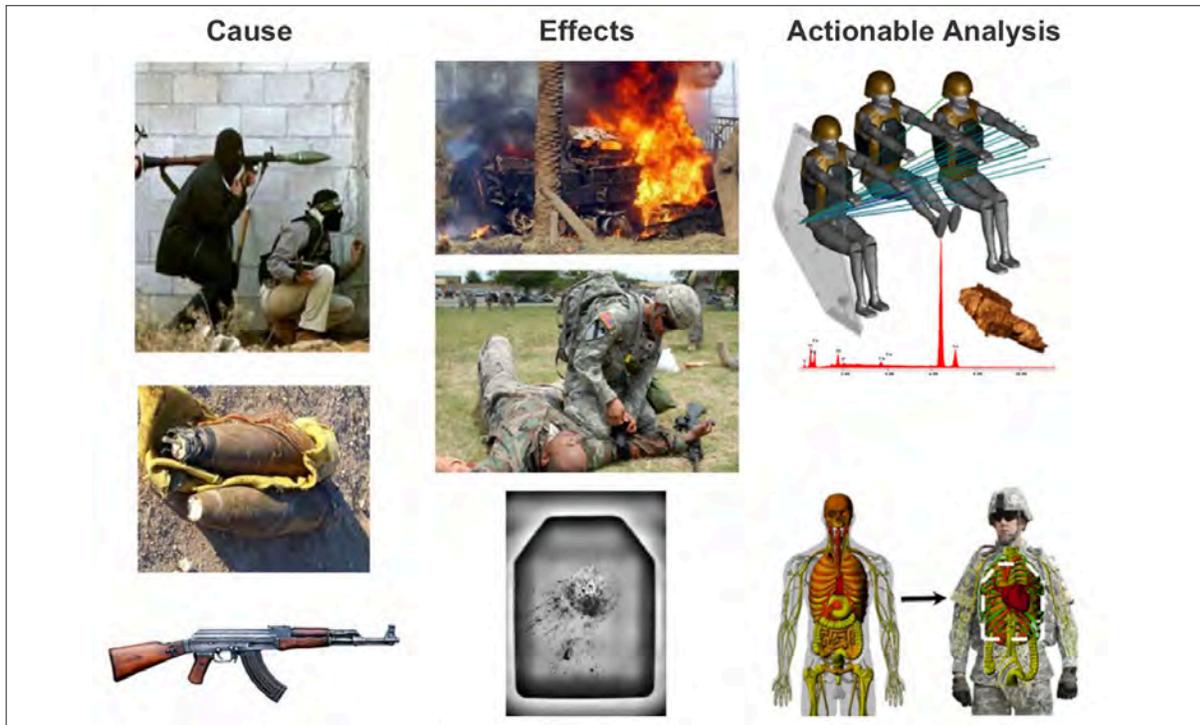
Partner Organizations	Unique Responsibilities
U.S. Army Aeromedical Research Laboratory	Provide analysis of aircraft and vehicle injury patterns
Combat Incident Analysis Team (Army)	Collect dismounted operations and intelligence incident data; provide subject matter expertise and analysis
National Ground Intelligence Center (Army)	Collect mounted operations and intelligence incident data; provide forensic vehicle analysis, information management support and services, subject matter expertise, and analysis
Marine Corps Combat Capability Development Command Operations Analysis Directorate	Provide Marine Corps-related operations research analysis and subject matter expertise
Marine Corps Intelligence Agency	Provide Marine Corps-related intelligence analysis and subject matter expertise
Armed Forces Medical Examiner System	Collect KIA injury data; provide KIA injury coding, subject matter expertise, and analysis
Naval Health Research Center	Collect WIA injury data; provide WIA injury coding, subject matter expertise, and analysis
Joint Trauma System	Provide WIA traumatic injury subject matter expertise and analysis
U.S. Army Combat Capability Development Command (DEVCOM) – Data & Analysis Center	Provide forensic evidence (e.g., ballistics, fragments, other metals) analysis, experimentation support and services, comparative analysis between live-fire tests and operational events, survivability and lethality modeling and simulation support and services, information management support and services, subject matter expertise, and analysis
Project Manager, Soldier Survivability, Program Executive Office Soldier (Army)	Collect damaged personal protective equipment (PPE); provide PPE analysis and subject matter expertise
Product Manager, Infantry Combat Equipment (Marine Corps)	Collect damaged Marine Corps PPE; provide PPE analysis and subject matter expertise

The JTAPIC program receives requests to perform analyses on theater combat-related events to improve survivability of Service members and vehicle platforms during combat. The integrated analysis that occurs within the JTAPIC partnership provides actionable decision support to inform solutions across the doctrine, organization, training, materiel, leadership and education, personnel, facilities, and policy (DOTMLPF-P)

domains that will prevent or mitigate traumatic injuries during all military operations and, ultimately, in combat.

The JTAPIC PMO and partners participate—to great effect—in international forums to improve survivability of U.S. and Allied forces’ Service members and vehicle platforms. In February 2020, the Under Secretary of Defense for Research and

FIGURE 5-2: Operational concept



Engineering recognized a JTAPIC partner, DEVCOM Data & Analysis Center, for its contributions to The Technical Cooperation Program (TTCP), an international collaboration on defense science and technology. JTAPIC helped create a community of interest within the TTCP's Land Systems Group, Action Group 3, aimed at mitigating battlefield trauma through a Soldier-centric approach to survivability. These contributions expedited national procurement activities that significantly contributed to saving Warfighters' lives or reducing the severity of their injuries.

Decision Support for Improved Injury Survivability

The JTAPIC program is in a unique position to provide a comprehensive analysis of any casualty-causing operational event. Table 5-2 describes the types of decision support that the JTAPIC program provides to its customers. Examples of support provided by JTAPIC in FY20 follow.

In FY20, JTAPIC provided event analysis for 13 casualty-causing incidents, including 483 casualties researched, hundreds of source documents referenced, and thousands of data points aggregated and ultimately included in COIRs.

Event Analyses

JTAPIC analyzes combat events across all Combatant Commands and produces a corresponding Current Operations Incident Report (COIR): a detailed operational and injury report of casualty-causing combat incidents, primarily from special operations forces, created by the Combat Incident Analysis Team, the JTAPIC PMO Medical Operations Cell, the Armed Forces Medical Examiner System, and other partner SMEs. As a result of unit-level Special Forces Group requests for analysis, JTAPIC COIRs have been featured in the "Special Operations Combat Medic Skills and Sustainment Course" and its recertification pathways to provide insight to recent enemy TTPs

TABLE 5-2: Type of decision support provided by the JTAPIC program

	Sentinal Event	Event Analysis	Trends	Requests for Information
Purpose	First time occurred; casualties significantly beyond expectations	Analysis of every casualty-causing combat incident	Monitor aggregate data for emerging outcomes, story untold, question not asked, and efficacy analysis	Inform materiel or non-materiel capability or requirement documents
Frequency	Immediate as identified	Per occurrence	Monthly, Quarterly	As requested
Production Time	Usually 3–10 days	Usually > 30 days	Usually > 30 days	Usually 1–6 months; can be 72 hours for congressional requests)
Deliverable	Analysis notification memo	Analysis notification as required	Trend chart with analysis and contextualization	Email, memo, product briefs, analysis, recommendations
Customer	Varies across DOTMLPF-P	Varies across DOTMLPF-P	Varies across DOTMLPF-P	Requester and stakeholders

in relevant geographic areas. COIRs support unit-level TTP and course-of-action development, steer training scenarios during unit pre-mission training cycles, and drive requirements.

Specific COIRs have been used to develop the following:

- **Combatting Terrorism Technical Support Office, Lethal Ground-Based Sensor Requirement:** An analysis of geographic proximity of special operations casualties from CY19 incidents prompted the development of, and continued assessment for, a requirement for a lethal ground-based sensor.
- **Pre-deployment Training:** The 10th Special Forces Group (SFG) requested all COIRs created for events involving the 10th SFG during the recent deployments to inform pre-deployment training for other elements of the 10th SFG that planned to deploy later in 2020.

- **Award Determination:** COIR reports from mass casualty incidents in FY20 have been provided to U.S. Central Command (CENTCOM) J-3 to verify exposures and injuries for meritorious awards.

Trends

- JTAPIC has been measuring compliance with the requirement for Services and Combatant Commands to submit a monthly exposure tracking report to JTAPIC per DOD Instruction 6490.11, “DOD Policy Guidance for Management of Mild Traumatic Brain Injury/Concussion in the Deployed Setting.” JTAPIC provides quarterly concussion (and potentially concussive exposure) reports, for Service members identified during COIR efforts, to the DOD Traumatic Brain Injury (TBI) Advisory Committee, which includes Service representatives, the Defense Health Agency (DHA), and other DOD and VA stakeholders.



Photo credit: Tech. Sgt. John R. Nimmo/U.S. Air Force

- Using data collected in 2019 from operations in Afghanistan and Iraq, JTAPIC analyzed 62 casualties from 24 engagements with barricaded shooters or enemy in defilade positions. This investigation revealed that pressured enemy retreats, where the enemy take cover in compounds, tunnels, and other predetermined or hasty defensive fighting positions such as culverts, destroyed buildings, or dense vegetation, are significant casualty-causing engagements. JTAPIC's DOTMLPF-P level of influence analysis has prompted Special Operations Forces to consider working groups to revisit training, rules of engagement, and materiel implications in this operational scenario.
- In response to the sentinel Al Asad, Iraq surface-to-surface missile attack on January 8, 2020, JTAPIC identified approximately 460 potential casualties, abstracted

To preview and request previous JTAPIC products, please visit <https://jtapic.arl.army.mil/jacs/pl/>

injuries and exposures, recorded estimated distances from blasts, and categorized the type of cover and other collateral data from medical records and operational reports. Classified analyses of distance and cover in the attack were synchronized with the Joint Technical Coordinating Group for Munitions Effectiveness (JTCEG-ME) analysis. This prompted a request for information (RFI) to interview Service members evacuated from theater following the attack as part of JTAPIC's Wounded Warrior Debrief Program. This ongoing project will be completed as pandemic-related travel restrictions ease.



Photo credit: Cpl. Alfred V. Lopez/U.S. Marine Corps

- A blast mitigation working group including CENTCOM Directorate of Logistics and Engineering, the U.S. Army Corps of Engineers, U.S. Army Engineer Research and Development Center, and Joint Program Committee (JPC)-5 is using computational modeling to better understand blast propagation inside bunkers. The goal is to reduce blast effects by recommending TTPs for CENTCOM to implement. At the request of JPC-5 in July 2020, JTAPIC provided information to inform the TPPs by updating the distance and cover product with information on identified casualties, additional elements for analysis, and clinical injury correlation. JTAPIC provided this product to JPC-5 for use by the working group, also in July 2020.
- The JTAPIC PMO continues to support the Warrior Injury Assessment Manikin (WIAMan) program in its effort to expand research on soldier survivability and quality of life after experiencing vehicle underbelly blast. The WIAMan program has requested radiological imaging from theater combat cases to compare injury types and fracture patterns to those observed in testing. The DHA Integrated Clinical Systems PMO is validating a process for this information exchange. JTAPIC provided the first theater cases for retrieval in June 2020.
- Combat operation incidents that involve military working dogs (MWD) often result in injuries to both handler and canine. The DOD MWD Working Group identified injury trending within human-canine Warfighter functional units as a research gap. JTAPIC and its partner, DEVCOM Defense & Analysis Center, are developing a Canine Trauma Scoring System and associated Visual Anatomical Injury Descriptor (VAID) based on the human Abbreviated Injury Scale (AIS) and VAID programs. The intent is to capture MWD injury data for comparison alongside handler data to potentially identify canine species-specific resilience, support PPE requirements development, and help track medical outcomes for MWDs and handlers as a functional unit.

Requests for Information

- In FY20 JTAPIC responded to 40 RFIs from various customers—including DHA, CENTCOM J-1, CENTCOM J-3, Veterans Benefits Administration (VBA), Asymmetric Warfare Group, Special Operations Command Surgeon's Office, DEVCOM Ground Vehicle Systems Center, Office of the Surgeon General, JTCG-ME, materiel and non-materiel development organizations, test and evaluation organizations, and capability requirements offices—to help inform decisions.
- In response to a request by the Asymmetric Warfare Group's Counter-Insider Threat Working Group, JTAPIC provided notional COIRs, intelligence overlays, and specifics of ballistic trauma incurred by U.S. Service members, during insider attacks, to be included in the Senior Leadership Handbook and Medical Annex for deploying Special Forces Assistance Brigades.
- JTAPIC answered 19 VBA RFIs in support of the VA's statutory duty to assist Service members obtaining decisions regarding claims of potentially concussive event exposure and mild TBI diagnosis during active-duty service, in order to adjudicate disability ratings.
- JTAPIC delivered a product to DEVCOM Ground Vehicle Systems Center, Ground Vehicle Survivability and Protection, Occupant Protection, detailing rollover accidents and casualties from April 2018 through April 2019. It aggregated rollover accidents captured in the U.S. Army Combat Readiness Center by vehicle type, including High Mobility Multipurpose Wheeled Vehicle, Mine Resistant Ambush Protection, Stryker, and Family of Medium Tactical Vehicles, and provided detailed wounded and fatality data. This product supports efforts to develop a standardized crash and rollover protocol.



Photo credit: Tech. Sgt. Shawn Nickel/U.S. Air Force

- In March 2020, DEVCOM Soldier Center, Soldier Performance Optimization Directorate responded to a congressional request from the House Armed Services Committee, Subcommittee on Tactical Air and Land Force, and the Defense Logistics Agency Administrative Support Center regarding whether, and how, body armor needs to be improved to protect female Service members. JTAPIC provided support to this request by analyzing location, type, and AIS severity of the injuries sustained by female Service members from small-arms fire in combat operations, and examined associated injury from damage to female Service members' PPE.

Submit an RFI at
<https://jtapic.arl.army.mil/jacs/rms/projects/new>



Photo credit: Mass Communication Specialist 2nd Class Walter J. Pels/U.S. DOD

- JTAPIC collaborated with the U.S. Army Aeromedical Research Laboratory on a combat-related injury retrospective study to support the Aviation Survivability and Tactics Team. This comprehensive analysis of two rotary wing platforms (Blackhawk and Apache) examined injuries sustained by Service members in combat aviation events in the context of specific event circumstances. This product provided the U.S. Army Futures Command Future Vertical Lift Cross-Functional Team with combat-driven data for risk reduction and technology maturation efforts.
- The CENTCOM CCJ1-JPA provided multiple casualty lists for JTAPIC to de-conflict and verify for award citations.
- The Director, U.S. Army TBI Program, on assignment to the Office of Science and Technology Policy, Executive of the President, requested information on mild TBI treatment and management in accordance with DOD Instruction 6490.11. This effort is in progress.



Photo credit: Staff Sgt. Brendan Mackie/U.S. Army National Guard

Way Forward

The JTAPIC program will continue to collect operational incident and accident information to inform solutions that can prevent or mitigate traumatic injury. Expertise provided by JTAPIC's 11 partner organizations results in the actionable products that customers use and value in their decision-making process to prevent or mitigate injury across the full range of military operations. Creating an updated online collaborative system for the program is critical to meet this mission goal.

The JTAPIC PMO and its partners, in conjunction with the U.S. Army Engineer Research and Development Center Information Technology Laboratory, developed a concept for a new collaborative system to house years of integrated medical, materiel, operations, and intelligence data related to combat incidents. The JTAPIC Information Management and Collaboration System (JINCS) design integrates the

previous JTAPIC Database, the JTAPIC Analysis and Collaboration System, the Combat Incident Analysis Team Database, and several other subsystems. JINCS will encompass a myriad of modules and applications—providing a collaborative work environment to capture and house data, track RFIs from submission to completion, store documents relevant analyses requests, and encompass tools to aid JTAPIC analyses all in one place, along with system-to-system interaction with other DOD data repositories. JINCS will allow DOD Common Access Card holders access to high-fidelity medical, materiel, operations, and intelligence datasets to mitigate or prevent injuries in combat across many disciplines.

For more information, contact JTAPIC at usarmy.detrick.medcom-usamrmc.list.jtapic@mail.mil

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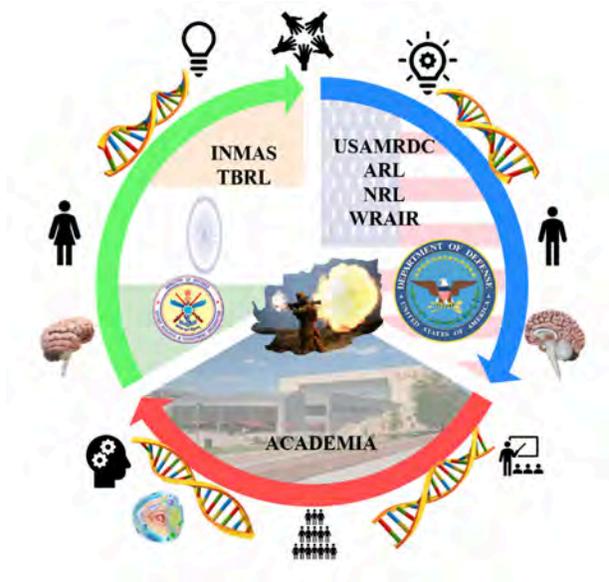


Photo credit: Sgt. Taylor Hoganson/U.S. Army

CHAPTER 6:

STRATEGIC INTERNATIONAL COLLABORATION FOR WARFIGHTER HEALTH

A mechanistic understanding of blast- and blunt-related traumatic brain injury (TBI) can inform the validation of anatomically accurate computational models, which expedite the identification, selection, and transition of injury prevention and treatment strategies to clinical trials and improve the design of personal protective equipment that could be translated to the commercial defense industry. Blast overpressure-induced TBI is understood to be a diffuse injury wherein damage to brain tissue is caused solely by the non-penetrating supersonic blast wave, although the current understanding of how the blast wave interacts with the body and leads to subsequent blast-related brain injury is limited. There are many hypotheses regarding the mechanisms of brain injury following blast exposure; however, there are no validated animal or computational models of blast overpressure-induced TBI to examine them. Accordingly, a collaborative effort was developed as part of the DOD Defense Trade and Technology Initiative (DTTI)—an international partnership organized by the Under Secretary of Defense for Acquisition & Sustainment and the Defence Research and Development Organization (DRDO), Indian Ministry of Defence (MOD)—to address 1) key challenges in the development of reliable animal models of TBI for blast injury research and 2) the technical gaps and recommendations made by the DOD Brain Injury Computational Modeling Expert Panel, a group established by the DOD Blast Injury Research Coordinating Office (BIRCO), that assessed the current and future use of computational modeling in non-impact blast-induced mild TBI (mTBI) research.



The lead organizations for this international collaboration were BIRCO (U.S. Army Medical Research and Development Command [USAMRDC]) and the Institute of Nuclear Medicine and Allied Sciences (INMAS), a laboratory associated with DRDO. Other participants included the USAMRDC-affiliated Biotechnology High Performance Computing Software Applications Institute (BHSAI) and Walter Reed Army Institute of Research (WRAIR), New Jersey Institute of Technology (NJIT), Naval Research Laboratory (NRL), and the U.S. Army Research Laboratory (ARL) (Figure 6-1). This partnership was designed to utilize expertise across the U.S. and Indian organizations to achieve the project objectives, specifically, leveraging the complementary expertise in blast-related TBI in terms of computational multi-scale modeling in the U.S. and advanced imaging tools and therapies developed in India.

PROJECT OBJECTIVES

1. Develop and validate a blast injury animal model for mild TBI (mTBI) using imaging techniques and histological procedures, as well as assessing changes in behavior and cognition
2. Develop, validate, and cross-validate a computational model for blast and blunt injury
3. Develop anatomically accurate head/brain models for blast/brain injuries from clinical and experimental data
4. Compare the blunt and blast data to develop a scaling ratio

i Acronyms and references used in this chapter are included in Appendices A and B.

This chapter outlines several key and representative studies from the collaboration that support the research outcomes listed on [page 99](#). In response to stakeholder feedback on the FY19 Report to the Executive Agent, overpressure measurements are reported in this chapter as both pounds per square inch (psi) and kilopascals (kPa).

FIGURE 6-1: Project team leads and collaborating investigators.



Research

Replicating Blast Injury in Animal Models

The underlying mechanism of blast overpressure-induced TBI is unclear. It manifests as a complex problem involving multiple mechanistic and biological injury pathways, including blood-brain barrier (BBB) leakage, increased oxidative stress, and neuroinflammation. To understand such subtle injuries, animal models that can mimic human blast overpressure-induced TBI are needed. Common animal models of blast overpressure-induced TBI are created in species such as rodents, swine, and primates.

The ideal blast condition can be created by detonating explosives in an open field; however, it is not trivial to control the conditions per experimental requirements. The challenges associated with open field blast include 1) involvement of trained personnel to handle the explosives; 2) availability of a large safe area for the execution of an experiment; 3) reproducibility of the experimental conditions; and 4) substantial costs. Apart from these logistic and regulatory challenges, other technical limitations, such as the variation in exposure levels resulting from changes in type, shape, and size of the explosive used, along with the geographic location of the experiment, affect the consistency of blast waveforms resulting from open field blast. All of these challenges make laboratory simulators a convenient surrogate for simulating primary blasts with precise control and greater repeatability.

Publications related to replicating blast injury in animal models include

Kuriakose et al., 2016
Mishra, Skotak, et al., 2016
Chandra et al., 2017
Skotak, Alay, Chandra, et al., 2018
Aravind et al., 2020
Arun et al., 2020

In the laboratory, blast waves can be generated using a shock tube with compressed gases, such as nitrogen and helium, or explosives. To replicate the physics and field conditions of blast exposure, a nine-inch square compressed gas-driven shock tube with a field-validated blast profile was developed at NJIT and used to simulate blast conditions in a rat model. An identical shock tube was built and installed at INMAS (Figure 6-2), which allowed studies to be replicated in two discrete locations. All construction parameters and specifications were finalized in accordance with the design provided by NJIT, and construction was monitored by the teams from both INMAS and NJIT. Measurement of the incident overpressure shock wave and secondary waves was completed by a series of pressure sensors distributed along the shock tube that recorded the biomechanical loading experienced by the animals when exposed to blast waves.

Rodent models of blast overpressure-induced TBI were generated by exposing animals to blast overpressure ranging in magnitude from 5.51–50.76 psi (38–350 kPa). In experiments at NJIT and INMAS, rats were exposed to a single blast wave, and their 24-hour survival outcomes were observed and recorded. No mortality was observed in animals exposed to blast intensity lower than 24.66 psi (170 kPa) or impulse of 300 Pa·s. However, the mortality rate gradually increased as overpressure increased from 24.66

to 43.51 psi (170 to 300 kPa) and reached 100 percent above 43.51 psi (300 kPa) or 500 Pa·s impulse. NJIT completed blast dose-response curves to model the effects of blast overpressure magnitude on mortality; these were compared with INMAS data. The curves generated by both institutions were similar at different blast overpressures, and all data points were integrated to generate a master dose-response curve using standardized experimental procedures (Figure 6-3). These data suggest that both the shock tube and animal model developed during this project produce replicable results and are strong candidates for use in blast injury studies.

FIGURE 6-3: Master dose-response curve from animal data collected at both NJIT and INMAS.

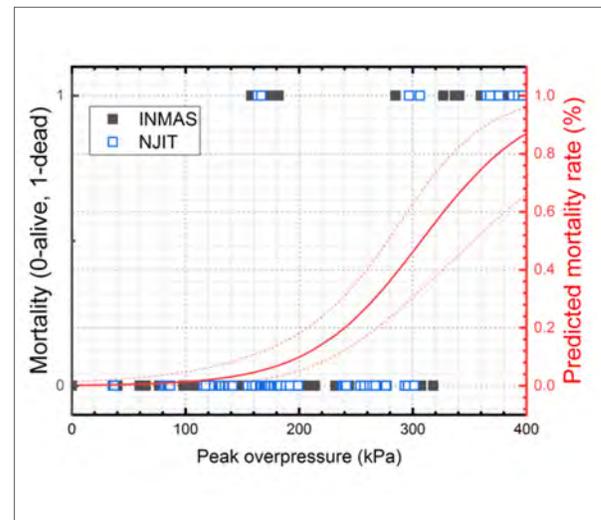


FIGURE 6-2: Nine-inch square cross-section shock tubes at (Left) NJIT and (Right) INMAS. The view from the back illustrates the reflector end plate, test section, and distribution of sensors along the shock tube.



Replicating Blunt Injury in Animal Models

Survival curves were also generated to compare rodent models of blunt impact developed at both WRAIR and INMAS. The impact acceleration model of diffuse TBI, also known as the “Marmarou weight-drop model,” consists of a tall structure that drops weights from varying heights. The model seeks to replicate the neurophysiological, histopathological, functional, and biochemical effects of diffuse TBI without focal lesions, such as the impact acceleration injuries common in automobile accidents and falls. Injury impact loads are administered by progressively increasing the weight applied or the height from which the weight is dropped (Marmarou et al., 2009).

Using a modified Marmarou weight-drop model and holding the weight for each drop at a constant 450 g, impact survival curves were generated at WRAIR and INMAS (Figure 6-4). Injury classifications were expressed as a



Photo credit: Spc. Ariel Solomon/U.S. Army

function of weight-drop lethality; specifically 1) mild-to-moderate TBI, < 75 cm (no lethality); 2) severe TBI-to-lethal, 75–200 cm (1–99 percent lethal); and 3) lethal, > 200 cm (100 percent lethal). Overall, these data confirm that the independent experiments at WRAIR and INMAS are reproducible within acceptable bounds of error, validating the model for future studies of behavior and pathology.

FIGURE 6-4: Comparison of WRAIR and INMAS survival curves for blunt impact. Both figures show raw data and their fitted sigmoidal survival curves. (A) Raw data from WRAIR (yellow dots) are prominent, and curves are shown without measures of uncertainty. (B) Raw data from INMAS (green dots) are prominent, and survival curves include 95 percent confidence intervals (dashed lines). Note the substantial overlap in confidence intervals between the fitted WRAIR and INMAS data.

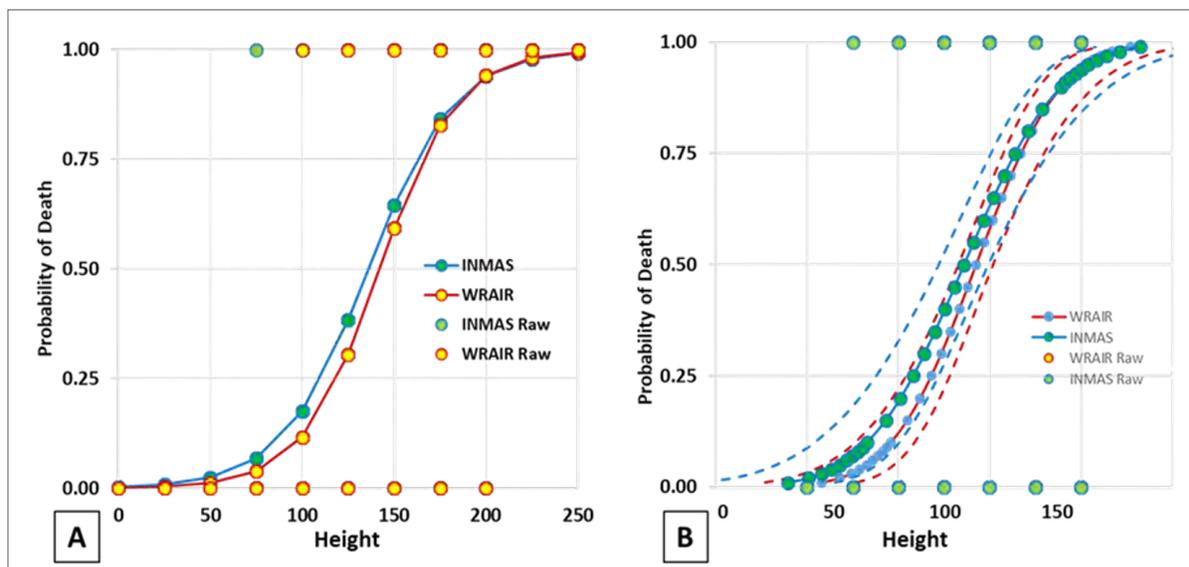




Photo credit: Cpl. Daniel R. Betancourt Jr/U.S. Marine Corps

Blast Injury Pathology

Comprehensive studies were carried out in animals with blast overpressure-induced mild-to-moderate TBI. These include the characterization of BBB permeability changes, the involvement of oxidative stress and its role in BBB breakdown, and neuroinflammation following blast overpressure-induced mild-to-moderate TBI.

Blast Compromises Blood-Brain Barrier Permeability

The BBB is a highly selectively permeable membrane that separates the brain from the circulatory system. The BBB is dynamically modulated by cellular interactions between endothelial cells, the tight junctions that join them, pericytes, and astrocytes that support the endothelial capillaries (Abbott, 2000; Abbott et al., 2010; Abdul-Muneer et al., 2015).

In a study conducted by the team at NJIT, rats were exposed to a range of blast overpressures in a field-validated shock tube, then BBB permeability was assessed by measuring the extravasation of

Publications related to research in this section include

Ordek et al., 2018
Sajja et al., 2018
Rama Rao et al., 2018
Kuriakose et al., 2018
Kuriakose et al., 2019

Evans blue and sodium fluorescein in the frontal cortex, striatum, somatosensory barrel-field cortex, hippocampus, thalamus, and cerebellum. Rats were exposed to sub-mild (5.08 psi [35 kPa]), mild (10.15 psi [70 kPa]), mild-to-moderate (18.85 psi [130 kPa]), and moderate (26.11 psi [180 kPa]) blast overpressures. These classifications were based on the 24-hour master dose-response curve work presented in Figure 6-3 and in the preceding section [Replicating Blast Injury in Animal Models](#).

Results suggested that exposure to blast overpressure induces the breakdown of the BBB and that brain regions express different degrees of

BBB permeability. The severity of BBB breakage was found to be directly proportional to increased blast overpressure, and differential damage was observed in six different regions immediately following blast exposure (Figure 6-5). In almost every region studied, statistically significant differences were observed in the levels of both extravasated dyes, a finding which highlights the diffuse nature of blast TBI. The most robust changes occurred in the frontal cortex, striatum, and thalamus for both tracers, whereas no statistically significant extravasation was observed in the cerebellum, a finding which aligns with results from previous investigations (Garman et al., 2011; Hue et al., 2016).

Blast Induces Oxidative Stress Throughout the Brain

Among the many pathological factors associated with either primary mechanical injury or secondary biochemical cascades, oxidative stress has been shown to play a major role in various models of TBI and occurs at both the structural level (spanning from the frontal cortex to the cerebellum) and the cellular level (neurons,

astrocytes, and microglia) (Bayir et al., 2006; Cornelius et al., 2013). The main inducers of oxidative stress are reactive oxygen species, which include superoxide, hydroxyl radical, and hydrogen peroxide (Koppula et al., 2012; Lewén & Hillered, 1998). Reactive oxygen species are normally produced in several metabolic reactions, including redox-reactions (oxidation/reduction) and oxidative phosphorylation, and in the normal process of electron transport chain reactions. There are many enzymes that produce free radicals during their catalytic reactions, including the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) family, cytochrome P450, cyclooxygenase, lipoxygenase, and xanthine oxidase. NOX is a multi-subunit enzyme that catalyzes the reduction of molecular oxygen and the oxidation of NADPH to generate superoxide radicals and plays a significant role in the pathophysiology of various forms of TBI. NOX has been shown to be up-regulated in the brain in a controlled cortical impact model of trauma and closed head injury models (Cooney et al., 2013; Choi et al., 2014; Ferreira et al., 2014; Song et al., 2013).

FIGURE 6-5: (A) Quantitation of Evans blue extravasation for 5.08, 10.15, 18.85, and 26.11 psi (35, 70, 130, and 180 kPa) blast overpressure, 15 minutes post-exposure in the frontal cortex, striatum, somatosensory barrel-field cortex (S1BF), hippocampus, and thalamus using a semi-log plot to capture difference in magnitudes. (B, C) The striatum was chosen for illustrative purposes and to qualitatively depict the differences between (B) 70 and (C) 130 kPa. Leaks appear longer and more intense with increasing overpressure in the same brain regions. * Indicates a difference in intensity compared to controls with $p < 0.05$; ** Indicates $p < 0.01$. Scale bar equals 100 μm .

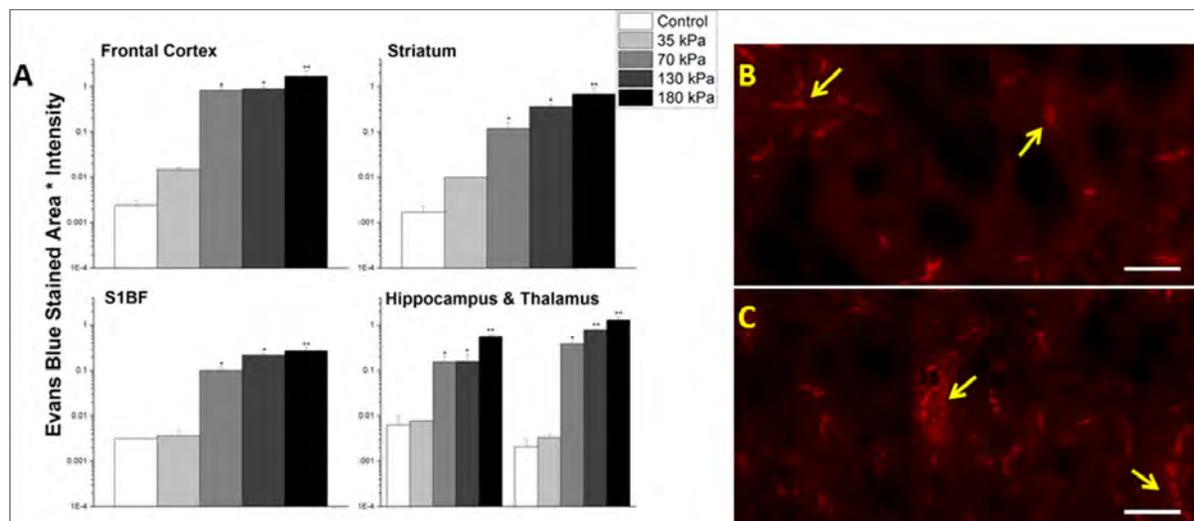




Photo credit: Lt. Col. Daniel F. Bohmer/U.S. Army

A study conducted at NJIT examined the spatial resolution and cellular distribution of two isoforms of NOX (NOX-1 and NOX-2) and changes in brain tissue extracted from rats exposed to moderate (26.11 psi [180 kPa]) blast. This was achieved by performing double-immunofluorescence analyses of two isoforms of NOX with markers of neurons (NeuN), astrocytes (glial fibrillary acidic protein [GFAP]), and microglia (ionized calcium binding adaptor molecule 1 [Iba-1]) in the frontal cortex, striatum, hippocampus, thalamus, and cerebellum. Results indicated that the protein expression of NOX isoforms increased significantly following moderate blast exposure, particularly in the cerebral hemisphere and cerebellum. NOX-1 and NOX-2 were more pronounced in neurons than in the astrocytes and microglia, particularly in the hippocampus and thalamus.

Blast Induces Acute and Chronic Neuroinflammation

BBB disruption induced by a blast overpressure wave generates a large amount of toxic and pro-inflammatory molecules—such as reactive oxygen and nitrogen species (Readnower et al., 2010; Wang et al., 2011), pro-inflammatory cytokines such as interleukin (IL)-1 β , and tumor necrosis factor alpha (TNF- α) (Perez-Polo et al., 2015; Valiyaveetil et al., 2013)—and permits the infiltration and accumulation of immune cells in the brain parenchyma (Dalle Lucca et al., 2012). Blast overpressure-induced TBI may result in a sustained activation of microglia and associated-inflammatory pathways, subsequently leading to chronic neuroinflammation.

A study conducted at NJIT examined the temporal and spatial activation of microglia in the vicinity of the vasculature at the acute and chronic stages of



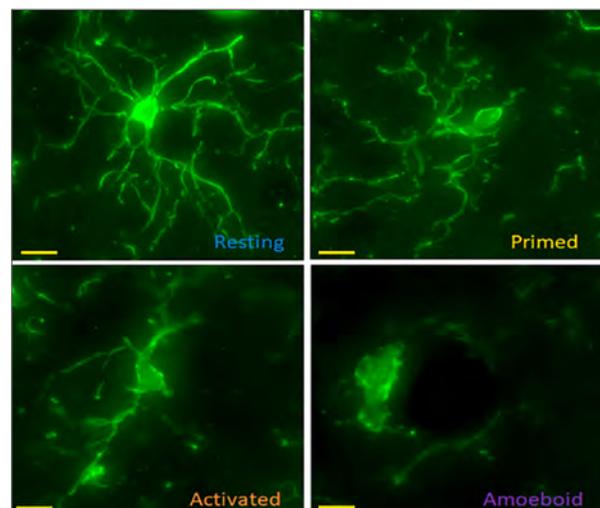
Photo credit: Lance Cpl. Danny Gonzalez/U.S. Marine Corps

blast overpressure-induced TBI in rats. The temporal and spatial resolution of the nucleotide-binding domain leucine-rich repeat family, pyrin domain containing 3 (NLRP3) inflammasome complex was also examined, which is a major pathway for the production of pro-inflammatory cytokine IL-1 β (Martinon et al., 2002) and its cellular distribution.

The evaluation of the morphological status of microglia stained with Iba-1 four hours after blast overpressure-induced TBI showed that microglia with different activation states—including resting, primed, activated, and amoeboid states—coexist within each section of the hippocampus and thalamus (Figure 6-6). Further, a quantitative analysis of microglia at 24 hours, three days, seven days, 15 days, and 30 days in both the hippocampus and thalamus showed a statistical decrease in resting microglia in animals exposed to blast at all time points. However, blast injury caused a significant increase in the percentage of microglia in the primed, activated, and amoeboid states,

as indicated by increased soma size and a lower number of processes at all time points.

FIGURE 6-6: Representative immunofluorescent images of microglia stained with Iba-1 four hours following blast overpressure-induced TBI showing different stages of microglial activation co-existing within the hippocampus. Scale bar = 300 μ m.



This work also focused on the activation state of microglia near the vasculature (Figure 6-7A-D). At four hours after blast exposure, total microglia less than 100 μm from the vasculature increased in number in both the hippocampus and thalamus (Figure 6-7E, F). When the data were parsed by microglial morphology, the percentage of resting microglia decreased following blast, while

primed microglia remained unchanged. The two active forms of microglia (active and amoeboid) increased significantly in both regions (Figure 6-7G, H). At four hours post-injury, the number of microglia in the vicinity of the vasculature in both the hippocampus and thalamus was significantly greater than that in vasculature-free areas. In both the hippocampus and thalamus of animals

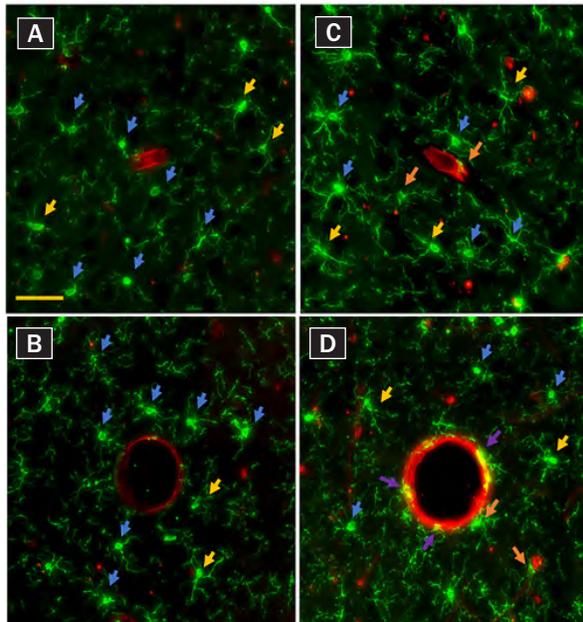


FIGURE 6-7: Microglial activation after blast exposure. (A & C) Presence of microglia (immunostained with Iba-1) in the hippocampus in control (A) and blast-induced (C) animals near small-diameter blood vessels showing extensive arborization of their processes (resting state). (B) Microglia in the resting state from control animals near larger blood vessels; (D) amoeboid microglia from animals four hours after blast exposure exhibiting a higher activation state near blood vessels with larger diameters. Scale bar = 300 μm . Arrow colors match microglial morphologies in Figure 6; blue = resting, yellow = primed, orange = activated, pink = amoeboid. (E–H) Quantitation of fluorescent images of Iba-1 stained microglia showing differential activation near blood vessels of smaller and larger diameter in both the hippocampus and thalamus. * $p < 0.05$ versus control; microglia at different stages were quantified from five regions of interest of 1 mm^2 per section from five different animals in each group.

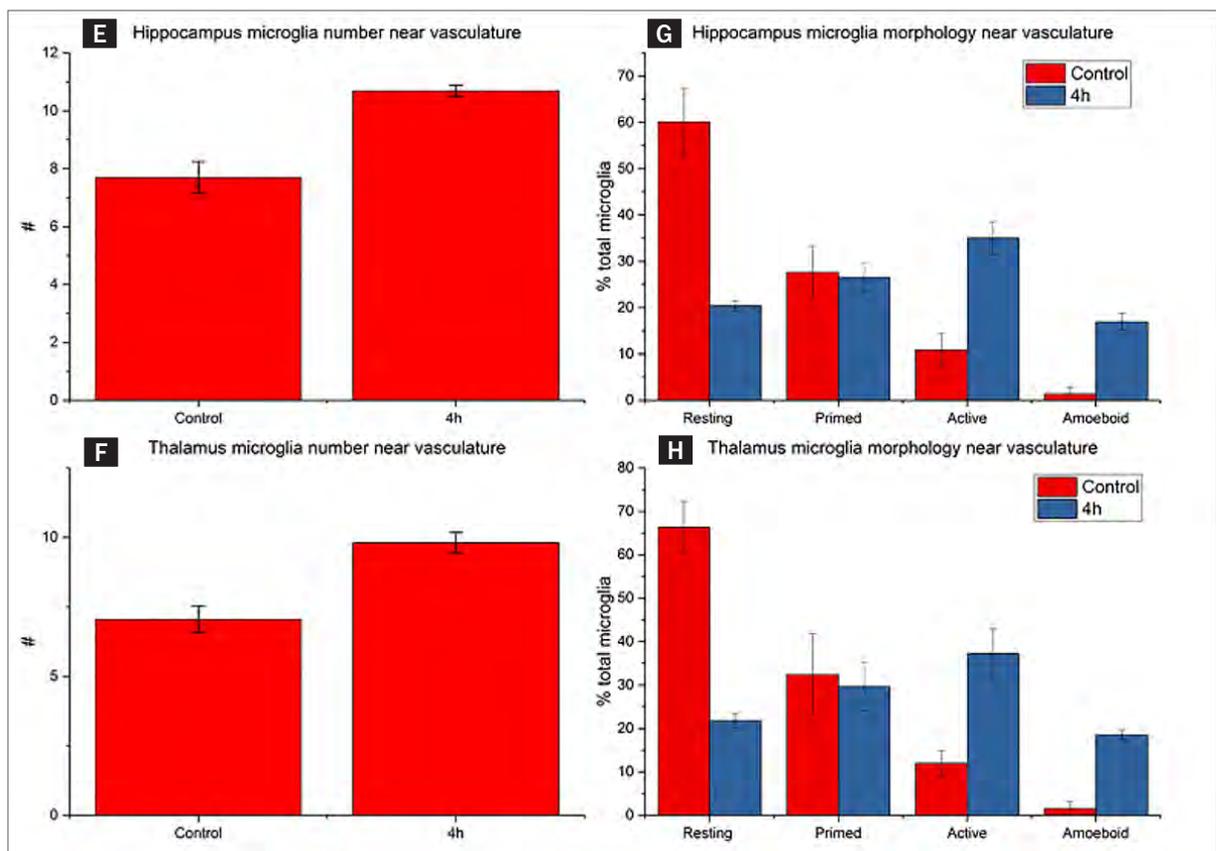




Photo credit: MC2 Alan Gragg/U.S. Navy

exposed to blast, nearly all amoeboid microglia were adjacent to the vasculature, and almost none were in the vasculature-free area. The number of microglia increased as early as four hours, peaked at seven days, and remained increased at 30 days after blast overpressure-induced TBI, with the exception of three days post-exposure. A similar increase in the thalamus was noted with a peak in microglia numbers at 15 days after blast overpressure-induced TBI, suggesting that blast overpressure-induced TBI results in robust activation of microglia near the areas of vascular rupture.

After observing sustained microglial activation caused by blast overpressure-induced TBI, researchers examined levels of the pro-inflammatory cytokine IL-1 β in the hippocampus and thalamus to compare neuroinflammation in both acute and chronic stages following blast exposure (Figure 6-8). The increase in IL-1 β showed a biphasic response in both the hippocampus and thalamus at acute stages of four hours and 24 hours, and at chronic stages of 15 days and 30 days post-injury. In both the hippocampus and thalamus, levels of IL-1 β peaked at four hours post-injury. Levels of IL-1 β in both regions began

to increase again at seven days but failed to show significance in the hippocampus. Levels of IL-1 β in the chronic stage peaked at 30 days post-injury.

Blunt Injury Pathology

Disruption of the BBB is one of the most frequently investigated mechanisms of injury in blunt TBI and has been commonly used as an indicator of the degree and extent of injury (Abdul-Muneer et al., 2013; Connell et al., 2011; Haorah et al., 2005; Haorah et al., 2007; Hue et al., 2016). Studies of Marmarou's closed-head injury model have indicated that transient BBB breakdown, followed by a relatively longer intracellular glial edema period, as the drivers of diffuse post-traumatic brain swelling (Marmarou, 1994; Foda & Marmarou, 1994). TBI patients may show diffuse brain swelling with maximal edema and increased intracranial pressure three to five days after injury (Lobato, 1993).

Researchers at NJIT performed Iba-1 and GFAP immunostaining to quantitate the post-blunt injury inflammatory cascade associated with mTBI and moderate TBI in rats during acute and chronic injury conditions. For the mTBI group, analysis of

FIGURE 6-8: Time course of changes in IL-1 β levels in the (Left) hippocampus and (Right) thalamus following blast overpressure-induced TBI. IL-1 β levels were measured by quantitative enzyme-linked immunosorbent assay (ELISA) in homogenates of the hippocampus and thalamus. A biphasic response of change was observed in animals exposed to blast overpressure-induced TBI. * $p < 0.05$ versus control (n = 5 in each experimental group).

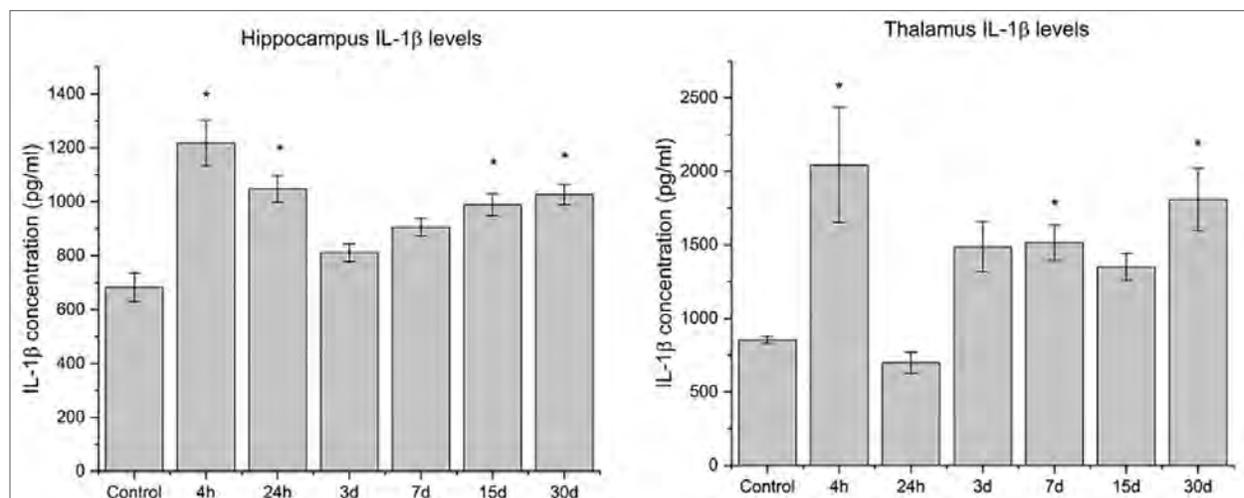




Photo credit: Staff Sgt. Mark Miranda/U.S. Army

Iba-1 positive cells showed microglial activation and an increase in microglial cells during the acute phase of injury. In the cortical region, a significant increase in the number of microglia was observed at four hours, one day, and five days post-injury. In the hippocampal region, microglial cell numbers increased significantly at four hours post-injury. When astrocytes were stained using the GFAP marker, an increased number of astrocytes and astrocyte hypertrophy were observed during both acute and chronic time points post-injury. GFAP positive cells were significantly increased at day five and day 10 post-injury in the cortex, indicating an injury-induced response in this region. The increased presence of both of Iba-1 and GFAP in neural cells suggests that blunt TBI induces glial alterations and neuroinflammation from the point of impact onwards and that these metabolites could be candidate biomarkers of brain injury. Results were similar for the moderate TBI group.

Metabolomic Profiles

Metabolomic Profiles Following Blast Injury

Blast waves are known to cause differential responses across brain regions. Cerebral and hippocampal atrophy due to altered metabolic status has been reported in the literature, which emphasizes the utility of examining the metabolic basis of the structural and pathological consequences of TBI. High-resolution proton magnetic resonance spectroscopy detects resonances from many brain metabolites and is being used to explore the evolution of the cerebral metabolic profile after TBI. Metabolomic analysis assesses simple low-molecular weight metabolites like amino acids, ketones, fatty acids, amines, organic acids, and nucleosides that are involved in various processes (Singh, Trivedi, Haridas et al., 2016; Soininen et al., 2009). Simultaneously, the metabolic profile established may serve as a

potential biomarker that can be used not only for prognostic purposes but also for discriminant analysis.

Researchers at NJIT compared the changes in several metabolites in the frontal cortex and hippocampus of blast-exposed rats and found disturbed energy metabolism. There were increased levels of acetate and reduced levels of glutamate in the frontal cortex and hippocampus. This effect was more pronounced in the hippocampus than in the frontal cortex by 24 hours post-blast.

These results suggest a compensatory up-regulation of ketone metabolism in vulnerable brain regions in response to energy deprivation and increased production of acetate, which indicates that astrocytes function as an energy source for neurons in blast-induced TBI. It is well known that the increased transport and utilization of non-glucose fuel in the brain occurs under conditions of hypoglycemia (Bernini et al., 2018; Prins & Giza, 2006; Prins & Matsumoto, 2014; Wolahan et al., 2017). Further, at the cellular level, loss of energy status may induce activation of the apoptosis cascade, leading to neuronal loss in the hippocampus and related clinical deficits. Aspartate aminotransferase, which converts aspartate into glutamate, may have been inhibited by blast injury and could further impact the citric acid cycle. Another possibility is that reduced glutamate levels may indirectly represent changes in the levels of α -ketoglutarate, a key intermediate in the citric acid cycle, as glutamate is converted to α -ketoglutarate in a reaction mediated by glutamate dehydrogenase (GDH). In fact, Arun et al. showed a decreased presence of the GDH enzyme in mice exposed to moderate blasts (Arun et al., 2013).

Metabolomic Profiles Following Blunt Injury

Researchers at NJIT evaluated tissue metabolites during the acute and chronic phases of mTBI and moderate TBI after blunt impact to provide a temporal view of metabolic alterations post-TBI using tissue metabolomics. Significant changes were observed in the intermediates of the citric acid cycle (succinate) as well as their amino acid precursors such as glutamate and aspartate, which, by transamination reactions, contribute to the de novo synthesis of the intermediates of the citric acid cycle. The metabolites observed in proton nuclear magnetic resonance spectra of hippocampal tissue were mainly associated with energy metabolism (succinate, aspartate, creatine, and lactate), ketone body metabolism (acetate), osmolytes (taurine and myo-inositol), neurotransmitters (glutamate, glutamine, and gamma-aminobutyric acid [GABA]), N-acetylaspartate (NAA), membrane metabolites (choline), alanine, and branched-chain amino acids (BCAA: leucine, isoleucine, and valine). This is likely because the hippocampus has a higher metabolic demand than other brain regions and is one of the most vulnerable regions in the brain for hypoxia (Penny et al., 1974; Schmidt-Kastner, 2015).

At four hours post-blunt mTBI, BCAAs and glutamine were significantly decreased as compared to controls while glutamate, myo-inositol, taurine, and creatine were significantly increased as compared to controls. At one day post-injury, rats showed significantly reduced

Publications related to metabolomic profiles include

Singh, Trivedi, Devi, et al., 2016
Singh, Trivedi, Haridas, et al., 2016
Singh et al., 2017
Rana et al., 2020

levels of BCAAs, succinate, and glutamine along with significantly increased levels of creatine, myo-inositol, and taurine. After five days, BCAAs, succinate, and glutamine were significantly reduced while taurine was significantly increased as compared to controls. At 10 days post-mTBI, significant increases were revealed in taurine, creatine, NAA, glutamine, GABA, and alanine, while aspartate decreased. These 10-day findings were persistent at day 30 along with a reduction in BCAAs and increases in both acetate and lactate.

At four hours post-moderate blunt TBI, a significant increase in acetate and significant decrease in succinate levels were observed as compared to controls. Succinate levels also remained at decreased levels one day post-injury as compared to control levels. Major metabolic upheaval was observed at five days post-moderate TBI, where BCAAs were significantly decreased as compared to controls, and taurine, lactate, creatine, and glutamate were significantly increased as compared to controls.

After multivariate analysis, pathway analysis was performed on results from one, five, and 30 days post-mTBI. Three biochemical pathways showed significant alterations at all three time points in the mTBI group as compared to controls. Disturbance of alanine, aspartate, and glutamate metabolism were observed at all three time points, while nitrogen metabolism was most affected after five days, and taurine and hypotaurine metabolism appeared to be the most significantly affected 30 days post-mTBI. In the moderate TBI group, disturbance of alanine, aspartate, and glutamate metabolism occurred at one day and 30 days post-injury; taurine and hypo-taurine metabolism appeared to be the most significantly affected in moderate TBI brains at day five. These results indicated that glutamine, taurine, NAA, alanine, myo-inositol, and creatine are metabolites that can discriminate between no injury, mTBI, and moderate TBI.

Material Systems for Measuring Blast Exposure

Commercially available pressure sensors generally used in blast experiments on surrogates and animal models are limited in their accuracy and ability to map spatially important regions in the brain. With an ultimate goal of establishing a blast overpressure-induced injury threshold, it is necessary to determine the pressure located at the point of injury in the brain. Therefore, it is important to develop a non-invasive sensor system that can directly report the pressure at desired locations in the brain, without being affected by external conditions.

A desirable approach would be to measure a photonic response using non-invasive techniques that have been shown to respond to external pressure sources, such as bio-templated fluorescent metal nanoclusters. Specifically, protein- and DNA-templated metal, such as gold (Au), nanoclusters exhibit changes (generally an increase) in the intensity of their fluorescence as a function of external pressure (Zhang et al., 2013). This provides a non-invasive means whereby the exact local pressure can be determined from a measurement of the fluorescence intensity of metal nanoclusters embedded in a model system under blast conditions as the first steps in establishing a fluorescence intensity-external pressure baseline.

Scientists at NJIT and ARL collaborated to accomplish the following goals: 1) establish the ability and a protocol to embed or synthesize (in situ) fluorescent gold nanoclusters (AuNC) in

Publications related to material systems for measuring blast exposure include

Mishra, Kumar, et al., 2016
West et al., 2016
Roberts et al., 2020

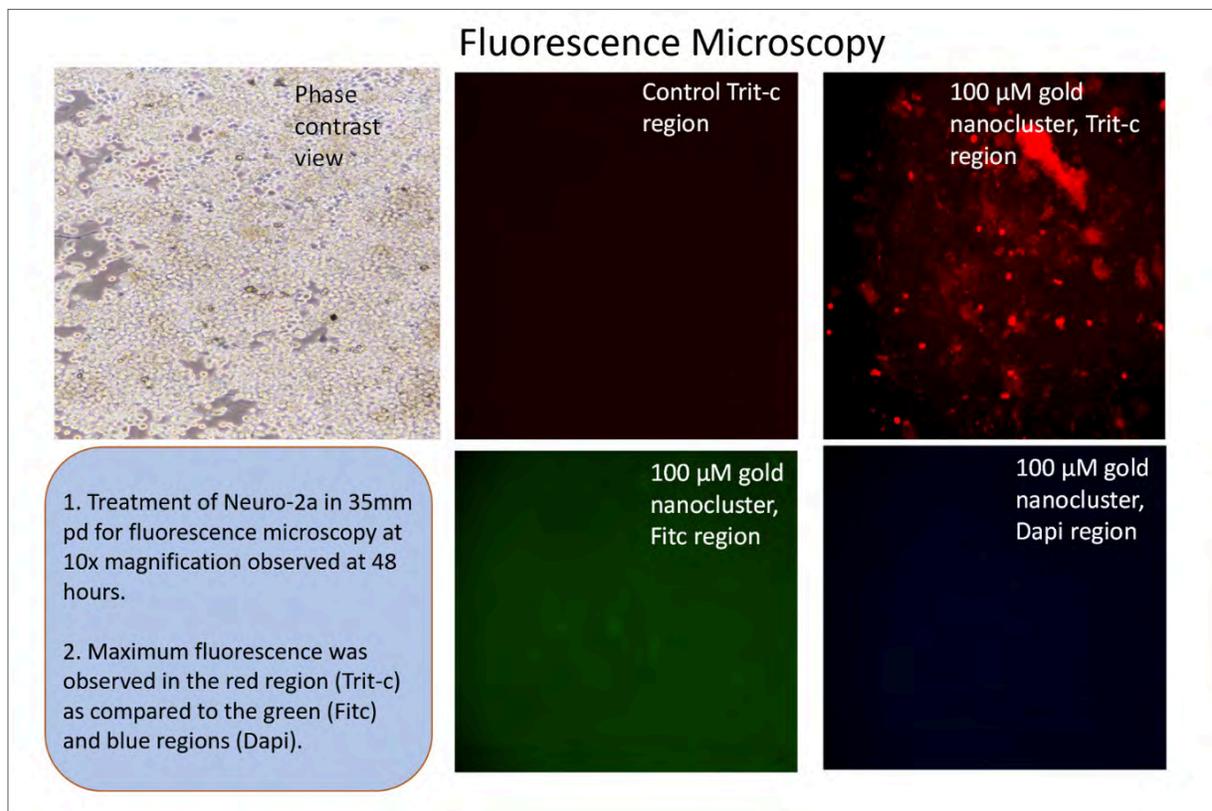
selected cell lines; 2) determine the fluorescence properties and cytotoxicity of cells in the presence of AuNCs; and 3) establish fluorescence intensity-pressure baselines for the cell-AuNC system.

Egg-white (EW)- and bovine serum albumin (BSA)-templated AuNCs were synthesized and embedded in Neuro-2a cells. The AuNCs were also directly synthesized in situ in Neuro-2a cells. Nanocluster accumulation in cells was evaluated by measuring fluorescence intensity with a flow cytometer. Under non-blast conditions, AuNCs exhibited a concentration-dependent increase in fluorescence intensity. BSA-templated nanoclusters emitted more fluorescence than EW-templated nanoclusters. Both the pre-synthesized BSA-AuNCs and AuNCs synthesized in situ by the Neuro-2a cells accumulated in neurons and were fluorescent

in the red (eleven-fold increase) and far-red regions (forty-fold increase) when excited by ultraviolet light (Figure 6-9).

To examine whether AuNC fluorescence responds to an external stimulus, nanocluster-incubated Neuro-2a cells were irradiated with high doses (1,000 Gy) of gamma radiation, resulting in a substantially greater fluorescent intensity of the AuNCs in irradiated cells compared to unirradiated cells. This suggests that AuNCs can be used as sensors for cellular injury induced by ionizing radiation and opens the door for their use as sensors for other external perturbations, such as blast overpressure exposure. Further experiments are required to establish a quantitative relationship between blast overpressure/high-energy radiation dosage and fluorescence intensity.

FIGURE 6-9: Triple-band fluorescence microscopic observations of 100 μM -concentration AuNC access to human Neuro-2a cell cultures. This was measured in a 35 mm Petri dish (pd) with 10x magnification in the red, green, and blue regions using tetramethylrhodamin-isothiocyanate (Trit-c), fluorescein isothiocyanate (Fitc), and 4',6'-diamidino-2-phenylindole (Dapi) fluorescent dyes, respectively.



Computational Modeling of Blast Injury

At NJIT, a geometrical model of a ten-week-old Sprague Dawley rat was generated by combining magnetic resonance imaging (MRI) of a rat head, micro-computed tomography (micro-CT) scan of the rat skull, and geometrical representation of the rat body. The magnetic resonance (MR) images facilitated the segmentation of soft tissues, which included the skin, brain, and dura mater. A geometrical model representing the average dimensions of a 50th-percentile rat body was simulated by skin material properties used to approximate the mechanical response of the rat head tissues.

A 3D geometrical model of the nine-inch shock tube was also generated based on specifications from the shock tubes developed at NJIT and INMAS. The model simulated a portion of the shock tube's test region that was 3.3 m in length, with the region of interest containing the full extent of the geometrical rat model being 0.6 m in length. The modeled rat head was placed in the center of the modeled shock tube test section in a prone position. The entire body of the rat model was fixed in all rotational and translational degrees of freedom to mirror the experimental methods of strapping down the rat body. The shock tube opening was subjected to simulated,

Publications related to computational modeling of blast injury include

Unnikrishnan et al., 2019
Townsend et al., 2019
Kahali et al., 2020
Rubio et al., 2020
Unnikrishnan et al., 2021

time-varying pressure loads calculated from experimental pressure measurements (14.5, 18.85, and 27.56 psi [100, 130, and 190 kPa] blasts) taken at the location of the simulated shock tube opening. Four animals were subjected to two blasts each; eight pressure measurements were taken for each blast (Figure 6-10).

For the lowest blast overpressure simulated, 14.5 psi (100 kPa), the maximum pressures observed in the rat brain were on the order of three times higher than the blast overpressure (a maximum observed pressure of 43.51 psi [300 kPa]). The pressure developed first in the anterior region of the brain, beginning in the olfactory bulb at 51, 54, and 64 μ s after the wave began to interact with the head-form for the 14.5, 18.85, and 27.56 psi (100, 130, and 190 kPa) blasts, respectively. This generated a pressure wave of a lower magnitude that traversed the brain uniformly, followed by an underpressure in the anterior

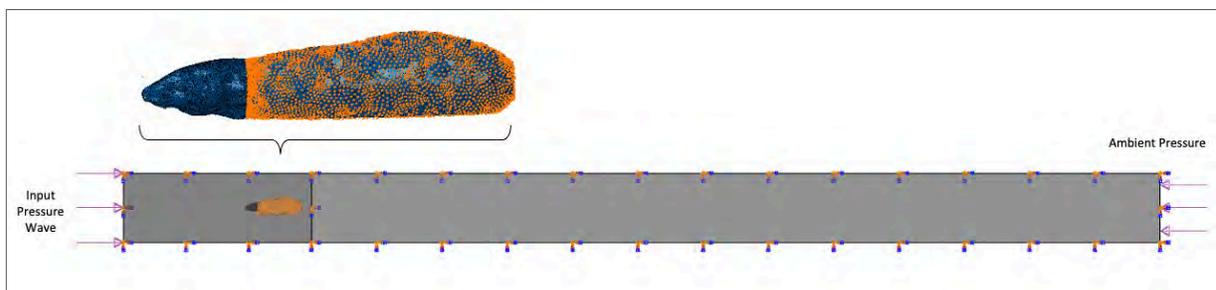


FIGURE 6-10: A lateral depiction of the input conditions used to simulate shock loading on the simulated rat head. The shock tube Eulerian mesh is shown in gray. Pink arrows show the pressure loading locations. The left face—the opening of the shock tube model—is loaded with 14.5, 18.85, and 27.56 psi (100, 130, and 190 kPa) blast pressure profiles. The right face is loaded with a constant pressure equivalent to the ambient pressure conditions. The orange and blue arrows indicate that a face is constrained in all degrees of freedom. This boundary condition was applied to the rat body, as shown in the above enlarged depiction of the simulated rat, and the walls of the Eulerian instance.

brain. The locations exhibiting the highest pressures occurred in the brainstem in all blast overpressure conditions. These high pressures were observed, in each case, over 1 ms after the shock wave passed over the specimen. This location of interest, posterior to the cerebellum in the brainstem, is the location in which the brainstem passes through the foramen magnum. Researchers discovered that the pressure was transmitted through the skull and loads the brainstem with an additional pressure wave (Figure 6-10). The pressure wave resulted in an oscillatory pressure: pressure developed shortly after the shock wave interacted with the specimen and decayed after approximately 3–4 ms, then increased again after 12.5 ms.

The temporal evolution of the maximum principal logarithmic strain in the mid-sagittal section of the rat brain was observed for the 14.5, 18.85, and 27.56 psi (100, 130, and 190 kPa) blast overpressure loads. The pressure wave caused no notable strains to develop and the maximum strains were also observed at the posterior brainstem and were more pronounced on the ventral side of the brainstem. Additionally, the pattern of strain development closely follows that observed with measures of stress development. The strain pattern does not appear to be influenced by the passing of the initial pressure wave. The initial development of strains within the brain appeared to occur shortly after the pressure wave begins to decay, but no apparent correlation was observed with the secondary pressure increase. The magnitude of the maximum logarithmic strain was found to increase with increased blast overpressure. This finding supports the hypothesis that the skull is loading the brain with additional pressures and stresses when exposed to blast.

Modeling Blunt TBI from Clinical Images

Advanced Neuroimaging

Typical injury mechanisms of blunt TBI include cortical damage due to coup and contrecoup impact often involving frontal, temporal, and occipital brain regions (such as in motor vehicle accidents). Brain trauma also leads to diffuse axonal injury secondary to abrupt acceleration/ deceleration and/or rotational/vibrational forces (Adams et al., 1982). These forces cause axonal shearing at the interfaces of tissues with differences in density and rigidity (Huisman et al., 2004), such as at the corticomedullary junction (subcortical white matter) and in the corpus callosum and the rostral brainstem adjacent to the cerebellar peduncles (pontine–mesencephalic junction). It has been postulated that diffuse axonal injury and disruption in connectivity of different brain regions plays a key role in the persistent neurological and cognitive impairments observed in the large proportion of patients who suffer from various symptoms for months after the injury (Lee et al., 2008). Despite the subjective severity of these symptoms, conventional imaging with CT or MRI often appears normal.

Novel, advanced MRI techniques have the potential to detect subtle changes underlying TBI and are emerging as powerful tools to understand the biological underpinnings of insult after injury. These techniques include 1) susceptibility-weighted imaging (SWI), which demonstrates superior sensitivity for paramagnetic deoxygenated blood products after TBI (Beauchamp et al., 2011), thus enabling the detection of micro-hemorrhages in mTBI which may explain focal neurologic deficits (Benson et al., 2012); 2) diffusion tensor imaging (DTI), which provides reliable information about white matter anatomy and can quantify pathology,

thus revealing microstructural axonal injuries; and 3) resting-state functional magnetic resonance imaging (rfMRI), a technique for exploring functional brain networks by exploiting the hemodynamic consequences of neuronal activity while the subject is at rest.

Researchers at INMAS utilized these advanced MR techniques to assess the physical insults induced by blunt impact to the brain. A total of 100 adults from a civilian population (ages 16–65 years) with mild or moderate TBI were recruited within seven days of injury. Routine clinical MRI sequences were followed by advanced techniques to perform a comprehensive analysis of structural and functional changes that could underlie post-concussion symptoms and the neurocognitive sequelae of TBI. An overview of the experimental workflow and results is presented in Figure 6-11.

Of the 100 cases evaluated, 78 were mild and 22 were moderate TBI according to the Glasgow Coma Scale (GCS). Common mechanisms of injury for mTBI were automobile accidents, falls, assault, and sports-induced collision injuries. Sites of impact for most of these cases were in the frontal, occipital, and temporoparietal regions. The most frequent symptoms observed within the first seven days of sustaining injury, as assessed

Publications related to modeling blunt TBI from clinical images include

Cotton et al., 2016
 D'Souza et al., 2017
 D'Souza et al., 2020
 Tan et al., 2020

by the Rivermead Post-concussion Symptoms Questionnaire (RPSQ) (King et al., 1995), were headache, sleep disturbances, and sensitivity to noise. When evaluated with MRI, the majority did not have any obvious abnormality visible on conventional sequences. It was therefore notable that SWI detected traumatic micro-bleeds that MRI conventional sequences found unremarkable in four cases. Advanced MRI sequences, including DTI and rfMRI, showed abnormalities even in uncomplicated mTBI cases. Additionally, there was significantly decreased functional connectivity within certain key resting state networks including the sensorimotor, central executive, anterior default mode, and auditory networks. DTI studies revealed an alteration in quantitative indices (i.e., reduction in fractional anisotropy [FA], increase in mean diffusivity [MD], and change both in radial and axial diffusivity in several white matter tracts), which is suggestive of a disruption of

FIGURE 6-11: Experimental workflow and findings from the blunt TBI imaging work at INMAS.

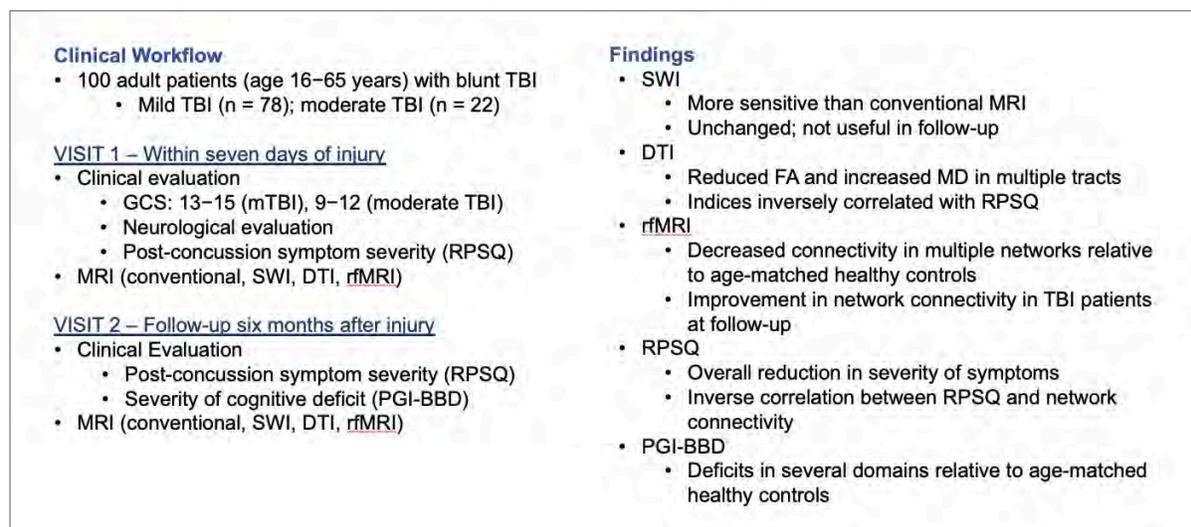




Photo credit: MC3 Madailein Abbott/U.S. Navy

microstructural white matter integrity. Significant correlations between neuroimaging metrics and the severity of post-concussion symptoms were also observed.

Follow-up studies six months post-injury showed a reduction in the severity of post-concussion symptoms, with nearly half of TBI patients reporting a complete resolution of symptoms. The generalized decrease in brain connectivity noted in multiple networks at the initial scan showed partial recovery in the chronic phase. A negative correlation between network connectivity and the severity of post-concussion symptoms was also observed at this time point. Subtle deficits in cognitive function were noted during detailed neuropsychological evaluation via the Post-Graduate Institute Battery of Brain Dysfunction (PGI-BBD) (Dwarka & Santosh, 1990), which correlated with the brain connectivity changes

observed on rfMRI. SWI sequences showed no additional value in the chronic time period.

Integration of MRI with Computational Biomechanics

Numerous studies on blunt head trauma have been conducted to understand the biological and biomechanical mechanisms of TBI. A validated computational head model could establish relationships between impact loading on the head and the internal biomechanical response for several input conditions that are difficult to recreate experimentally. The biomechanical response generated from such simulations can shed light on injury criteria by correlating the spatially sensitive simulated peak stresses/strains in the brain with the severity of brain injuries from clinical assessments. In addition, the exploration of different approaches to cross-correlate clinical MRI assessments of

injury with biomechanical assessments of the same injury is a missing link in validating and enhancing biomechanical models of injury. Thus, a combination of the knowledge bases of both communities can provide the best assessment and prediction of injury.

Scientists from NRL, WRAIR, and INMAS created a correspondence between image-based clinical assessment and computational simulation methodologies to establish the feasibility of their interdependence and suggested a framework for relating the two. Such a framework can improve biomechanical injury criteria for blast, ballistic, and blunt impact injuries as well as support computationally informed medical assessments and treatment. This multi-fidelity finite element (FE) computational model represented the dynamics of a pedestrian fall and the subsequent structural response of the human head due to such an impact and was validated using data from

human cadaver tests. This hybrid (biodynamics and biomechanics analyses) approach simplified the simulation and provided the effect of human body kinematics to calculate stress and strain distributions in the brain.

The study, based on MRI findings, considered two characteristically different cases of pedestrians who sustained mild blunt trauma to the head: an automobile accident and an accidental fall (Figure 6-12). The biodynamics of both incidents were modeled using the case reports documented by the hospital, as well as clinicians' assessment of the most likely trajectory of the event and the impact. These models were integrated with medical data assessment modalities (e.g., MRI) to predict brain injury and support medical diagnosis.

To simulate the kinematics of a pedestrian fall, an articulated human biodynamic model was used

FIGURE 6-12: Simulation results showing the biodynamics of the falls, resulting in blunt impact to the head. (A) Head position just before hitting the ground. (B) Head hitting a hemispherical object (blue) and rotating about joint T1 and producing the forces and the moment applied to the head and neck. (C) Head hitting a 2 cm radius hemisphere in Case 1. (D) Head hitting a 6 cm radius hemisphere in Case 2.

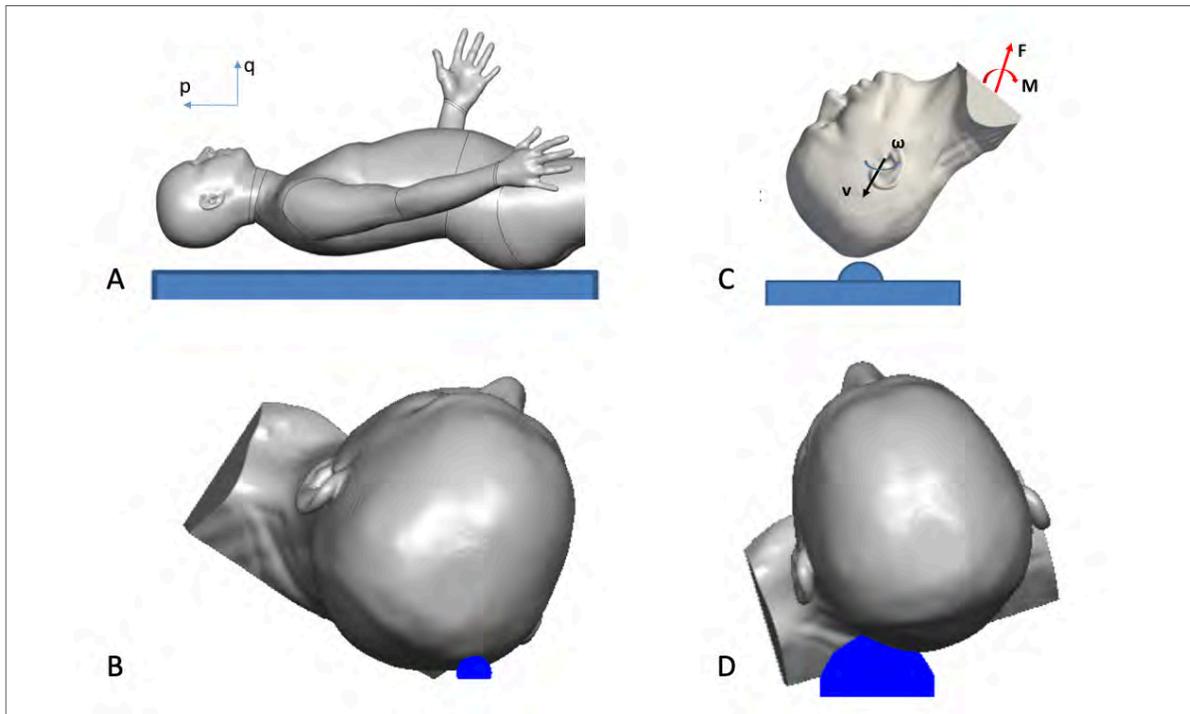




Photo credit: MC3 Madailein Abbott/U.S. Navy

and partitioned into 16 major body components and 15 joints. The fast-running biodynamics model provided the proper initial and loading conditions for the high-fidelity head FE model, including the translational and rotational velocities of the head and the forces and moments at the bottom of the neck before the head collides with the obstacle. To simulate the biomechanics of blunt impact to the pedestrian due to the fall, NRL's high-fidelity human head-neck FE model was developed from high-resolution MRI scans, utilizing 4.5 million tetrahedral elements to discretize the complicated geometry, and includes 29 different tissue components (Cotton et al., 2016). The human head model was validated against experimental tests of blunt impact to the head (Saunders et al., 2018).

The research team conjectured that excessively high tensile pressure contributes to brain injuries at coup and contrecoup sites in the MRI images.

The higher kinetic energy at impact created a localized effect by indenting the skull and creating a large deformation in the coup region, with relatively no effect on the contrecoup side of the brain. These findings suggest that the energy absorbed at the impact site plays an important role in the type of injury (i.e., local lesion versus coup-contrecoup injury) as observed from the relative decrease in displacement between brain and skull motion. This principle can be applied to study other injury types that can originate from mechanical trauma to the brain.

Mapping areas of injury, established from neuroimaging analysis, to local tissue stress and strains, from biomechanical simulation, demonstrates a plausible framework to relate clinical diagnosis with computational prediction (Tan et al., 2020). The results from the computational simulation are evidence that the injury observed with brain imaging can



Photo credit: Capt. Jessica Tait/U.S. Air Force

better inform standardized clinical practices and care across multiple locations. This approach can support a critical need for improved injury assessment in blunt impact events and is planned to be extended to other threat types and improved equipment design for mitigation of these injuries.

Interspecies Scaling Ratio for Blast Loading

The aim of this research was to introduce correspondence rules (i.e., a framework to relate injuries) between a human and a pig for simulated blast-induced shock wave loading using FE modeling. The NRL high-fidelity head-neck FE model for the human (described in the previous section) was used and a new high-fidelity head-neck FE model for the pig was created. Validation of both models was completed using blunt impact tests based on the literature for

humans (Saunders et al., 2018) and blast data based on the literature for pigs (Tan et al., 2017).

The human and pig head-neck models were placed in the same body position so that blast overpressure loading could be applied to the left temple. No mechanical damage was considered in these models even at the highest strains and strain rates. Both FE models were simulated within the CoBi FE solver for multiple explosive charge weights and a fixed standoff distance for multiple peak incident overpressures, utilizing fixed boundary conditions for both heads at the neck. In each case, the transient blast overpressure loading on the head was created using the ConWep model (Kingery & Bulmash, 1984) for a spherical open field explosion in air. The blast exposure analyses were presented in terms of both local and global measures of brain dynamic response.

Toward the objective of developing interspecies correspondence rules, this research examined 1) analysis of the human and porcine subjects using the same 2,4,6-trinitrotoluene (TNT)-equivalent overpressure loads to assess the differences in tolerance to blast (the equal charge weight study) and 2) determination of the TNT-equivalent explosive weights that produce a similar volume of injured brain tissue in human and porcine models (the equal injury study). The studies and results are described in Saunders, Tan, and Bagchi (2019) and Saunders, Tan, Qidwai, et al. (2019). In both tasks, the insult-injury correlation was analyzed by comparing the overpressure load required to produce a certain level of injury through the assessment of positive and negative pressure injury criteria, spatial injury patterns, and temporal injury evolution, to potentially develop correspondence rules.

In the equal charge weight study, time histories of the injury evolution showed that the pig appeared to have a higher tolerance to blast than the human for the positive pressure criterion (34.08 psi [235 kPa]) but not for the negative pressure criterion (-14.5 psi [-100 kPa]). In the human model, the percentage of the brain affected using the negative pressure injury prediction was substantially lower (nearly a full order of magnitude) than the prediction based on the positive pressure criterion. Finally, the increase in injury over time in both the pig and human, for both the positive and negative pressure criteria, was not linear as was initially expected.

In the equal injury study, to elicit the same volume of injured brain tissue, the pig required overpressures that were 50 to over 100 percent higher than what was required for the human. This is likely because pigs have a much thicker skull than humans. For the positive pressure injury, the cerebrum and brainstem in the pig and human exhibited almost identical levels of injury. At lower total volumes of injured brain tissue, the volume of injured tissue in the cerebellum

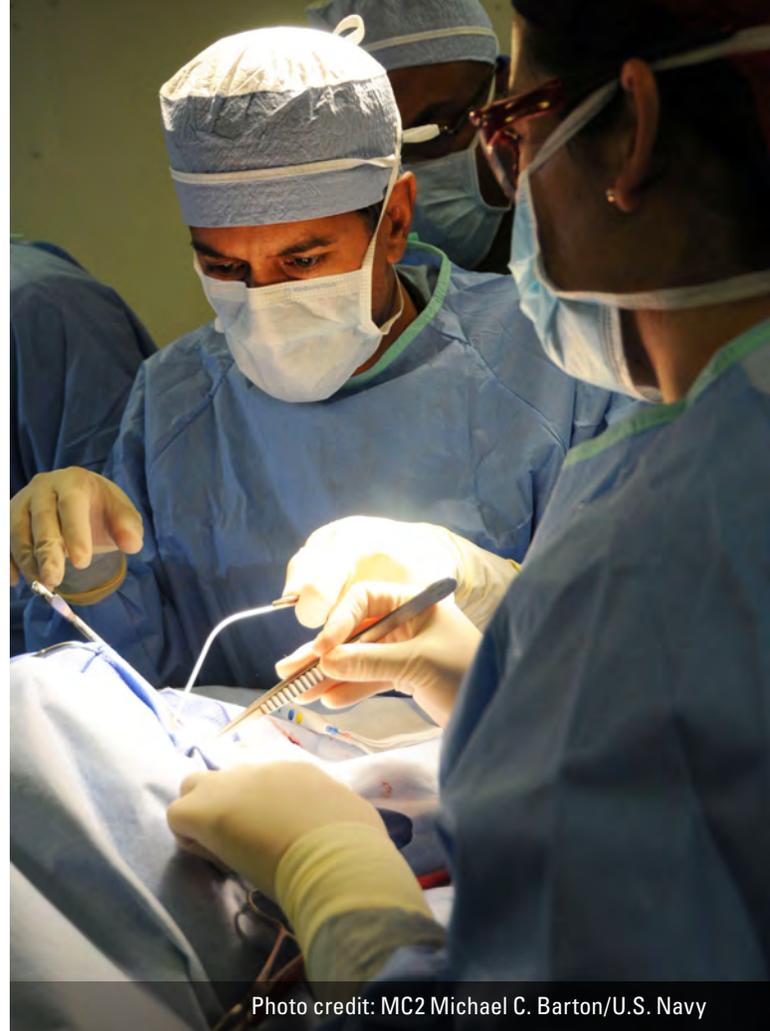


Photo credit: MC2 Michael C. Barton/U.S. Navy

was nearly identical between the pig and the human; however, at higher total injury volumes, the volume of injured cerebellum began to differ between the species.

Lastly, the total volume of injured tissue for each injury criterion was plotted against the charge weight for all simulated cases in both the human and pig; and linear regression was applied as a first-order approximation of the injury evolution with charge weight. This method enables the correspondence between the two species by selecting either a volumetric percentage of brain affected to determine either the charge weight needed, or the peak overpressure the target is subjected to, for either the positive or negative injury criteria. Further development of this interspecies scaling ratio for blast loading is integral to the translation of primary blast animal modeling to the human condition and will better inform clinical injury prediction and mitigation strategies.



Photo credit: Cpl. Reece Lodder/U.S. Marine Corps

Way Forward

This multi-national collaboration established several mechanisms underlying the adverse effects of blast exposure faced by Service members during combat and in training. As a result of the achieving the project's major research goals, both the Office of the Secretary of Defense and the Indian DRDO are interested in building upon the successes of this project by initiating a new phase of this effort.

The research outcomes of the U.S.–India Project Agreement established that a single high-level blast and/or blunt insult to the head can cause a variety of neuropathological dysfunctions and adverse behavioral effects. The next phase of this effort seeks to understand and resolve the effects of repetitive low-level blasts typically faced by Service members during combat and in training, an injury threat recently recognized by the military medical community. Combat readiness depends on sustained training with a broad variety of heavy weapons and artilleries, which have unique blast pressure signatures. Published data on the effects of blast exposures

during training are scarce, but available post-training indicators suggest adverse effects on the neurocognitive performance of Service members, including decreased reaction time, loss of sleep quality, and development of anxiety and mood disorders.

To date, a comprehensive approach to studying repetitive blast exposures has not been undertaken. In-depth experimental and computational modeling studies of this cumulative injury will facilitate the development of appropriate preventive, mitigative, and therapeutic strategies. From these computational models, the nature of these subtle, complex injury modalities can be better understood, and an exposure dosimeter can be designed using operational principles. The development of a field-deployable blast-dosimeter based on the inputs of these studies will assist in appropriate decision-making and institution of optimal management strategies in combat. Follow-on work will also take a comprehensive approach to studying the complex issue of polytrauma after a blast event.



Photo credit: Maj. Thomas Cieslak/U.S. Army

RESEARCH OUTCOMES

1. A state-of-the-art field-validated shock tube was installed at INMAS, identical to the installation fabricated at NJIT. The project personnel were able to combine the experimental data collected at both U.S. and Indian labs to establish blast injury dose-response curves. This model predicts the gradation of blast overpressure-induced TBI (mild, moderate, severe, and lethal) in rodent models as a function of blast overpressure intensity. An additional dose-response model has been developed for blunt closed-head TBI using data from INMAS and WRAIR.
2. A blast overpressure dose-response curve in a rodent model was developed for a single shock wave, indicating that exposure to blast overpressure in the range of 24.66–43.51 psi (170–300 kPa) produces mild to moderate TBI in this rodent model. Single exposures below 24.66 psi (170 kPa) elicit no measurable changes, and exposures above 43.51 psi (300 kPa) are lethal.
3. Injury severity levels depend on the magnitude of both blast overpressure and impulse. This project established that a single blast can affect the whole brain, causing a multiregional biomechanical injury that evolves into measurable cellular pathological changes (e.g., chronic inflammation). Blast overpressure-induced TBI was shown to differ from blunt TBI, which predominantly displays a focal injury pattern. The injury pathology and progression pathways are different for blast and blunt TBI, though they show synergistic tendencies.
4. In blast overpressure-related TBI, three major mechanistic and biological injury pathways have been identified and validated: 1) increased levels of oxidative stress, 2) BBB disruption, and 3) chronic neuroinflammation. These mechanisms appear synergistic but are characterized by unique temporal evolution patterns, which depend on the injury severity and exhibit distinct region-specific spatial and temporal evolution. The importance of these pathways in blast overpressure-related TBI etiology has been confirmed with a variety of techniques including proteomics, metabolomics, histology, immunohistochemistry, electrophysiology, and imaging analysis independently performed by laboratories in both countries.
5. Anatomically accurate computational models for rats, swine, and humans have been developed for blast and blunt conditions and validated against experimental data, which take variable brain material properties into consideration. The validation of the human model includes accident reconstructions based on MRI injury descriptors developed by the INMAS research team.

Additional publications from the collaboration include

Sajja et al., 2016
Sundaramurthy et al., 2018
Skotak, Alay, Zheng, et al., 2018
Skotak et al., 2019
Younger et al., 2019
Misistia et al., 2020
Subramaniam et al., 2021

07



Photo credit: Staff Sgt. Jacob Bailey/U.S. Air Force

CHAPTER 7:

THE PSYCHOLOGICAL HEALTH CENTER OF EXCELLENCE

Contributions to the Science and Implementation of Strategies for the Treatment and Recovery of Psychological Health Disorders that Service Members may Experience after Sustaining a Blast Injury

Invited chapter contributed by PHCoE

The mission of the Psychological Health Center of Excellence (PHCoE) is to improve the lives of Service members, Veterans, and their families by advancing excellence in psychological health care, readiness, and prevention of psychological health disorders. PHCoE is uniquely positioned to collaborate across the DOD, Department of Veterans Affairs (VA), and other agencies to provide leadership and expertise, inform policy, and drive improvements in psychological health outcomes. PHCoE supports the delivery of psychological health care services to our Service members through research into resilience-building, prevention, treatment, and recovery. PHCoE focuses on the tools, resources, and analytic and research capabilities required for identifying evidence-based practices for military psychological health. PHCoE's analytic and research capabilities further serve to inform members of Congress and DOD senior leadership about psychological health gaps, strengths, issues requiring attention, and the evaluation and status of existing programs.

PHCoE's work informs the prevention, treatment, and reset aspects of blast injury research. PHCoE's promotion of resilience strategies and evidence-based treatments addresses adverse psychological health outcomes that can result after blast injuries. Blast injuries, or experiencing a blast event without sustaining injury, can lead to adverse psychological health outcomes such as post-traumatic stress disorder (PTSD), depression, and substance use disorders. Using traumatic brain injury (TBI) as an example, in a study of more than half a million active-duty Service members who served in Iraq and Afghanistan, a little more than 5 percent were diagnosed with TBI, and 61.5 percent of those diagnosed with TBI had a comorbid mental health or chronic pain diagnosis (Adams et al., 2017). Service members with comorbid TBI and mental health conditions have poorer outcomes and a higher utilization of health care (Lu et al., 2019; Adams et al., 2017; Edwards-Stewart et al., 2020). Studies suggest that mental health conditions, particularly PTSD, are associated with the development of persistent post-concussive syndrome (PCS) (Lu et

MISSION

Improve the lives of our nation's Service members, Veterans, and their Families by advancing excellence in psychological health care, readiness, and prevention of psychological health disorders

VISION

Be the trusted source and partner for facilitating evidence-based research and practices across the continuum of care to enhance the psychological health of the military community

VALUE

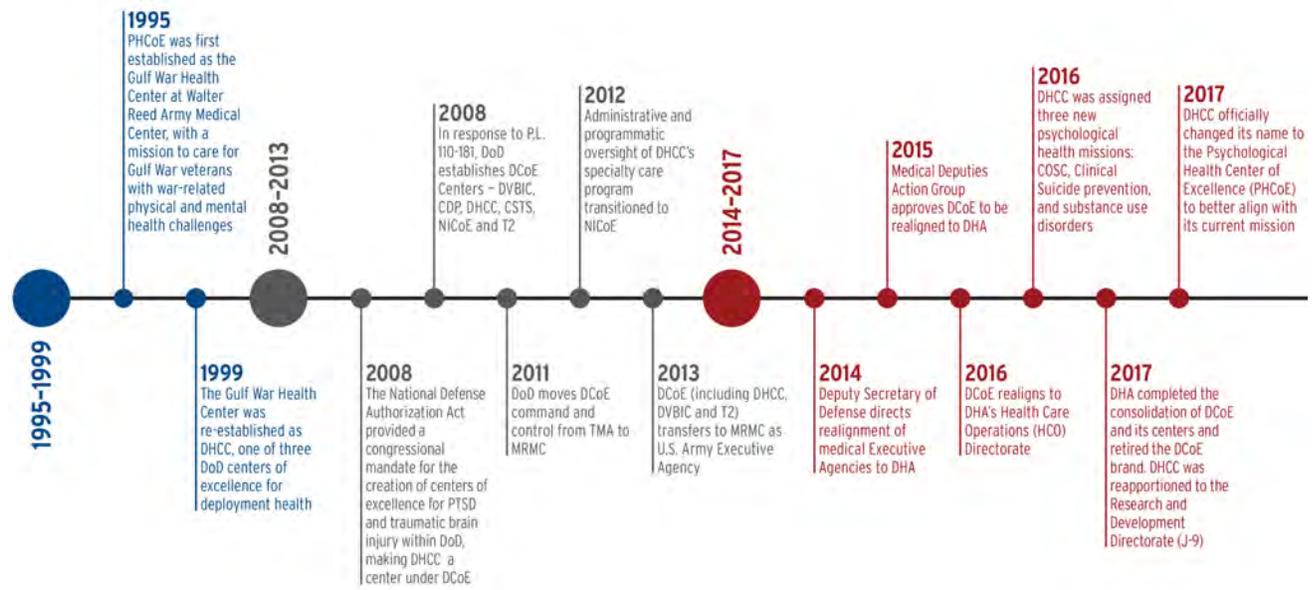
PHCoE provides leadership and expertise, advances policy, and drives improvements in psychological health. We are uniquely positioned to support operational readiness through collaboration across DOD, VA, and other agencies

al., 2019; Bergersen et al., 2017). PCS symptoms may include headache, sensitivity to light or sound, malaise, fatigue, irritability, depression, anxiety, emotional lability, memory and cognitive impairment, dizziness, and sleep disturbances (VA & DOD, 2016). Indeed, PTSD symptom severity contributed 59 percent of the variance found in PCS while sleep and depression symptoms only contributed an additional 1 percent each (Lu et al., 2019). PHCoE relies on scientific and clinical research, including that from the blast injury research community, to promote evidence-based care for and outreach to Service members with mental health conditions.

SCOPE

- ✓ Psychological health consultation and expertise
- ✓ Improve care quality through evidence-based research and practice
- ✓ Facilitate increased access to care while reducing barriers to care
- ✓ Advance the science of psychological health through development of empirically based information and products

FIGURE 7-1: PHCoE historical timeline



History

The historical origins of PHCoE began in 1995 when the Gulf War Health Center at Walter Reed Army Medical Center was established with the mission to care for Gulf War Veterans with war-related physical and mental health challenges (Figure 7-1).

In 1995, the DOD also instituted the Comprehensive Clinical Evaluation Program (CCEP) to provide systematic clinical evaluations for the diagnosis and treatment of conditions related to service in the Gulf War. The Gulf War Health Center developed and implemented the tertiary treatment component of the CCEP, a three-week specialized care program for Veterans with medically unexplained physical symptoms, which focused on individual and group therapy, patient education, physical and occupational therapy, and alternative medicine.

The Gulf War Health Center was renamed and repurposed in 1999 as the Deployment Health Clinical Center (DHCC). DHCC was responsible for coordinating the evaluation of Service members seeking care for post-deployment health concerns,

using the DOD and Veteran's Administration Post-Deployment Health Clinical Practice Guidelines, which replaced the CCEP in 2001. DHCC then added a second track to its specialty care program for Service members with trauma spectrum disorders or significant challenges with post-deployment reintegration. This second line focused on individualized behavioral health and

Key Mandates

- FY08 NDAA, Sec. 1621
- FY08 NDAA, Sec. 1622
- Executive Order 13625 of August 31, 2012, Improving Access to Mental Health Services
- Executive Order 13822 of January 9, 2018, Caring for Veterans in Transition
- DODI 6490.10 Continuity of Care
- DODI 6490.16 Suicide Prevention
- DODI 6490.08 Stigma
- DODI 6490.05 COSC
- DHA-PI 6490.01 inTransition Program

medical care, group therapy, psycho-education, and complementary and alternative treatments.

In 2008, the National Defense Authorization Act (NDAA) established a congressional mandate for the creation of centers of excellence within DOD for PTSD and TBI. As a result, DHCC became a center within the Defense Centers of Excellence (DCoE) for Psychological Health and Traumatic Brain Injury. The NDAA charged the DHCC with implementing plans and strategies for the prevention, diagnosis, mitigation, treatment, and rehabilitation of PTSD and other mental health conditions. In 2012, administrative and programmatic oversight of DHCC’s specialty care program transitioned from DCoE to the National Intrepid Center of Excellence.

In February 2016, DCoE and its centers, including PHCoE (then DHCC), transitioned for a second time, to the Defense Health Agency (DHA) from the U.S. Army Medical Research and Materiel Command (now the U.S. Army Medical Research and Development Command). In October 2017, DHA disestablished DCoE and redistributed its three centers (DHCC, the Defense and Veterans Brain Injury Center [DVBIC, now called the TBI Center of Excellence (TBICoE)], and the National Center for Telehealth and Technology [T2]), within the DHA to better align with DHA’s mission. With this redistribution, DHCC was



Photo credit: SrA Christian Clausen/U.S. Air Force

renamed PHCoE. In October 2017, PHCoE and DVBIC (now called TBICoE) became divisions under the Research and Development Directorate of the DHA (J-9), and T2 was repurposed across the DHA.

PHCoE serves as a centralized source of psychological health expertise to military leadership and stakeholders across the Military Health System (MHS), the Services, the VA, and the Office of the Secretary of Defense. PHCoE additionally provides psychological health expertise to the White House and multiple executive branch departments, and to a wide network of associated non-military agencies including the Substance Abuse and Mental Health Services Administration (SAMHSA),

FIGURE 7-2: Agencies and entities supported by PHCoE, in addition to those listed in text

Stakeholders, Customers, Cross-Agency Partners		
<ul style="list-style-type: none"> • Uniformed Services University of the Health Sciences • University of Washington • Naval Medical Center San Diego • The TriService Nursing Research Program Military Family Research Interest Group at Navy Medicine Readiness and Training Command San Diego 	<ul style="list-style-type: none"> • Walter Reed Army Institute of Research • VA Suicide Prevention Research Impact NeTwork • PREVENTS- the President’s Roadmap to Empower Veterans and End a National Tragedy of Suicide • Centers for Disease Control and Prevention’s National Center for Injury Prevention Special Emphasis Panel 	<ul style="list-style-type: none"> • Army Study to Assess Risk and Resilience in Service Members • Gambling Research Exchange Ontario • DHA J-9’s Science & Technology Management Process Integrated Product Team • Telemedicine & Advanced Technology Research Center

National Institutes of Health, Congress, partners in academia, and multiple stakeholders through the International Initiative for Mental Health Leadership and the SAMHSA-led Interagency Coordination Committee on the Prevention of Underage Drinking. Other agencies and entities PHCoE supports are listed in Figure 7-2.

Mission

PHCoE's mission and vision inform organizational goals to improve psychological health service delivery for Service members, Veterans, and their families and beneficiaries (Figure 7-3). Each of

these components contributes to the framework through which PHCoE translates efforts to enhance health outcomes, maximize force readiness, and optimize value.

PHCoE's operations comprise seven capabilities: prevention and outreach; implementation science; evidence synthesis and gap analysis; health services and population research; surveillance and medical intelligence; policy analysis and development; and evidence-based practice support (Figure 7-4).

FIGURE 7-3: PHCoE's goals and objectives

<p>Goal 1: Enhance the readiness of the military community through provision of psychological health consultation and expertise to the Services and military.</p> <ul style="list-style-type: none"> 1.1 Strengthen collaborative relationships with psychological health leads for the Services 1.2 Assess regularly the needs of the Services and military commands as they relate to psychological health of the warfighter 1.3 Provide consultation, resources, and recommendations for enhancing psychological health 1.4 Evaluate DHA's impact on support to the Services and military commands
<p>Goal 2: Become the primary DHA hub of evidence-based research and practice to improve the quality, effectiveness, and efficiency of psychological health care and prevention of psychological health disorders in the military community.</p> <ul style="list-style-type: none"> 2.1 Translate existing knowledge and evidence-based practice into clinical care 2.2 Increase adherence to evidence-based practice 2.3 Improve the quality and efficacy of psychological health programs 2.4 Provide expert training and consultation 2.5 Evaluate DHA's impact on care quality improvement
<p>Goal 3: Increase access, reduce barriers, and encourage optimal use of psychological health resources across the Military Health System.</p> <ul style="list-style-type: none"> 3.1 Increase psychological health literacy 3.2 Educate and train providers on evidence-based practices 3.3 Promote and support system-level care delivery approaches to increase access to care 3.4 Analyze, influence, and facilitate policy development 3.5 Evaluate DHA's impact on increasing access, reducing barriers, and encouraging optimal use of psychological health resources
<p>Goal 4: Advance the science of psychological health: create and manage empirically-based information and products to support optimal psychological health and readiness across the enterprise.</p> <ul style="list-style-type: none"> 4.1 Surveil and identify trends in psychological health data to develop recommendations to improve the system of care 4.2 Identify critical research and practice gaps 4.3 Evaluate effective prevention and treatment strategies for psychological health 4.4 Translate psychological science into practice 4.5 Disseminate evidence for emerging psychological health concerns and treatments 4.6 Produce research and evidence synthesis products that directly inform translational science 4.7 Increase shared knowledge through scientific consultation 4.8 Evaluate DHA's impact on the advancement of psychological health science across the Military Health System

FIGURE 7-4: PHCoE’s capabilities

Prevention & Outreach	Prevention & Outreach: Promote mental health, link beneficiaries with services, and support efforts including public mental health campaigns, stigma reduction, and transitions
Implementation Science	Implementation Science: Systematically apply methods of science to study and promote the adoption of evidence-based practice change in pilot and/or enterprise settings
Evidence Synthesis & Gap Analysis	Evidence Synthesis & Gap Analysis: Evaluate and translate the latest research evidence on pertinent psychological health treatments and topics to support the Military Health System (MHS) to inform future research activities and funding, clinical practice, and policy
Health Services & Population Research	Health Services & Population Research: Generate new findings and knowledge by conducting psychological health research and analyses, leveraging existing and novel data sets, and health-related behavior surveys
Surveillance & Medical Intelligence	Surveillance & Medical Intelligence: Utilize administrative data to answer epidemiological questions and to characterize current trends within the MHS care delivery system
Policy Analysis & Development	Policy Analysis & Development: Review, create, and analyze pertinent psychological health policies
Evidence-Based Practice Support	Evidence-Based Practice Support: Develop and disseminate empirically-based information and products

All products, programs, and initiatives detailed in this section can be found on the PHCoE website at pdhealth.mil

Current Initiatives

Several of the operational capabilities shown in Figure 7-4 highlight current PHCoE initiatives that may relate, in part, to psychological health disorders that Service members may experience after a blast injury. These specific capabilities fall primarily under three of PHCoE’s branches: Psychological Health Research, Performance and Analytics, and Psychological Health Promotion.

Psychological Health Research Branch

The Psychological Health Research Branch comprises three main lines of effort: Evidence Synthesis & Research Gaps Analyses, Health Services & Population Research, and Dissemination & Implementation Research (Figure 7-5).

FIGURE 7-5: Organizational structure of the Psychological Health Research Branch



Evidence Synthesis & Research Gaps Analysis

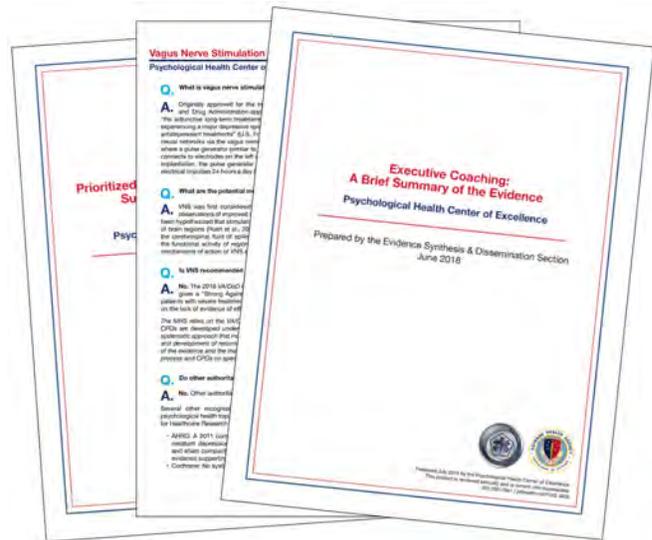
PHCoE's ES&G effort produces reports to inform evidence-based psychological health practices in the MHS. ES&G activities help to:

- Consolidate the latest evidence for effective treatments and methods of care
- Identify gaps in research and clinical knowledge to inform future research directions
- Guide evidence-based clinical practices and policies

Systematic, rigorous, and transparent methods are used to evaluate the available evidence on topics of particular importance to improving the psychological health of Service members and their families. Stakeholder groups are engaged to ensure PHCoE's products reflect the areas of greatest need. Collaborative partnerships with Evidence-based Practice Centers are also used ad hoc to minimize potential bias.

ES&G produces four main types of reports for stakeholders: Evidence Briefs, Systematic Reviews, Rapid Reviews, and Research Gaps Analyses.

Psych Health Evidence Briefs: PHCoE regularly produces expert-reviewed evidence briefs on existing and potential treatments for psychological health conditions that are commonly experienced by Service members. Psych Health Evidence Briefs provide short (typically two-page) summaries of the available scientific evidence and clinical guidance to inform providers, patients, and others who may have questions about the effectiveness of these treatments. The briefs are updated every three years to include the latest evidence and guidance. To date, PHCoE has disseminated more than 80 evidence briefs on treatments for PTSD, pathological gambling, major depression, postpartum depression, suicidality, and disorders related to substance use, alcohol use, cannabis use, and stimulant use, as well as on adjustment,



Find PHCoE's evidence briefs, systematic and rapid reviews, and research gaps reports at pdhealth.mil/research-analytics/evidence-synthesis-research-gaps-analysis

generalized anxiety, obsessive compulsive, and panic disorders.

Systematic Reviews: In addition to the numerous and succinct evidence briefs, PHCoE conducts a few large-scale systematic reviews each year that identify and promote evidence-based psychological health practices in the MHS. These reviews employ well-established and rigorous methods incorporating Cochrane and GRADE approaches to process and evaluation. Recent examples have included comprehensive reviews of screening instruments for gambling disorder, present-centered therapy for PTSD, and prediction models for suicide attempts and deaths.

Rapid Reviews: PHCoE produces rapid reviews for MHS stakeholders who request evidence summaries within relatively tight deadline. Rapid reviews provide timely information about the state of the science for specified topics that may inform psychological health care decisions. The "rapid review" has emerged in response to the need for evidence summaries that can be produced in a shorter period of time than the more labor intensive

and comprehensive systematic reviews. Although there is no standard methodology, rapid reviews involve modifying aspects of the systematic review. In the last year, PHCoE has delivered rapid reviews of alcohol prevention programs, telehealth interventions for treatment of behavioral health disorders, alcohol-related sexual assault/harassment, the effect of bereavement leave on recovery outcomes, and differences in suicide risk factors between National Guard and active-duty Service members.

Research Gaps Analyses: PHCoE employs a systematic process for identifying and prioritizing psychological health research gaps in the MHS. The goals of these efforts are to inform and prioritize research funding and increase the likelihood that comprehensive research portfolios will target areas of greatest need and potential for impact. This process is conducted and refined regularly to produce research recommendations reports for selected topic areas. Recent efforts have reported prioritized gaps in the research of suicide prevention, adjustment disorder, substance use disorder, PTSD, and depression in the military.

Health Services & Population Research

PHCoE's Health Services & Population line of research accesses and analyzes large health and administrative datasets to facilitate research gap and implementation efforts, as well as to support stakeholder and collaborator research efforts

(Figure 7-6). This program brings together large datasets from around the military, enabling PHCoE to conduct longitudinal analyses and to deliver reports and publications that inform policy and decision-making. A wealth of programmatic data is obtained via electronic systems that automatically import medical record information from across the MHS.

The broad scope of these combined datasets enables PHCoE to conduct statistical analyses and modeling of an extremely diverse range of topics; analyses that might not be easily accomplished with more discreet data sources available elsewhere. PHCoE has at least 10 ongoing data analysis projects and a dozen projects complete in response to health services and psychological health questions from military leaders and stakeholders, including requests from:

- U.S. Naval Special Warfare Command
- Joint Service Explosive Ordnance Disposal Military Acceptance Board
- Centers for Disease Control and Prevention
- Office of the Surgeon General of the Army, Behavioral Health Division
- U.S. Special Operations Command (USSOCOM)
- TBI Center of Excellence
- Uniformed Services University of the Health Sciences

FIGURE 7-6: Health Services & Population Research line of effort

<p>Health Services & Population Research</p> <ul style="list-style-type: none"> • Large Datasets Collect, aggregate, and analyze large datasets to answer health services and population research questions • Outcomes and Policy Deliver research reports and policy memos to leadership and MHS stakeholders to inform psychological health care delivery 	<p>Health Services & Population Research Dataset</p> <p>Large Tri-Service dataset compiled from:</p> <ul style="list-style-type: none"> • Defense Manpower Data Center • Aviation Resource Management System • Digital Training Management System • Medical Operational Data System • MHS Data Repository • Theater Medical Data Store • DOD Suicide Event Report • Drug and Alcohol Management Information System • Physical Disability Case Processing System • Behavioral Health Data Portal
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Dissemination & Implementation Research

PHCoE conducts pilot research on the dissemination and implementation of evidence-based treatments through its Practice-Based Implementation (PBI) Network. The PBI Network is an infrastructure that bridges the gap between mental health research and clinical practice in the DOD and the VA and serves to more rapidly translate research findings by facilitating practice changes.

The PBI Network uses a stepwise approach to research translation and implementation that was developed by integrating several evidence-based implementation frameworks and strategies. Six coordinated steps are continuously refined and updated through close collaboration with stakeholders and from new evidence from implementation science. The goals of PBI Network pilots are to increase provider knowledge and accountability, promote coordination and information sharing, and reduce costs by testing practice change initiatives prior to broader dissemination throughout the MHS. The PBI Network thus far has completed implementation pilot tests of PTSD checklist screening, the Screening, Brief Intervention, and Referral to Treatment (SBIRT) approach to alcohol misuse, mobile and web psychological health applications, and cognitive processing therapy training. The latest PBI Network activity is exploring implementation of written exposure therapy for PTSD, and use of intensive outpatient programs to treat military sexual trauma.

Recent Key Accomplishments from the Psychological Health Research Branch

- Conducted research gap analyses, results of which informed the direction of research and Congressionally Directed Medical Research Programs funding decisions for substance use disorders (2017), adjustment disorders (2018), and suicide prevention (2019) research.
- In response to requests from leaders and stakeholders, produced two-page summary briefs in 2019-2020 on the current evidence for 62 psychological health treatments

- Conducted more than 25 systematic reviews and rapid reviews to address important clinical questions, identify research gaps, and inform policy
- Analyzed large military datasets combined from multiple sources to provide uniquely comprehensive, population level health services and psychological health data, including data and analytic support to TBICoE's research of TBI among Navy USSOCOM Service members
- Conducted pilot research on the application of dissemination and implementation science for adoption of evidence-based psychological health practices and improved clinical care, including, most recently, research on methods to implement Cognitive Processing Therapy-Trained Trauma Specialists

Performance and Analytics Branch

The Performance and Analytics Branch delivers analytic and evaluation solutions to a wide range of issues impacting the mental health of Service members. Leveraging its experience in program evaluation and data analytics, the branch provides relevant, timely, and actionable information supporting evidence-based decision-making. The Performance and Analytics Branch works to improve psychological health care in the MHS by delivering information to the clinicians and health administrators who need it.

Analytic services include:

- Clinical surveillance: How often does a condition occur? What kind of care is delivered?
- Program evaluation: Is an innovation successful? How much does care cost?
- Medical intelligence: Where should clinicians intervene? What opportunities exist to improve care?
- Data visualization: How is information best communicated? What information is most important?

The Performance and Analytics Branch most often uses medical administrative data (i.e., data that is



Photo credit: Tech. Sgt. Robert Cloys/U.S. Air Force

routinely collected as part of care delivery or third-party billing) to support analytic efforts. The datasets used contain information about care delivered directly in military treatment facilities as well as civilian-sector care covered by TRICARE and include (among other things):

- Patient demographics (e.g., age, sex, military status)
- Diagnoses recorded (International Classification of Diseases diagnostic codes)
- Medical procedures/activities performed (based on a variety of medical procedural codes)
- Care settings (e.g., primary care, specialty mental health, emergency department)
- Prescriptions written and medications dispensed
- Provider information (e.g., medical specialty, credentialing level, assigned clinic)
- Cost of care delivered

Administrative health data are best-suited to answer questions that describe health care, health conditions, or changes over time in the MHS. For example, administrative data helps answer questions like:

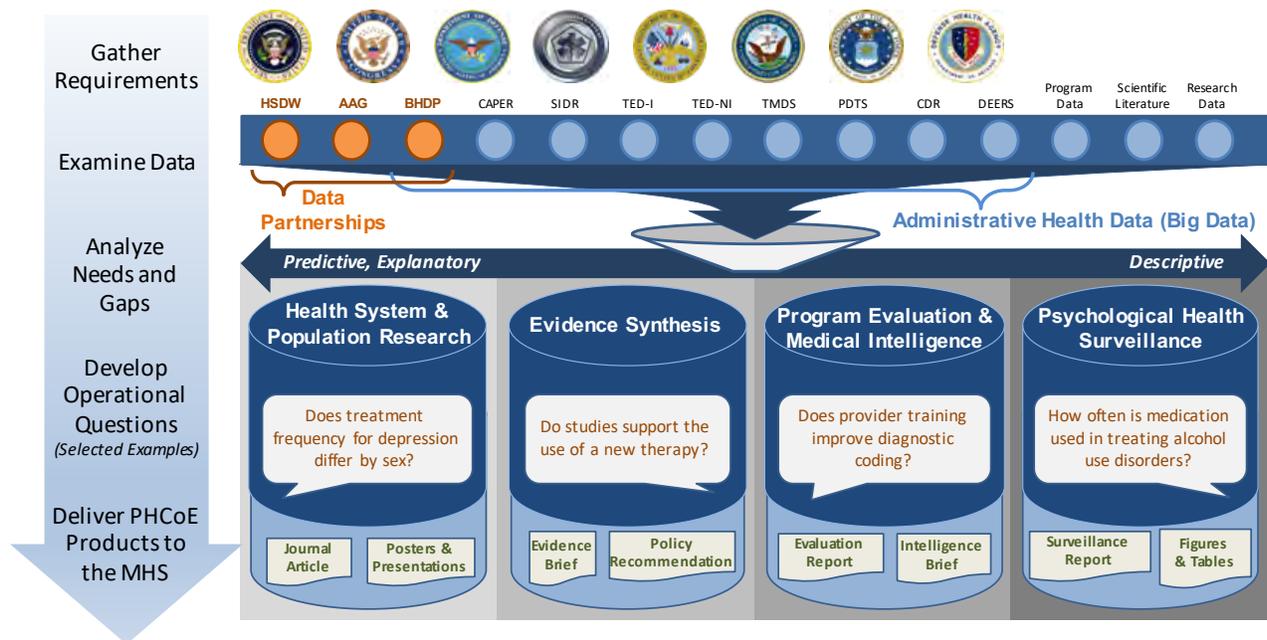
- How many patients with a history of blast injury were also seen for mental health concerns?
- What are the most common diagnoses for pediatric patients?

- On average, how many mental health encounters do blast injury patients have in a given year? How much do those encounters cost?
- How many active-duty Service members filled an opioid prescription last year?

PHCoE works with dynamic data to deliver actionable intelligence to MHS stakeholders at all echelons in near real-time. As illustrated in Figure 7-7, PHCoE gathers requirements from diverse stakeholder groups and works with data from a wide range of source systems to develop and deliver knowledge solutions describing current state or forecasting trends. Broadly speaking, as shown in Figure 7-7, inquiries are divided into four types: Health Systems & Population Research, Evidence Synthesis, Program Evaluation & Medical Intelligence, and Psychological Health Surveillance. The first two types are generally managed by the Psychological Health Research Branch and the latter two are typically serviced by the Performance and Analytics Branch.

Collectively, PHCoE's access to these data allows it to describe current state and to monitor trends over time from the individual to the enterprise. By providing accurate and timely data analysis and interpretation, PHCoE functions as a force multiplier for psychological and behavioral health implementation efforts.

FIGURE 7-7: PHCoE’s process to develop and deliver knowledge solutions to MHS challenges



The center works closely with stakeholders to refine inquiries and identify the most salient information to produce actionable data and recommendations that inform clinical practice, policy determinations, and decision-making for the MHS.

- Supported ad hoc requests for analyses of behavioral health administrative data
- Expanded PHCoE’s analytic capabilities adding geospatial analysis, CarePoint access, and economic forecasting and modeling to its repertoire of analytic tools

Recent Key Accomplishments from the Performance and Analytics Branch

- Delivered a suite of analyses related to opioid prescription practice and opioid misuse to stakeholders in support of efforts to both understand the scope of the opioid epidemic within the MHS and assess the effectiveness of prevention strategies
- Provided primary care behavioral health program managers with quarterly and monthly information on program performance at the enterprise, Service, and installation levels
- Produced provider-specific performance and context surveillance tools to enhance primary care behavioral health implementation support efforts

Psychological Health Promotion Branch

The results of PHCoE’s research, evidence synthesis, and analytic efforts not only inform care practices, but also are actively translated by PHCoE into the implementation of programs and services that directly reach Service members to prevent and treat psychological health conditions (Figure 7-8). The Psychological Health Promotion Branch at PHCoE promotes a culture of support for psychological health by engaging in initiatives that prevent mental illness, link beneficiaries with services, and support health promotion and risk reduction efforts. Ongoing projects and initiatives include prevention and early intervention programs such as the Combat and Operational Stress Control (COSC) Program and the Chaplain-Mental Health Collaboration, and outreach

FIGURE 7-8: PHCoE’s outreach initiatives

Outreach	Prevention & Early Intervention
<ul style="list-style-type: none"> • Real Warriors Campaign – Multimedia public awareness campaign to reduce stigma, educate about mental health and encourage help-seeking • inTransition – Provides mental health care assistance/coaching support to Service members across transitions • PHCoE Outreach and Psychological Health Resource Center (PHRC) – 24/7 service to answer any questions 	<ul style="list-style-type: none"> • Combat and Operational Stress Control – Aligns Services’ COSC programs with DODI • Embedded Mental Health – Align and synergize Service-specific models and find unified definitions • Stigma Reduction – Focuses on decreasing barriers to mental health care, including stigma, and increasing mental health care access and engagement • Chaplain-Mental Health Collaboration – Exploring how to enhance collaboration between ministry teams and mental health

initiatives exemplified by the Psychological Health Resource Center, the Real Warriors Campaign (RWC), and the inTransition program. The RWC is a multimedia public awareness campaign to reduce stigma, encourage help-seeking behavior and educate Service members, Veterans and their families, leaders, and providers about psychological health and available resources. The inTransition program supports a reduction in the number of Service members who disengage from mental health care by providing behavioral health care assistance and coaching support for gaps in care during Service members’ times of transition.

PHCoE’s outreach initiatives additionally include participating in speaker and conference activities for all the Services throughout the military system, the provision of direct resource services, development and implementation of resilience and stress control programs, and serving as the lead agent for ancillary mental health provider groups. For example:

- The PHCoE Outreach Team conducts presentations and booth activities at conferences and other Service member resource and information dissemination venues across the country such as Yellow Ribbon events.

- PHCoE is the lead agency for administering the Psychological Health Resource Center, a 24/7 call center providing psychological health information and resources to Service members, their family members, and Veterans.
- PHCoE is the implementation arm for the COSC mission for DHA and serves as the lead agency for the facilitation and standardization of COSC across the Services.
- PHCoE is the lead facilitator for the Chaplains Working Group, the only venue for Chaplain-Mental Health Collaboration across the DOD which aims to enhance collaboration between ministry teams and the mental health provider community.
- PHCoE has developed and delivered webinars that provide education on psychological health topics for the Chaplain community and promote collaboration with mental health providers.



Photo credit: Capt. Andy Thaggard/U.S. Army



Recent Key Accomplishments from the Psychological Health Promotion Branch

Real Warriors Campaign

- The RWC reached more than 1.2 million people on social media in 2020 who viewed RWC’s 1,620 posts 2.8 million times, leading to 32,860 comments, shares, and other engagement actions.
- 194,407 individuals visited the campaign website – <https://www.realwarriors.net/> – in 2019, resulting in 1,341 Service members, Veterans and family members seeking immediate psychological support through the Real Warriors website.

inTransition

- Performed 171,688 outbound outreach calls to Service members preparing to be separated from the military or reservists/National Guard members transitioning back to their civilian jobs, conducted 28,197 intake assessments, and opened 8,161 coaching cases (Figure 7-9).
- In FY19, the inTransition program incorporated specific call center outreach to recently separated Service members with a history

of TBI. This initiative contacted 445 Service members with moderate or severe TBI in FY19 and 383 in FY20.

- Collaborated with the Veterans Crisis Line to facilitate next-day follow-up for care coordination after a police dispatch or emergency room visit by Service members in crisis.
- Maintained a satisfaction rating of 95 percent for Service members and 98 percent for providers as measured by the Interactive Customer Evaluation system.



FIGURE 7-9: PHCoE’s monthly inTransition coaching cases during FY20

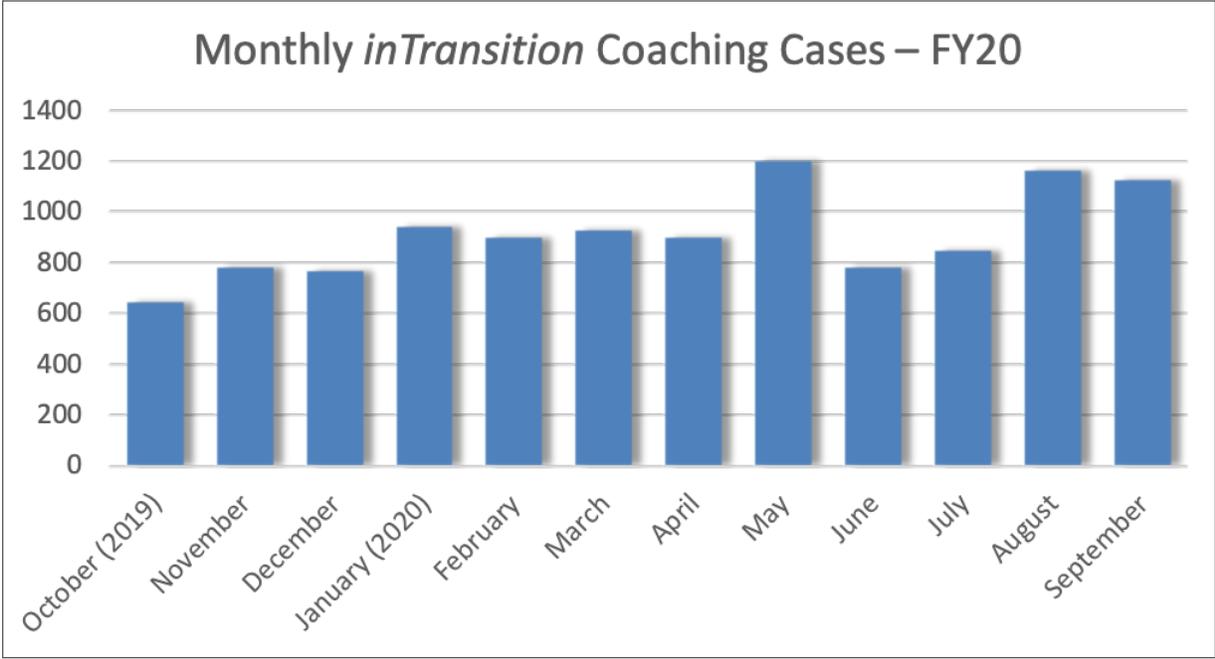


Photo courtesy of PHCoE



Comments from Interactive Customer Evaluation Cards:



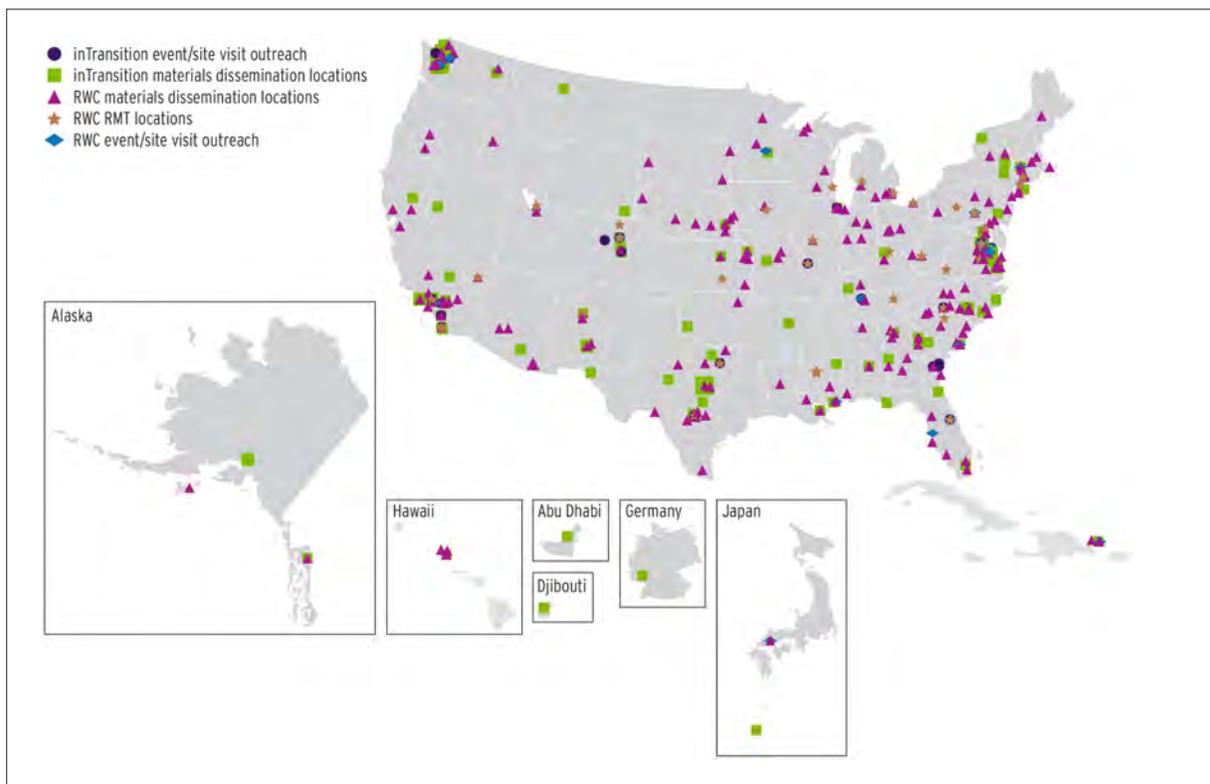
“My coach has been phenomenal. He has been very friendly and super helpful. You could definitely tell he is passionate about helping others and was persistent in doing so.”

“This was a life saver. I had appointments made and received a bunch of information. Thank you for helping me when I felt helpless.”

“Great program! Loved how we can do everything over the phone. I live in a rural area of Texas and this worked out perfect. My contact was very much in tune with our conversations and helped me develop a forward path. Thank you!”



FIGURE 7-10: Map of PHCoE’s inTransition and Real Warriors Campaign sites



Outreach Team

- Conducted strategic outreach at 67 conferences, events, and site visits in 2019, including exhibiting at 14 Yellow Ribbon Reintegration Program events, directly interacting with 3,872 Service members, their loved ones, and providers at these events.
- Facilitated three radio media tours and two audio news releases promoting help seeking by Service members in need of psychological health services, potentially reaching more than 38.4 million listeners.
- Distributed 66,706 pieces of outreach material for PHCoE products and services to military treatment facilities across the globe.

COSC Team

Conducted an annual data call that reported on COSC educational, clinical, and support activities across the Services:

- Provided subject matter expertise at the Marine Corps COSC annual meeting, consulting on revisions to Unit Marine Awareness and Prevention Integrated Training and Operational Stress Control and Readiness curricula.
- Conducted a full review of COSC programs delivered in deployed and operational settings to identify best practices and identify gaps for future program evaluation.
- Collaborated with Walter Reed Army Institute of Research to facilitate an implementation campaign on iCOVER, a front line intervention designed to address “freezing” during a firefight.

Communications and Social Media Outreach

A key underpinning to PHCoE's impact and effectiveness is the promotion and dissemination of PHCoE's programs, products and services among key customers and stakeholders throughout the military mental health community through a comprehensive communications and social media program. These public awareness endeavors serve to meet the goals of increasing access to information, reducing barriers to care, and encouraging optimal use of psychological health resources. Through the timely dissemination of scientific evidence for emerging psychological health concerns and treatments, PHCoE enhances psychological health literacy and provides support for patients, providers, and commanders within the MHS.

PHCoE's communications and social media program has: 1) helped to maintain PHCoE's front-runner online presence and visibility across the DOD through fluid and dynamic marketing tactics and continual evaluation of the effectiveness of digital engagement strategies; 2) created an active and engaging social media platform within the military health community to increase the reach of valuable PHCoE resources and information and provide practical and scientifically sound psychological health content; and 3) established the PHCoE website as a 'one-stop-shop' where military mental health stakeholders can find up-to-date information and resources about identification and treatment for PTSD and other psychological health disorders, clinical support tools, provider training, research findings, relevant policies, resources related to access and barriers to care in the MHS, and a shopping

cart page to order free hard copy mental health-related brochures, fact sheets, and infographics.

Recent Communications and Social Media Accomplishments

- Published more than 50 Clinician's Corner blogs on current topics of interest for psychological health care providers in the MHS.
- Received 341,591 page views and 217,458 visits to the PHCoE website, including a 40 percent increase in referral traffic to the website from Facebook.
- Since October 2019, increased the number of PHCoE Facebook page followers by 16.6 percent and increased the total reach (number of people who see any content from the page) by 322.
- Relunched a dormant Twitter account that had been previously managed by DCoE in October 2019. Since then, have increased followers by 2 percent and achieved nearly 500,000 impressions, or an average of 40,000 impressions per month.
- Disseminated more than 25,000 free hard copy mental health resources to military and community mental health organizations and facilities around the world.



Recent Publications with Relevance to the Blast Injury Research Community

Under Review: Longitudinal investigation of diagnosed psychological and physical health outcomes among U.S. Navy special warfare combatant craft crewmen.

Publications including at least one PHCoE co-author: Cole, W. R., Brockway, J., Fann, J., Ahrens, A., Hurst, S., Hart, T., Vuletic, S., Bush, N. E., & Bell, K. (2019). Expressions of emotional distress in active duty military personnel with mild traumatic brain injury: A qualitative content analysis. *Military Psychology, 31*(2), 81-90.

Edwards-Stewart, A., Smolenski, D. J., Peters, Z. J., Quah, R. F., Bush, N. E., Campbell, M. S., Skopp, N. A., Belsher, B. E., & Kennedy, C.H. (2020) More than expected? Assessing departures from additivity in health care utilization after mild traumatic brain injury in military personnel with pre-existing mental health conditions. *The Clinical Neurologist, 34*(6), 1124-1133.

Hoyt, T., Repke, D., Barry, D., Baisley, M., Jervis, S., Black, R., McCreight, S., Prendergast, D., Brinton, C., & Amin, R. (2020). Development of a leader tool for assessing and mitigating suicide risk factors. *Military Medicine, 185*(1/2, Suppl. 1), 334-341.

Maltz, B., Hoyt, T., Uomoto, J., & Herodes, M. (2020). A case analysis of service member trauma processing related to creative art therapy within a military intensive outpatient program. *Journal of Clinical Psychology, 76*, 1575-1590.

Otto, J. L., Smolenski, D. J., Stewart, L., Workman, D. E., Kincaid, M., Belsher, B. E., Bush, N., & Evatt, D. P. (In press). Explosive Ordnance Disposal personnel in the U.S. military have higher risk of insomnia and posttraumatic stress disorder: A large retrospective cohort study. *Annals of Epidemiology*.

Peterson, A. L., Foa, E. B., Resick, P. A., Hoyt, T., Straud, C. L., Moore, B. A., Favret, J. V., Hale, W. J., Litz, B. T., Rogers, T. E., Stone, J. M., Villarreal, R., Woodson, C. S., Young-McCaughan, S., & Mintz, J., for the STRONG STAR Consortium. (2020). A nonrandomized trial of prolonged exposure and cognitive processing therapy for the treatment of combat-related posttraumatic stress disorder in a deployed setting. *Behavior Therapy, 51*, 882-894.

Stolee, J. D., Hoyt, T., & Brinton, C. T. (2020). Preliminary findings of a four-session psychoeducational group for combat-related posttraumatic stress disorder. *Military Behavioral Health, 8*, 283-291.

Wray, A. M., Hoyt, T., Welch, S., Civetti, S., Anthony, N., Ballester, E., & Tandon, R. (2019). Veterans engaged in treatment, skills, & transitions for enhancing psychiatric safety (VETSTEPS). *Psychiatric Rehabilitation Journal, 42*, 277-283.



Photo credit: Lance Cpl. Timothy Lenzo/U.S. Marine Corps

Way Forward

PHCoE will continue to serve as the DHA nexus for psychological health evidence-based research and clinical practice to improve the quality, effectiveness, and efficiency of psychological health care and the prevention of psychological health disorders in the military community. PHCoE will also strengthen collaborations between the Services and academic partners to prioritize research and practice needs in psychological health.

Connect with PHCoE



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Photo credit: Kelby Sanders/U.S. Navy

CHAPTER 8:

DOD BLAST INJURY RESEARCH AND DEVELOPMENT ACCOMPLISHMENTS



The DOD Blast Injury Research Coordinating Office’s (BIRCO) Executive Agent (EA) support mission is to coordinate DOD blast injury research investment and leverage expertise to develop strategies that prevent, mitigate, or treat blast injuries. To inform the EA of accomplishments throughout the DOD blast injury research and development community, BIRCO requested data from DOD organizations engaged in medical and non-medical blast-related research that occurred in FY20. The 130 submissions that BIRCO received are reported in the following chapter, organized by three key blast injury research program areas: Injury Prevention, Acute Treatment, and Reset. Each accomplishment adds to the knowledge base for blast injury research and development and refines the strategies that prevent blast injury or allow injured Service members to return to duty and maintain an active lifestyle.

The accomplishments featured in this chapter are included as they were received by BIRCO from the research and development community, with as few edits as possible. In response to stakeholder feedback on the FY19 report, overpressure measurements are reported in this chapter as both pounds per square inch (psi) and kilopascals (kPa). Acronyms are defined within the text of each accomplishment, with the exception of select, well known acronyms that are only defined once.

Please contact BIRCO for more information on any of these efforts at usarmy.detrick.medcom-usamrmc.other.medical-blast-program@mail.mil.

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Injury Prevention

Research on blast injury prevention considers the entire spectrum of potential injuries, from primary to quinary. There were three overarching themes to injury prevention accomplishments this year: understanding mechanisms of injury; monitoring blast exposure and determining thresholds of injury; and evaluating personal protective equipment (PPE). The design of prevention systems and strategies requires an understanding of the mechanism of injury; thus, significant research efforts focused on determining blast injury mechanisms using animal and computational models. A subset of these studies seeking to better understand mechanisms of blast injury focused on cavitation (the formation and collapse of microbubbles in the fluid surrounding brain tissue). Researchers are implementing strategies to longitudinally monitor Service members' exposure to blast overpressure, and the acquired data will help refine safety thresholds for human exposure to blast, support the design of protection systems, strengthen guidelines for the safe use of weapon systems, and identify biomarkers of injury and potential treatment targets. Finally, studies are underway to evaluate the performance of PPE, including helmets and body armor, against blast injury and to investigate novel materials that improve their injury prevention capabilities.

Understanding Mechanisms of Injury

Studying Injury Biomechanics with a 3D Model of Primary Neural Cells in a Collagen Hydrogel

Traumatic brain injury (TBI) due to blunt impact leads to altered brain function and is highly associated with long-term impairment in injured personnel. The underlying cellular mechanisms of TBI are both complex and poorly understood, raising diagnostic and management challenges. Ongoing *in silico* research predicts injury severity with finite elements of a headform exposed to various impact modes. When classifying cellular damage due to these impact modes, it is crucial to have

established cellular injury thresholds derived from the biomechanics of the cells.

In this study, researchers from University of Wisconsin–Madison developed a highly controllable *in vitro* model comprising primary neural cells embedded in a 3D, type-I collagen hydrogel. A custom-designed-and-manufactured device was used to apply impacts at strain rates of 1–40 s^{-1} , where far-field strains were programmed to be 0.25–0.35. The deformation response was characterized within the 3D population of cells, as well as across individual cells and the complex branched neurites. Specifically, local strains were mapped onto individual cell surfaces and analyzed to understand the distinct post-injury behavior of individual cells within neural networks. While experiencing the same far-field strain, some cells survived and remained healthy, and some died or became damaged. It was observed that mean tensile strain in the deformed configuration correlates most strongly to cellular death. More data are being collected and analyzed to achieve threshold-of-injury determination with a high degree of statistical confidence. Live staining protocols were administered before and after impacts. High-resolution fluorescent images showed that certain cells underwent critical membrane compromise or apoptotic pathway activation which would eventually affect cell viability. These findings suggest that blunt impacts lead to varying neuronal reactions, particularly demonstrating a strong link between strain/strain rate and irreversible cellular damages. This data is crucial for the establishment of the first physics- (and biology-) based cellular injury criterion for blunt and tertiary blast TBI.

This work is being continued under the Physics-Based Neutralization of Threats to Human Tissues and Organs (PANTHER) program and has expanded to investigate and detail cellular injury thresholds for repetitive head impact and inertial, acceleration-based loadings.

This project was sponsored by the Office of Naval Research (ONR).

Neurospheroids Display Neural Network Dynamics: An In Vitro Model for Studying TBI

Three-dimensional brain cultures can facilitate the study of central nervous system injury and function, and one of the most important components that they represent is neuronal activity on a network level. Researchers from Brown University and the University of Wisconsin–Madison, as part of the PANTHER program, investigated network activity in rodent cortical spheroids while maintaining the networks intact in their 3D state. These neurospheroids replicate in vivo brain stiffness and cell density; they contain the neuron and glial cell types of the brain; they are electrophysiologically active; and form capillary-like structures. In these studies, neural networks developed in culture by nine days and became more complex over time.

To detect network activity, neurons were imaged in rat and mouse spheroids labelled with the calcium indicator dye Oregon Green 488 BAPTA-1 or in mouse spheroids expressing GCaMP6f. Network activity was evident when spheroids were electrically stimulated, was abolished with glutamate blockade, and was altered by GABAergic blockade or partial glutamate blockade. Network properties were quantifiable, including correlations and distances between somas, which were calculated with micron-scale spatial resolution. Spheroids of as few as 4,000 brain cells gave rise to emergent network events, including oscillations. Spheroids subjected to compressive injury of 30 percent strain and 75 s^{-1} strain rate, with a custom uniaxial impact device, exhibited disrupted networks. These results show that network activity in self-assembled mouse and rat spheroids was consistent with in vivo network events. This opens the door to experiments on neuronal networks that require fewer animals and enables higher throughput experiments on network-perturbing alterations in neurons and glia.

This work has led to several new projects within PANTHER, at the fundamental, single cell, and subcellular levels, as well as the in vivo level, to quantify changes in electrophysiology and signaling

activity pre, post, and during mild TBI (mTBI), including blast-induced TBI and repetitive TBI events.

This project was sponsored by ONR.

Relating Blast with Brain Injury at the Cellular Level

A major gap in blast-induced head injury research is understanding the damage incurred by blast overpressure at the cellular level. When the head is impacted by blast-like mechanical forces, the resulting pressure wave transmits to the interior of the brain, which comprises over 100 billion neurons and their intra/extra-cellular matrices. To investigate the effect of blast-like load on the electrochemistry, physiology, and structure of neurons, researchers from the University of Texas at Arlington sought to correlate blast-induced mechanical trauma to cellular-level damage in extracellular matrices and axons.

The first experiment focused on the physiological damage to extracellular matrices caused by a blast wave. In this study, the researchers used reactive molecular dynamics to simulate shock wave-induced cavitation collapse via water hammer within the perineuronal net (PNN) — the near-neuron domain of a brain's extracellular matrix. The model developed for this work focused on the damage in hyaluronan (HA), which is the main structural component of the PNN. The roles of cavitation bubble location, shock wave intensity, and the size of the cavitation bubble on the structural evolution of the PNN were investigated. By observing how HA responded to the water hammer, it was clear that local damage to the PNN increased by the jet formed during bubble collapse. This is further corroborated by the case with no bubble, in which even a high-velocity shock wave was not enough to break the HA. The results of the research presented herein suggest that the larger the bubble size, the greater the impact on the HA. This work was published in *Scientific Reports* (Wu & Adnan, 2017) and further built-upon in a subsequent *Multiscale Science and Engineering* publication (Wu & Adnan, 2020).

The next study was designed to address the extent of blast-induced electrochemical damage to axons. Electrochemical damage in an axon is characterized by analyzing action potential change as a function of blast-induced deformation and swelling in the axon. The researchers modeled a segment of swelled axon by combining a one-dimensional cable theory model to capture the electrical activity in the pre- and post-swelled region and a two-dimensional finite element model for the swelled region. The action potential model suggests that axonal swelling has a direct impact on the action potential transport across the axon. This research was published in the *Journal of Computational Neuroscience* (Wu, Gilpin, et al., 2020).

The final related experiment began with the development of a single axon model by which structural damage induced by a blast wave could be ascertained. This model consists of microtubules (MT), microtubule-associated protein tau (MAPT), and lipid bilayer cell membrane (LBCM). Using the mechanical properties of MT, MAPT, and LBCM, a viscoelastic model of the axon was developed based on the composite shear-lag theory to predict mechanical behavior and damage under dynamic loading conditions. The researchers found that structural damage in a neuron is characterized by one of the following damage mechanisms: 1) microtubule-tau protein separation, 2) microtubule failure, or 3) tau protein stretch. The deformation process is highly rate dependent: at a smaller loading rate, deformation is governed by tau protein stretch but at a higher loading rate, microtubule failure determines overall axonal failure. This research was published in *Scientific Reports* (Wu & Adnan, 2018), further built upon in work published in the *Journal of the Mechanical Behavior of Biomedical Materials* (Khan et al., 2021), and the subject of a review published in *Multiscale Science and Engineering* (Khan et al., 2020).

Fundamental insights obtained through such studies have the potential to foster development of future novel capabilities, such as rapid diagnosis of TBI and improved protective equipment design, to improve safety and protection of Service members.

This project was sponsored by ONR.

Characterization of the Indirect Mechanism of Blast Exposure

Despite years of research, it is still unknown whether, and how, explosion-induced blast waves cause non-impact TBI. The proposed causes of blast-induced TBI include a direct mechanism (i.e., the interaction of the blast wave with the head) and an indirect mechanism (i.e., the interaction of the blast wave with the body). In the absence of human studies of blast-induced TBI, which are unfeasible, animal models can advance understanding of the potential underlying mechanisms of this injury. To this end, a few studies have reported changes in the brain tissues of animals exposed to a head-only blast (Sawyer et al., 2016; Rodriguez et al., 2018), supporting the direct-mechanism hypothesis. However, the role of the indirect mechanism in causing such an injury remains inconclusive, mainly due to the lack of careful experimental studies that appropriately isolate the indirect mechanism from competing possibilities, and the lack of comprehensive computational studies that systematically investigate its potential effects on the brain vessels and tissues.

Researchers at the Biotechnology High Performance Computing Software Applications Institute (BHSAI), a subordinate organization of the Telemedicine and Advanced Technology Research Center, in collaboration with the New Jersey Institute of Research (NJIT) and the University of Utah (UT), conducted an interdisciplinary study to characterize the potential role of the indirect mechanism in causing blast-induced TBI. Using

medical images acquired by UT and intravascular-pressure measurements from torso-only exposures (i.e., blast exposures limited to the torso of a rat) conducted by the NJIT, the BHSAl team developed computational models to answer a key research question: can the indirect mechanism of blast exposure cause damage to the brain? If so, does it damage the brain vasculature, the brain tissue, or both?

To address this research question, the BHSAl team developed 3D computational models of the neck and cerebral vasculature of the rat and characterized the energy transfer from the blast overpressure to the body via the blood vessels (Rubio et al., 2020). In addition, BHSAl developed a 3D computational model of a rat brain to investigate the effect of a torso-only blast exposure on the biomechanical responses (i.e., the strain) of the brain tissues.

From computer simulations, when compared to a blast-free condition, results showed that a torso-only exposure increases the peak mass flow rate at the base of the brain by up to 255 percent and increases the wall shear stress throughout the entire cerebrovascular network by up to 289 percent (Figure 8-1A). In contrast, simulations showed that a torso-only exposure causes minimal strain (< 1 percent) in the brain tissues (Figure 8-1B). Together, these data suggest that the indirect mechanism of TBI is responsible for an abrupt and abundant surge of blood to propagate from the torso to the neck and the cerebral vasculature, increasing vascular wall shear stresses, which may induce vascular injuries. However, acute strain-induced damage to brain tissues due to the indirect mechanism of blast exposure is not supported by the calculations.

This effort was funded by the Defense Health Program and managed by the Military Operational Medicine Research Program (MOMRP).

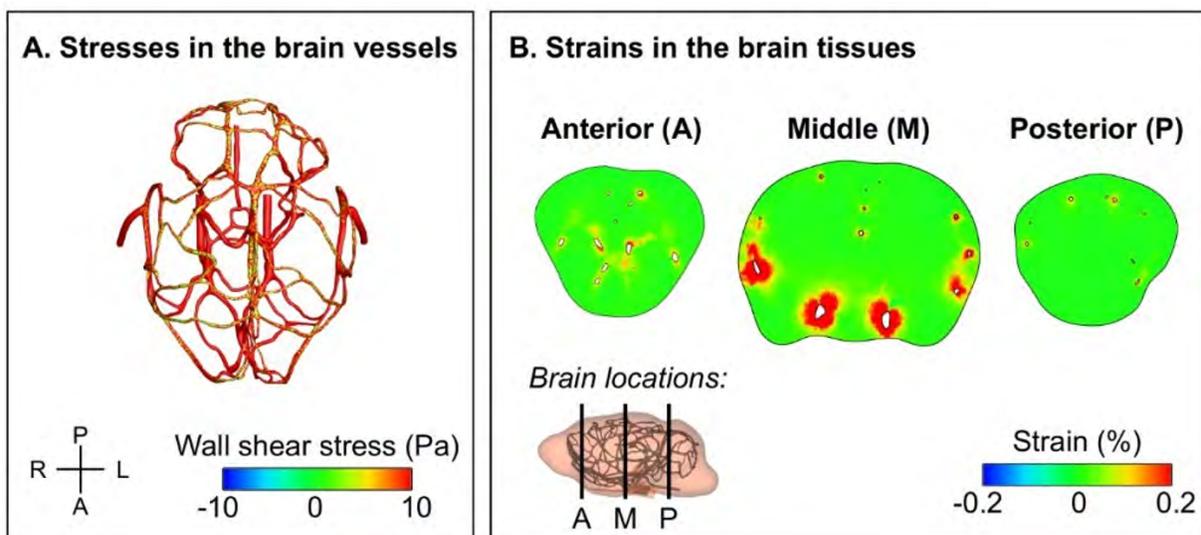


FIGURE 8-1: (A) Differences in peak stresses in the cerebral vasculature of a rat between a blast-free condition and a torso-only blast-exposure condition, which indicates that the indirect mechanism considerably increases the wall shear stresses in the brain vasculature, potentially leading to vascular injury. (B) Differences in peak strains in the brain tissues of a rat between a blast-free condition and a torso-only blast-exposure condition, which indicates that the indirect mechanism induces very small increases in strains in the brain tissues that are unlikely to damage the brain tissues. Figure originally featured in Rubio et al. (2020) and is licensed under [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).

Project Steering Committee Meeting and Training Workshop for the U.S.-India Project Agreement on Experimental and Computational Studies of Blast and Blunt TBI

As described in detail in [Chapter 6](#) of this report, an international collaboration to understand the mechanisms of blast and blunt TBI conducted experimental and computational modeling research over the past several years. In early FY20, the project team met in-person at the Institute of Nuclear Medicine and Allied Sciences to review the project accomplishments to-date, conduct joint blast and blunt TBI experiments to close data gaps, analyze the collected data, and discuss preparations for the final project report. On the last day of the meeting, both the U.S. and India teams participated in planning for the next six months of the project.

The project team shared proposed research outputs from the third year of the project, which included the development and refinement of functioning systems for carrying out animal and surrogate experimental models of blast and blunt injury. For example, data from experiments in which rats were exposed to blast will be used to study the various parameters of blast-related injury via immunohistochemistry. Additionally, data gathered from intraventricular intracranial pressure sensors implanted in blast and blunt-injured rats will inform computational models of the rat brain. An anatomically accurate computational model of the rat brain is useful for developing a mutual correspondence between rats and pigs, to better understand blast loading causing mild and moderate brain injury.

This multi-site, multi-national effort established scientifically credible mechanisms underlying the adverse effects of blast and blunt injuries faced by Service members, both during combat and in training. As a result of the successful achievement of major research goals established by the U.S.-India Project Agreement, both parties

are interested in building on this success by initiating a new phase of the effort, utilizing a comprehensive computational modeling approach to better understand the phenomenon of repetitive blast exposures as well as the complex issue of polytrauma.

This research was funded by allocations from the U.S. Joint Capability Technology Demonstration Transition, U.S. Army Research Laboratory (ARL), and the Indian Ministry of Defence.

A Multi-Scale Theoretical and Experimental Platform for Understanding Cavitation Deformation Dynamics

Blast overpressure waves have been shown to induce cavitation in soft materials, including tissues, but a thoroughly understood mechanism by which cavitation bubbles and fracture in soft tissues lead to acute damage and tissue death has not been established. Researchers from the University of Massachusetts Amherst, along with those from the Universities of Pennsylvania and California, San Diego, have developed methods that allow cavitation phenomena in soft tissues, especially brain tissue, to be measured and understood for both low and high strain rate events. The emphasis is on establishing quantitative relationships across a range of time and spatial scales to help establish new precise measurement and diagnostic methods, as well as the development of new phantom materials for qualifying new protective materials. These relationships also aid the establishment of thresholds for critical exposure, thus helping to inform guidelines for protecting Service members.

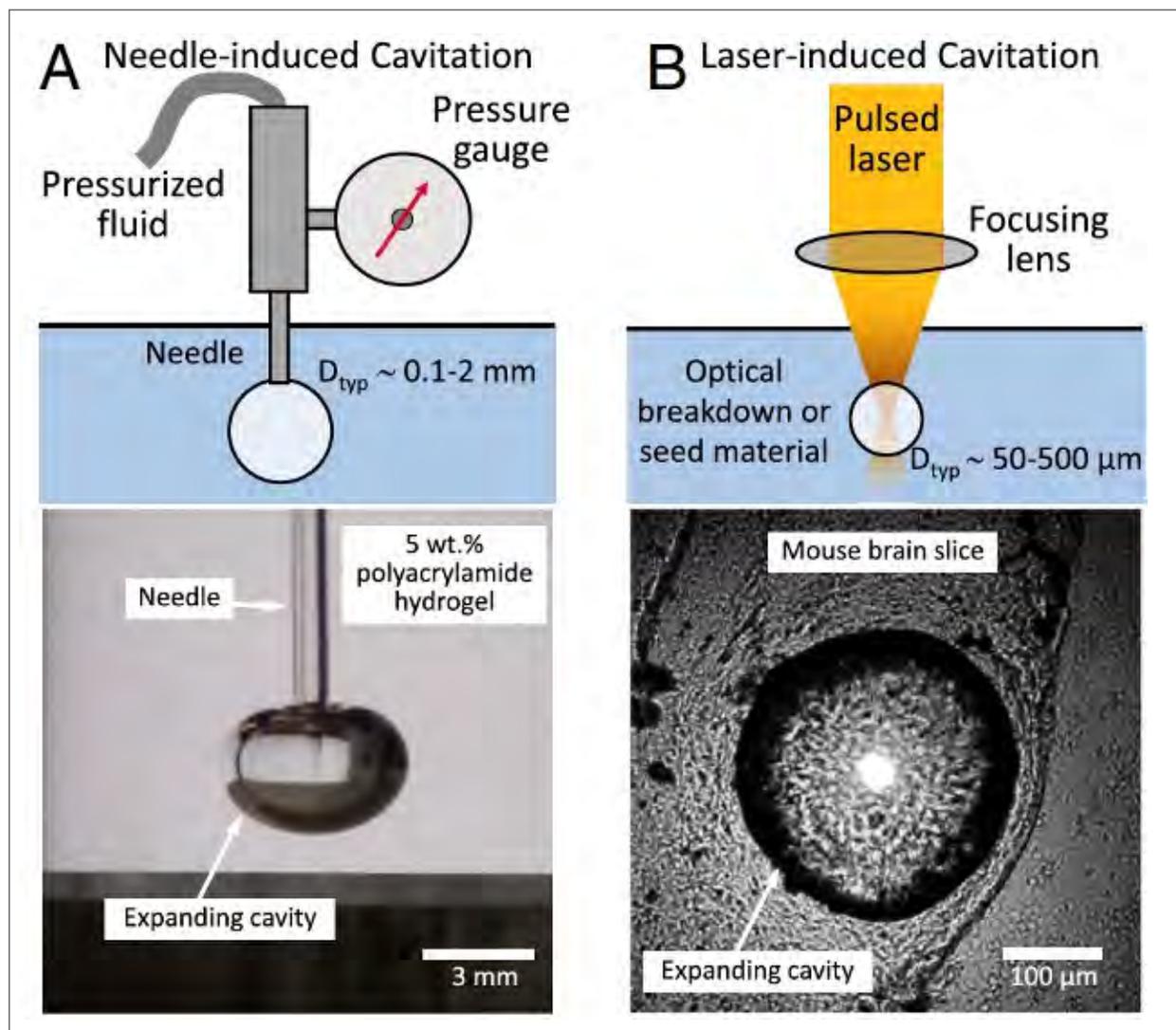
The first effort toward this research goal combined the previously developed methods of needle-induced cavitation (NIC; Figure 8-2A) and seeded laser-induced cavitation (SLIC; Figure 8-2B), with new finite element analysis models to provide insight into the pressure required to cause irreversible interfacial fracture in mouse brain tissue. Researchers quantified fracture

propagation as a function of location within the brain, as well as cell (astrocyte) stress response and death due to cavitation and tissue fracture. In addition, the researchers developed a new 2D-SLIC method for characterizing murine brain tissue and used digital image correlation with nanosecond resolution to measure strain during cavity expansion in brain tissue. The developed methods and numerical models combine to provide the high strain rate behaviors of brain tissue.

The second relevant effort combined NIC, SLIC,

precise synthetic polymer network chemistry, and molecular dynamics (MD) simulations to develop and experimentally validate a new structure-property theory for cavitation and fracture. The researchers established that macroscopically observed expansion mechanisms (i.e., cavitation and fracture) can be connected to molecular level damage of the network structure in gel materials. This work provides a quantitative foundation for systematically designing protective and phantom materials that properly manage damage-inducing loads.

FIGURE 8-2: (A) Schematic of and image from NIC measurement method for assessing cavitation-related properties in soft materials. (B) Schematic of and image from SLIC. Image shows expanding cavity in a mouse brain slice. Images originally featured in Barney et al. (2020) and are licensed under [CC BY-NC-ND](https://creativecommons.org/licenses/by-nc-nd/4.0/).



Lastly, the researchers developed and characterized MD-simulated, phase-separated networks to guide experimental investigation into heterogeneous network cavitation and fracture. It was demonstrated that failure of polymer networks, comprising heterogeneous phase-separated microstructures, is independent of local elastic properties. This accomplishment helps to identify the characteristics of heterogeneous materials, such as brain tissue, where damage-inducing cavitation events originate.

This project was sponsored by ONR.

A Computational Cavitation Simulation Framework for Predictive Modeling of Non-Spherical Bubble Dynamics and Soft Matter Response for Blast Injury Protection

Novel challenges have motivated the need to develop an understanding of bubble dynamics in and near soft materials, particularly in biological tissues. While models have been developed to successfully predict cavitation erosion to metallic surfaces, the theoretical foundation underlying these models is no longer valid when considering soft matter, due to its unique deformation and failure mechanisms. These mechanisms are a function of the complex microstructure and the extreme conditions of loading (large strains at high strain rates). The objective of this research project is to conduct numerical simulations for bubble dynamics prediction in and near soft (viscoelastic) materials to further the development of preventative technologies that protect Service members.

To achieve the project objective, the following three goals have been established. The first is to develop and validate the high-order Eulerian framework-based numerical solver (i.e., state-of-the-art code, multi-component flow code [MFC]) for mass transfer due to phase change and viscoelasticity. This open-source tool was published in *Computer Physics Communications*

(Bryngelson et al., 2020). The second goal is to leverage data-assimilation methods to determine the material properties of gels in the high strain rate regime after laser-induced spherical bubble cavitation. The final goal is to analyze the energy balance of spherical, laser-induced single-bubble cavitation in water and gels. This will advance the understanding of energy attenuation mechanisms, including damage, by and in soft materials in the high strain rate regime. In concert, these three objectives will provide insights regarding how to mitigate potential damage mechanics and conditions due to cavitation in soft matter.

Considerable progress has been made toward achieving the identified objectives. For the first objective, the six-equation model was incorporated into the thermodynamic relaxation procedures for mass transfer due to phase change, and a hypoelastic model for viscoelasticity has been implemented into MFC. MFC was utilized to predict spatially and temporally resolved field data (i.e., pressure, velocity) to complement companion experiments on cavitation bubbles and investigate non-spherical collapses (Schmidmayer et al., 2020). Current efforts are underway to continue validating the numerical implementation with acoustically induced cavitation experiments. For the second objective, various data assimilation approaches were benchmarked using experimental data from laser-induced cavitation bubbles and spherical bubble results from the state-of-the-art inertial microcavitation rheometry (IMR) solver. The results showed that ensemble-based data assimilation methods are an effective tool for such parameter estimation, also informing the underlying physics of the bubble collapse in observed experiments. For the third objective, the experimental data were used to conduct an energy balance analysis of growth and collapse of the bubble. Using the bubble wall trajectory solved from IMR matching experimental results, spherical, expanding piston numerical simulations are solved to compute the acoustic and outward-propagating shock wave in liquid water and soft

matter. Current efforts are underway to compare the shock wave trajectory and amplitude with the experiments to determine the attenuation rate due to viscoelasticity. In conjunction with the MFC solver and data-assimilation efforts, fundamental and precise insights are being obtained regarding the conditions and mechanisms for damage to soft matter due to cavitation.

Fundamental understanding of the physical impact of blast overpressure on bodily tissue will lead to the development of more effective PPE and enhance the lethality of the Warfighter.

This project was sponsored by ONR.

Strain and Strain Rate-Dependent Neuropathology of Blast-Related TBI

Blast-induced TBI has become an increasingly prevalent subcategory of brain injury with the expanded use of improvised explosive devices (IED). These injuries involve the propagation of high-rate pressure waves interacting with neural tissue. The neural microenvironment provides a complex modeling challenge, involving both spatially varying cell types and cellular density as well as heterogenous extracellular matrix composition and density. This innate complexity hinders the ability of many in vitro injury models to reliably predict cellular injury on a larger scale, magnifying the need for a mechanical understanding of cellular injury. An active area of particularly challenging study, important to the understanding of blast TBI, is high strain rate (10^4 – 10^6 s⁻¹) injury where experimental techniques tend to be destructive or under-characterized. In this study, a fast, inertial microcavitation-driven injury modality was used to investigate the mechanical thresholds of cellular sub-structure stability and cellular viability immediately following high-rate, large deformation experienced in blast-induced TBI.

Three-dimensional in vitro models of neural cell networks are cast in 48-well cell culture plates. Primary Sprague Dawley rat cortices are isolated

from post-natal day 0–1 rat pups. Isolated cortical cells are suspended in a rat-tail collagen-I solution, cast into 3D cylindrical hydrogels as described in Scimone et al. (2018), and undergo synaptogenesis for seven days in vitro prior to microcavitation injury. Single bubble injury events are induced via a pulsed neodymium-doped yttrium aluminum garnet (Nd:YAG) laser and the dynamics of the cavitation bubble are recorded at 270–480k frames per second. A ‘damage’ image is acquired immediately following injury and subsequently fixed in paraformaldehyde and sucrose and immunostained for cytoskeletal markers of interest. Bubble dynamics are analyzed through a recently developed inertial microcavitation rheometry (IMR) technique described in Estrada, et al. (2018).

Ongoing research suggests the existence of radially distinguishable cellular disruption modalities as a function of applied mechanical strain, strain rate, and stress. IMR analysis of high-speed cavitation dynamics allows accurate and highly specific understanding of the full injury history for each cell in an injured sample, with the ability to localize the stress-strain regime cellular projections experience. Taken together, this study is the first of its kind to present a complete atlas of the strain and strain rate-dependent pathology of blast-induced TBI at the cellular and subcellular level.

This project was sponsored by ONR.

A Phenomenological Model for Cavitation

A phenomenological model of cavitation has been developed, based on observations that both large relative negative pressures and large negative time derivatives of pressure are required for cavitation onset. Researchers at Sandia National Laboratories simulated two cavitation experiments to generate cavitation scaling parameters for relative pressure drop and rate of pressure drop. The results show that the model, while simple, is effective at reproducing results from laboratory experiments of cavitation.

The parameters were then used in conjunction with a human surrogate computational model to predict, at any position in the head, the probability of intracranial cavitation caused by exposure to a blast event. The results suggest that the magnitude of blast overpressure observed in field data is sufficient to cause intracranial cavitation. The analysis indicates that the helmeted head, when compared to the unhelmeted head configuration, results in a decrease but not elimination of cavitation exposure (Figure 8-3). When density functions of cavitation probability versus cumulative brain volume are combined with an injury severity model, the results show helmet efficacy at low and moderate risk levels. However, the

convergence of unhelmeted and helmeted probability density functions at high-to-excessive risk thresholds indicates the helmet offers diminishing protection at elevated exposure levels, relative to the unhelmeted baseline (Figure 8-4).

Future investigation and collaboration with neuroscience subject matter experts are needed to contextualize the current computational results. While the present work contributes specific and quantified predictions of intracranial cavitation location and severity, more research is required to apply these results to clinical settings with population-based brain injury participants and controls. The relationship between the

FIGURE 8-3: Probability of cavitation in unhelmeted and helmeted scenarios.

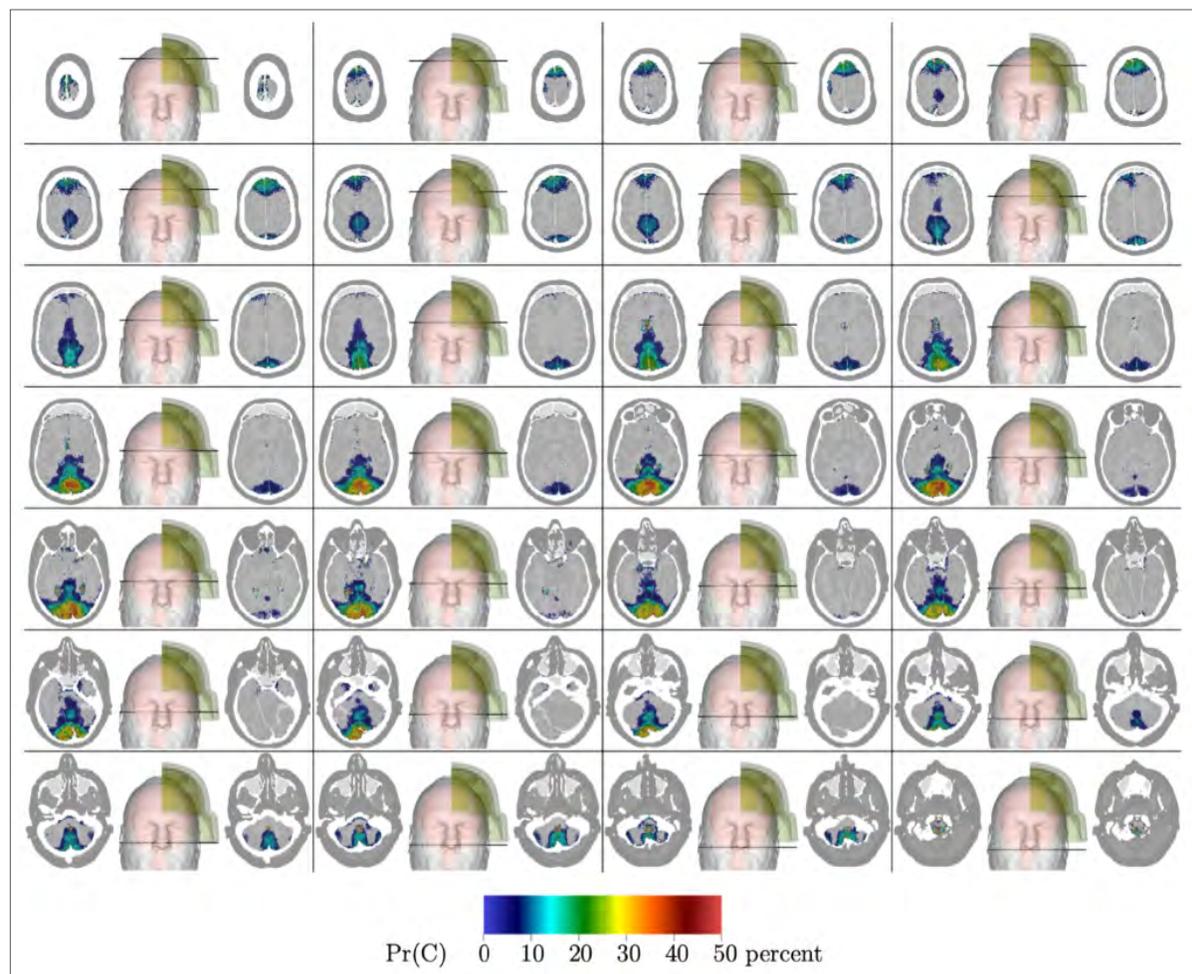
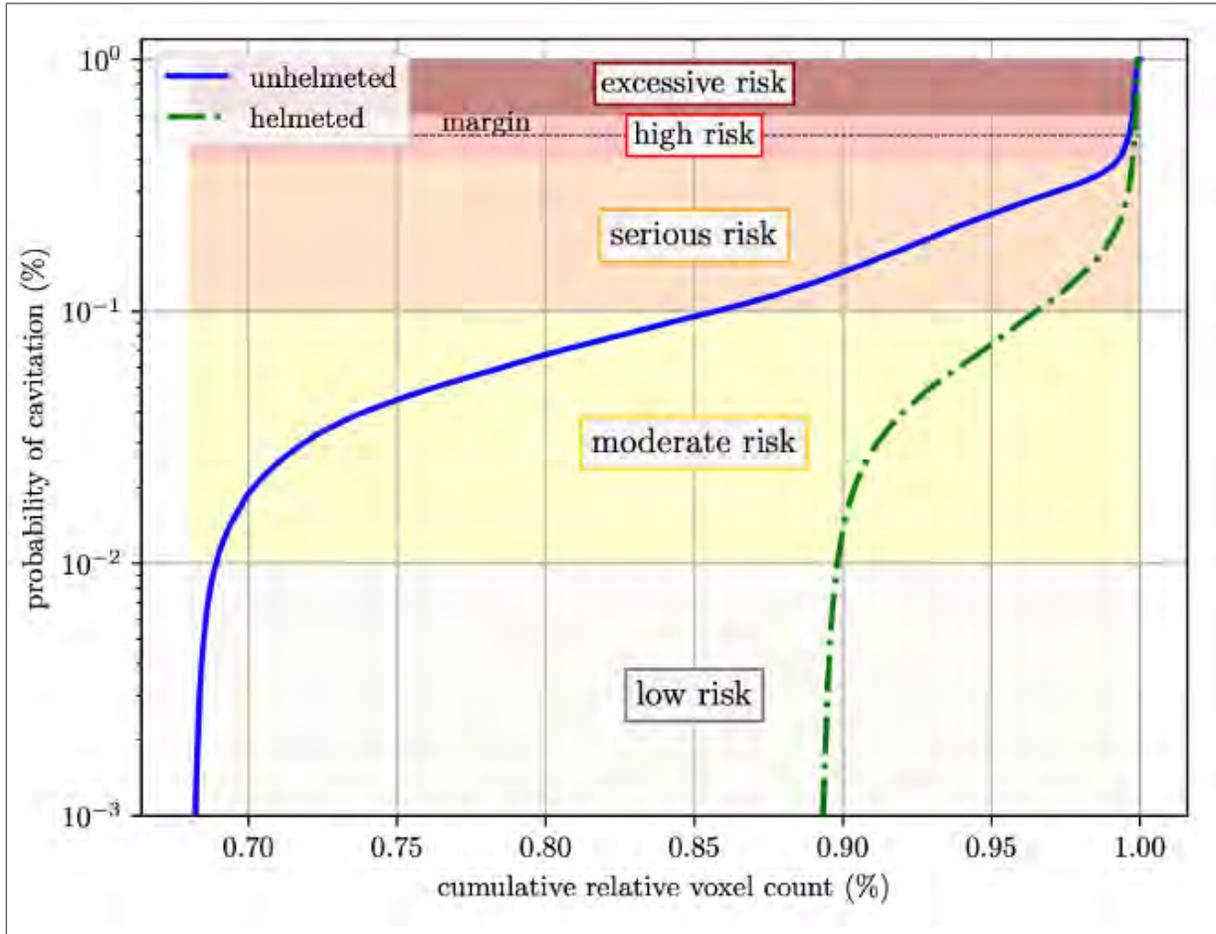


FIGURE 8-4: Probability of cavitation by fine aggregation risk category.



intracranial cavitation predictions and their anticipated clinical sequelae remains a topic in need of exploration.

This project was sponsored by ONR.

Passive Sonar for Cavitation Detection in the Brain

Blast-induced TBI has become a signature wound of modern military activities and the leading cause of death and long-term disability among U.S. Soldiers. Despite the severity and prevalence of blast-induced TBI, the limited understanding of its mechanisms has impeded the development of protective, diagnostic, and treatment strategies. Several potential mechanisms have been proposed for blast-induced TBI; of these,

microcavitation is gaining increasing support as one of the key mechanisms. However, there is a lack of non-invasive cavitation imaging techniques for reliable microcavitation detection in the brain. This has been the major roadblock for studies investigating the microcavitation mechanism. Existing techniques for 3D passive transcranial cavitation detection require the use of expensive and complicated hemispherical phased arrays with 128- or 256-elements. The objective of this study was to investigate the feasibility of using four sensors for transcranial 3D localization of cavitation (Figure 8-5A and 8-5C). Differential microbubble cavitation detection, combined with the time difference of arrival algorithm, was developed for the localization using the four sensors. Numerical simulation using k-Wave

was performed to validate the proposed method for transcranial acoustic source localization. Experimental evaluation was performed in a water tank with an ex vivo human skull (Figure 8-5B). The accuracy of the localization method with the skull was measured to be 1.91 ± 0.96 mm, which was not significantly different from that without the skull (1.73 ± 0.54 mm) when the cavitation source was located around the geometric center of the sensor network. The accuracy decreased as the cavitation source moved away from the geometric center of the sensor network. Its accuracy was not significantly affected by the sensor position relative to the skull (Figure 8-6). In summary, the four-sensor network offers a simple and accurate method for transcranial 3D cavitation localization.

This project was sponsored by ONR.

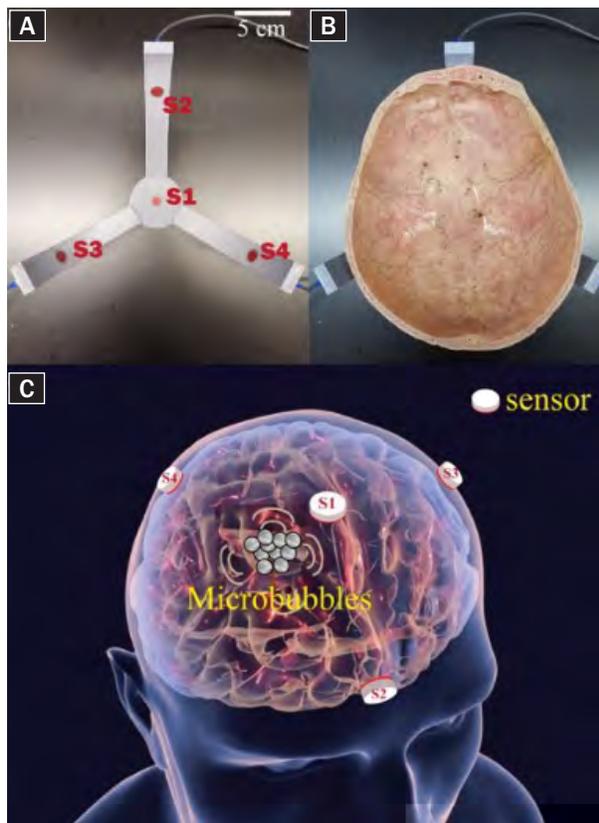


FIGURE 8-5: (A) Design of the sensors for transcranial cavitation localization. (B) Picture of sensors with an ex vivo human skull. (C) Illustration of how the sensors will be used in human for transcranial cavitation localization.

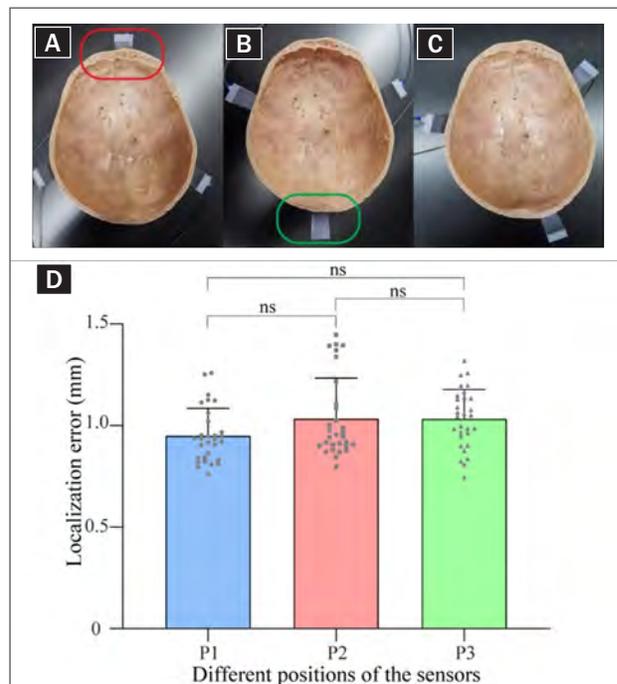


FIGURE 8-6: The cavitation localization accuracy was not affected by the sensor positioning. (A) Position 1: sensor 2 in contact with the midline of the frontal bone. (B) Position 2: sensor 2 in contact with the midline of the occipital bone. (C) Position 3: sensor 2 off the midline of the frontal and occipital bones. (D) The localization error of transcranial cavitation localization was not significantly different for different sensor positions.

Development of a Minimally Invasive, Ultra-High Strain Rate Inertial Microcavitation Rheology Technique and Quantification of Cavitation-Induced Material Deformations

The recent recognition and use of cavitation in biological and other soft material systems has motivated the development of understanding bubble dynamics in and near soft materials. Applications include the study of biological tissues, specifically for in vitro blast-induced TBI studies, to investigate high-rate neuronal deformation. Laser-induced cavitation is a thermally driven inertial process with the ability to characterize material behavior at high-strain rate (10^3 – 10^8 s^{-1}) deformations. Through the integration of an appropriate theoretical framework, material stresses and strains during cavitation can be estimated for homogeneous, isotropic materials through inertial microcavitation rheometry (IMR), a

recently developed tool to characterize the non-linear viscoelastic properties of soft materials at high strain rates.

Researchers at the University of Wisconsin–Madison used the IMR technique to characterize two types of polyacrylamide gels at high strain rates; a simple, yet compliance-matched surrogate material for native brain tissue. The quasi-static shear modulus and viscosity of the hydrogels were $\sim O(1)$ kPa and $\sim O(10^{-1})$ Pa respectively, while IMR analysis concluded dynamic strain stiffening parameters of 0.5 for soft and 1 for stiff polyacrylamide gel. As the bubble nears first violent collapse, the surrounding material deviates to inelastic behavior with a critical Mach number of 0.08. In addition to material degradation, experimental observations include various material instabilities near the bubble wall. For a fluidlike, soft gel material, it is typically found that a cavitating single bubble will split into multiple smaller bubbles, while for a soft solid-like gel, there are wrinkles, creases, and folds forming near the bubble wall. These strain localizations and stress concentrations would further induce more significant material failure in subsequent bubble rebounds. This work was published in *Extreme Mechanics Letters* (Yang et al., 2020).

Experimental results motivate future studies aimed at better resolving the change in materials physics near the collapse point, which could feature dynamic instabilities, significant strain localization, and material damage near the bubble wall. This will improve the fundamental understanding of the high-rate deformation behavior of soft biological materials in order to predict constitutive properties, ultimately establishing safety thresholds in soft biological materials exposed to blast.

This project was sponsored by ONR.

Modeling High Strain Rate Microcavitation in Soft Materials: The Role of Material Response in Bubble Dynamics

Cavitation-based rheometry is a promising tool for understanding the mechanical behavior of soft materials, such as brain tissue, at high strain rates relevant to blast-induced trauma. It requires both inertial cavitation experiments and a theoretical modeling framework. Laser-induced cavitation experiments probe the mechanical behavior of soft materials at high strain rate (10^3 – 10^8 s⁻¹) deformations. Then, a numerical modeling capability for inertial microcavitation, that incorporates all the dominant physics, is necessary to extract accurate information from experimental data regarding the mechanical behavior of the soft material. The purpose of this study is to establish that inertial microcavitation rheometry is an effective method for mechanical characterization of soft materials.

To model inertial microcavitation, Rayleigh-Plesset-based approaches are commonly used to capture the cavitation dynamics; however, these approaches place a limit on the constitutive models that may be employed to describe the soft material and cannot consider violent bubble collapse that involves appreciable compressible behavior. To circumvent this limitation, Brown University researchers have developed a finite-element-based numerical simulation capability for inertial microcavitation of spherical bubbles that enables the incorporation of more complex constitutive laws and substantial compressibility. In this research, the investigators consider non-linear elastic and power-law viscous constitutive laws and present a deeper investigation of the role of the elasticity and rheology of the soft material on the consequent cavitation dynamics. Simulations are applied by comparing computational results with experimental data from high strain rate inertial microcavitation of polyacrylamide gel, to mechanically characterize this material at high strain rates (Figure 8-7). The role of compressibility during violent spherical bubble collapse was also explored, which

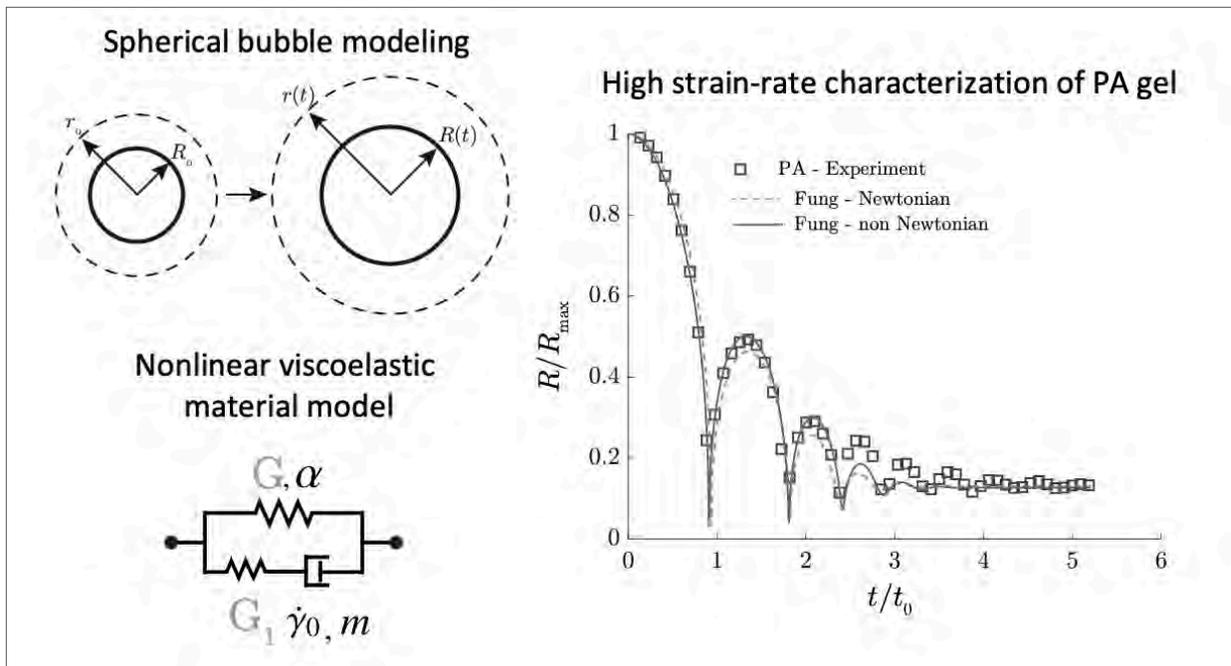


FIGURE 8-7: Demonstration of the inertial microcavitation rheometry (IMR) framework. (Upper left) Spherical bubble idealization. (Lower left) Material model schematic. (Right) Comparison of experimental laser-induced cavitation data and IMR model predictions for a polyacrylamide (PA) gel.

elucidated the limits of Rayleigh-Plesset-based modeling imposed by appreciable compressibility of the surrounding material during violent collapse. Based on this research, a Mach-number-based threshold for violent collapse was proposed ($Ma \approx 0.1$). Finally, researchers considered the sampling frequencies required in experiments to obtain accurate estimates of the material parameters.

Material models for brain tissue at high strain rates obtained through cavitation rheometry may be used in predictive simulation-based study of the effects of blast loading on deformation in the brain, which will lead to better protection for Warfighters through improved understanding of injury mechanisms.

This project was sponsored by ONR.

Predictive Modeling of Spherical and Non-Spherical Bubble Dynamics in Soft Matter Applied to Blast Injury and Protection

Despite the wealth of knowledge on cavitation in water, predicting bubble dynamics in soft matter has remained elusive until recently, when integrated efforts combining experiments, theory, and computation enabled the development of validated models describing the oscillations of bubbles in soft materials. Such advances have allowed the development of cavitation-based rheometry techniques capable of characterizing, in a controlled and repeatable fashion, soft matter subjected to deformations at rates and magnitudes representative to those produced by blasts. Additionally, the knowledge thereby acquired may help elucidate the role of cavitation in blast injuries. Key FY20 research accomplishments in this space from a team at the University of Michigan have come in two areas.

First, validated models for spherical bubble dynamics were used to investigate cavitation

nucleation in water (Mancia et al., 2020). The homogeneous cavitation threshold is an intrinsic material property of recognized importance to a variety of applications requiring cavitation control. However, acoustic measurements of the cavitation threshold in water differ from those predicted by classical nucleation theories. This persistent discrepancy is explained by combining novel methods for acoustically nucleating single bubbles at threshold with numerical modeling, to obtain a nucleus size distribution consistent with first principles estimates for ion-stabilized nuclei. Acoustic cavitation at threshold was identified as a reproducible subtype of heterogeneous cavitation, with a characteristic nucleus size distribution. Knowledge of the nucleus size distribution could inspire new approaches for achieving cavitation control in water and soft materials.

Second, a theory describing departures from spherical oscillations in soft matter was developed and validated (Gaudron et al., 2020). Though bubbles typically retain their spherical shape during a large part of their growth and collapse during non-linear oscillations, experiments indicate that bubbles lose their spherical symmetry in the last stages of collapse. The developed theory was used to predict the onset of non-spherical oscillations in forced and free oscillations of bubbles in soft materials (Murakami et al., 2020). This behavior may affect subsequent rebounds and oscillations, thus potentially leading to erroneous inference of constitutive properties.

Overall, these studies have reduced the uncertainty in predictions of cavitation dynamics in soft matter. The developed theory and models allow a better control of cavitation, and a more accurate characterization of soft materials. These advances could lead to the development of more effective protection gear for Warfighters, as well as a better understanding of blast-induced injuries.

This project was sponsored by ONR.

Methods for Controllably Generating Single, Spherical Acoustic Cavitation Events and Low-Cost Techniques for Monitoring their High-Rate Dynamics in Soft Matter

Cavitation has long been known to lead to injury and/or damage in tissues and other soft materials. This has led to the development of its use in therapeutic applications as a surgical ablation tool, as well as its investigation as a source of tissue damage in blast-induced TBI. To understand the mechanisms by which cavitation causes damage in tissues and soft materials, the responses of such materials to the high-rate stresses and strains generated within them by cavitation must be understood. These high strain rate properties can be assessed through the combination of appropriate theoretical models and experimental measurements of material responses to cavitation.

Numerous experimental limitations have been addressed to characterize the responses of materials to cavitation. Monitoring the high-rate dynamics of cavitation events typically requires ultra-high framerate, prohibitively expensive cameras. To allow the high-speed dynamics of cavitation events to be monitored without the use of such cameras, researchers from the University of Michigan developed a low cost, high-speed flash system combined with a multi-flash-per-camera-exposure ‘ghost-imaging’ method (Sukovich et al., 2020). This team developed flash source enabled imaging at effective framerates up to 17 MHz at a cost of only \$40 USD. This has the potential to improve experimental measurements of cavitation dynamics community-wide. It also makes it feasible to monitor the high-rate dynamics of non-symmetric cavitation bubbles, which require multiple cameras to resolve.

Studies of cavitation often rely on laser-induced cavitation (LIC) to generate cavitation bubbles, due to the high temporal and spatial control afforded by LIC. However, the nucleation conditions during LIC are unlikely to be representative of those experienced in tissues, for instance, during TBI.

University of Michigan researchers have therefore refined ultrasound-induced cavitation (UIC) techniques to allow the controlled generation of single spherical bubble types that can be easily reproduced in simulations, in order to assess the high-rate properties of materials. This has enabled the experimental study of the cavitation events from the time point of nucleation, which has typically been ignored in the case of LIC due to the complicated physics associated with laser nucleation events. UIC bubbles are likely more representative of those responsible for injury during TBI and thus crucial for understanding how damage is generated during such events. Such an understanding is essential to establish thresholds for the conditions required to generate cavitation in tissues during blast events, as well as for developing protocols and safety measures to ensure that said conditions are avoided in the field.

This project was sponsored by ONR.

Cavitation Damage to Cellular Membrane

To understand the primary mechanisms of blunt injury, researchers at Arizona State University developed an innovative experimental approach for reliable injury criteria and a more accurate prediction of injury specific to the characteristics of military-relevant mechanical inputs (Figure 8-8). The innovative experimental setup allows the characterization of impact and cell damage or cell injury correlations at the cell population level. This study, using fibroblast cells as a model, indicates that input acceleration alone does not result in cell damage. On the contrary, the research team observed a material-dependent critical pressure value, above which a sudden decrease in cell population and cell membrane damage were observed. Their results showed this critical pressure is associated with the onset of cavitation bubbles in a cell culture chamber, and the dynamics of cavitation bubbles in the chamber induces localized compressive pressure cycles, with an amplitude greater than the acceleration-induced pressure on cells. The study also found

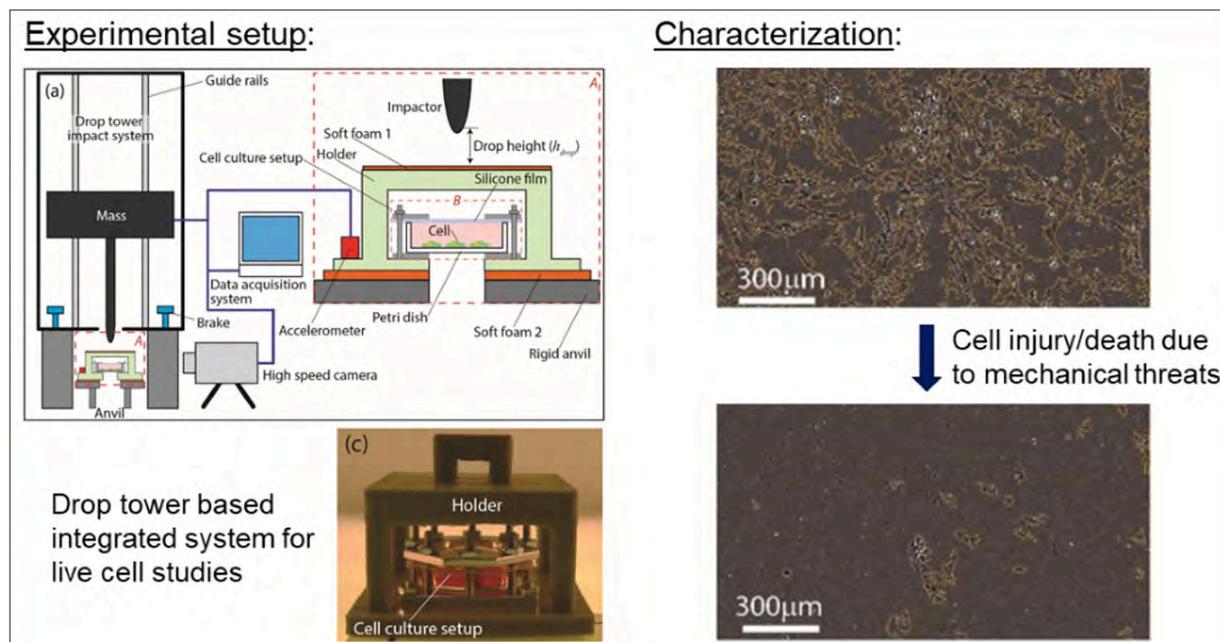


FIGURE 8-8: (Left) The innovative experimental method that applies a well characterized and controlled mechanical impact to live cells. (Right) Quantitative characterization of cell injury and death due to mechanical threats. Images originally featured in Kang et al. (2020) and are licensed under [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).

that the rate of pressure change with time for cavitation-induced pressure is more than ten times faster than acceleration-induced pressure.

The researchers will utilize this innovative technique to hasten new findings on impact-induced cellular pathways that may trigger cell death (e.g., necrosis, apoptosis). Such findings will pave the way for innovative technical advances in designing effective protective equipment, and new biomedical technology for post-injury treatment of Service members.

This project was sponsored by ONR.

How Do Neuroglial Cells Respond to Ultrasound-Induced Cavitation?

Low pressure regions inside the skull can cause vapor contents in the cerebral spinal fluid to expand and collapse, a phenomenon known as cavitation. When these microbubbles collapse, shock waves are radiated outward and are known to damage surrounding materials in other applications, like the steel foundation of boat propellers, so it is of particular concern that similar forces may be imparted on vulnerable brain tissue (Figure 8-9).

Using cell-laden microfibers, the longitudinal morphological response shown by mouse astrocytes during cavitation in vitro was visually analyzed. Astrocytic damage is evident immediately after cavitation, as their processes retract, when compared to a control sample. Forty-eight hours later, the astrocytes appeared to spread across the fibers, as normal. This study also analyzes the gene expression changes that occur post-cavitation via quantitative polymerase chain reaction (qPCR) methods. After cavitation, many pro-inflammatory genes are upregulated, including tumor necrosis factor alpha (TNF- α), interleukin (IL)-1 β , complement component 1q (C1q), Serping1, nitric oxide synthase 1 (NOS1), IL-6, and Jumonji domain-containing protein D3

(JMJD3). This research was published in *Global Challenges* (Wrede et al., 2020).

Together, these results confirm that surrounding cavitation is detrimental to astrocytic function and present opportunities to further the understanding of how protective headgear can minimize or eliminate the occurrence of cavitation. This study can be used as a platform in efforts to eliminate cavitation in the brain through advanced helmet design. Further research focusing on the response of multiple types of neuronal cells after experiencing surrounding cavitation will be vital in continuing the advancement of TBI prevention and care.

This project was supported by ONR.

FIGURE 8-9: An illustration of how head trauma can create microbubbles in the skull that collapse and damage nearby brain cells. Illustration by Mica Post.

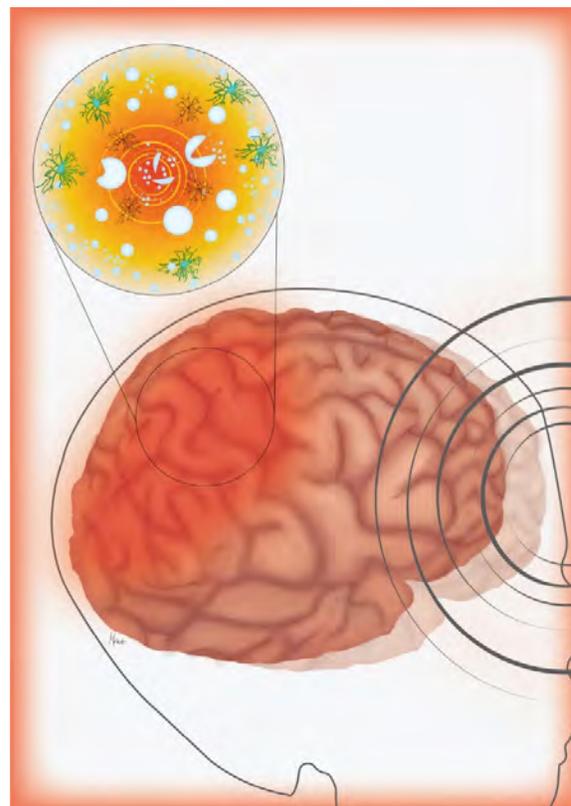




Photo credit: Spc. Jamaal Turner/U.S. Army Reserve

Blast Exposure Causes Acute and Chronic Neuronal Degeneration in the Cochlear Nucleus

Acute and long-term hearing impairments, including tinnitus, are major disabilities experienced by Warfighters in recent military operations, due largely to the increased use of IEDs. An incomplete understanding of mechanisms underlying the acute and long-term auditory dysfunctions resulting from blast exposure has stymied the development of effective countermeasures. To better understand these mechanisms, researchers at the Walter Reed Army Institute of Research (WRAIR) exposed rats to single and tightly coupled repeated blasts using an Advanced Blast Simulator, and determined the extent of neuronal degeneration in brain regions involved in auditory signal processing. Silver staining in the auditory cortex, medial geniculate nucleus, lateral lemniscus, inferior colliculus, and cochlear nucleus revealed significantly increased neuronal cell degeneration in the

cochlear nucleus, including the cochlear root of the eighth nerve, at 24 hours, 14 days, 1 month, 6 months and 1 year after blast exposure. No significant difference in degenerated neurons in the cochlear nucleus was observed between the groups of rats receiving single or repeated blast exposures. Unlike the cochlear nucleus, no significant changes in neuronal degeneration were observed in other brain regions involved in auditory signal processing. Disruption of the tympanic membrane was observed immediately after blast exposure, with healing occurring at one month. The sustained neurodegeneration in the cochlear nucleus might play a major role in long-term hearing impairments after blast exposure, including tinnitus, and proper use of suitable hearing protection devices could provide significant protection.

This study was supported by MOMRP/Joint Program Committee (JPC)-5.

A 3D Finite Element Model of Blast Wave Transmission from the External Ear to the Cochlea

A 3D finite element (FE) model of the human ear, including the ear canal, middle ear, and cochlea, was developed to predict the blast overpressure transmission from the ear canal through the middle ear into the cochlea. This is the first FE model with 3D structures of the entire ear to simulate the cochlear response to blast overpressure at the entrance of the ear canal, using Ansys Mechanical and Fluent in a fluid-structure interface coupled analysis in the time domain. The model was validated using experimentally measured blast pressure transduction from the ear canal to the middle ear and cochlea in human cadaveric ears or temporal bones. Results from the FE model showed significant displacement of the tympanic membrane, middle ear ossicles, and cochlear basilar membrane when 4.35 psi (30 kPa, 183 dB) blast overpressure was applied at the ear canal entrance. This model provides a computational tool for prediction of blast wave transmission from the ear canal to the cochlea and has applications for assisting the prevention, diagnosis, and treatment of blast-induced hearing loss in Service members. This work was published in *Annals of Biomedical Engineering* (Brown et al., 2021).

This effort was managed by the Congressionally Directed Medical Research Programs (CDMRP) with support and programmatic oversight by MOMRP/JPC-5.

Prevention of Blast-Induced Auditory Injury Using a 3D Printed Helmet and Hearing Protection Device

Repeated blast exposures result in structural damage to the peripheral auditory system (PAS) and the central auditory system (CAS). However, it is difficult to differentiate injuries between these two distinct pathways: 1) mechanical damage in the PAS caused by blast pressure waves transmitted through the ear and 2) damage in the

CAS caused by blast wave impacts on the head or TBI. A novel study was conducted in chinchillas using a 3D printed chinchilla “helmet” as a head protection device, along with hearing protection devices (HPD; e.g., earplugs), to investigate protection of the CAS and PAS under repeated blast exposures (Jiang et al., 2021). Chinchillas were divided into four groups (ears open, with earplug only, with both earplug and helmet, and with helmet only) and exposed to three blasts at blast overpressure of 15–20 psi (103.42–137.90 kPa). Hearing function tests (e.g., auditory brainstem response) were performed before and after blast exposure on days one, four, and seven. The biomechanical modeling and animal experiments using helmets and HPDs demonstrate a novel methodology of investigating blast-induced damage in the PAS and CAS, and mitigation via protective equipment. Outcomes of this study will help improve injury prediction and prevention of hearing damage in Service members.

This effort was managed by CDMRP with support and programmatic oversight by MOMRP/JPC-5.

Monitoring Blast Exposure and Determining Thresholds of Injury

Health Hazard Assessments and Blast Overpressure Assessments Performed During the Acquisition of Army Weapon Systems

The U.S. Army Public Health Center (APHC) performed blast overpressure (BOP) analyses on six weapon systems/test events during FY20. These BOP analyses support the Health Hazard Assessments (HHA) or consultations associated with each materiel item. The following weapon systems were assessed to determine their lung injury-related BOP effects: the Tube-Launched, Optically-Tracked, Wire-Guided Missile mounted on the Joint Light Weight Tactical Vehicle with the Gunner Protection Kit 2.0; the M72E8 Light Anti-Armor Weapon; the M72E10 Light Assault Weapon



Photo credit: 1st Lt. Erica Mitchell/U.S. Army National Guard

Anti-Structure Munition; the Mark 84 buried ordnance; and the Hellfire R9E buried ordnance (two separate test events). Each of these weapon systems or munitions provides a unique capability to produce large blast events designed to enhance the lethality of Warfighters and to protect them during combat.

BOP data were collected from each weapon system to determine the blast exposure to operators using each system. Data collection took place at U.S. Army Redstone Test Center (RTC), U.S. Army Aberdeen Test Center (ATC), and the Naval Surface Warfare Center Dahlgren, with blast test devices located at crew positions simulating the location of personnel during firing/detonation events. Different conditions were tested for each weapon system using variations in charge, elevation, hatch and ramp configuration, zone, line of fire, round conditioning temperature, firing postures, cartridge

types, munition burial depth, soil type, and location of the blast event, depending on the properties of the weapon system.

These data were then sent to APHC and analyzed using the BOP-HHA software version 2.1. This software was developed by the U.S. Army Medical Research and Development Command (USAMRDC) under a contract with JAYCOR Corporation (now L3Harris). The software uses an algorithm based on a biomechanical model of the thorax that calculates the amount of “push,” or mechanical work, imparted to the thorax by a blast pressure wave. The BOP-HHA algorithm uses the calculated work values and information about injuries from over 1,000 blast-exposed animal specimens to estimate lung injury risk and determine the allowable number of rounds (ANOR) to which a Soldier can be exposed in a single 24-hour period without producing more than one percent incidence of any lung injury.

The ANOR and quantitative probabilities of lung injury, for all lung injury severity levels, were determined for the conditions tested by RTC/ATC/Dahlgren for each crew position specific to each weapon system. The hazard probability and severity are used to assign a risk assessment code and resultant risk level for BOP exposure to each weapon system.

Most BOP analyses are published by APHC in the HHA Reports used by Safety and Occupational Health professionals during the acquisition process. Other analyses are conducted on a consultative basis and provided to customers via a report or email depending on the request. APHC expects the BOP analysis results to be included in training materials and operator manuals relevant to the materiel items/systems that were evaluated, so that commanders can use the information to make more informed decisions regarding blast exposure during training.

APHC also serves as the office of primary responsibility (OPR) for Line of Inquiry (LOI) 3 (Exposure Environment) for the Section 734 Blast Overpressure Study (BOS), which is responding to Section 734 of the National Defense Authorization Act (NDAA) for FY18 and related subsequent legislation. As the OPR for this LOI, APHC is responsible for meeting the following objectives: 1) review safety precautions for weapons, breaching charges, and events in different blast environments; 2) review compliance with existing safety precautions and standard operating procedures; 3) review features of the environment that may contribute to BOP-related changes in health and performance; 4) develop interim brain injury risk criteria for use with HHAs and Service member Occupational Health Assessments (SOHA) in accordance with Military Standard (MIL-STD)-882E; (5) conduct SOHAs on Tier 1 Weapon Systems and breaching charges identified by Section 734 BOS leadership; (6) estimate medical and lost time cost avoidance; and (7) archive exposure data collected during SOHAs in Service member records (e.g.,

Defense Occupational and Environmental Health Readiness System-Industrial Hygiene). APHC has been working on meeting these objectives since FY18 and has conducted SOHAs on three Tier 1 Weapon Systems thus far (Wall and Door Breaching Charges and the M107 Sniper Rifle).

This research was supported by APHC.

Blast Load Assessment Sense and Test (BLAST): Tools to Prevent Repeated TBI and Chronic Traumatic Encephalopathy

The cumulative exposure to overpressure from multiple subconcussive blast events may cause physical effects. To provide better estimates of blast exposure levels to operators in combat training, and to determine best practices for safety precautions, researchers recognized the need for a standardized methodology for analyzing body-mounted blast sensor data. When blast sensors are worn on the body, the body orientation relative to the blast and body position influences the data recorded, due to the effects of shock reflections and shielding (Figure 8-10). Blast gauges mounted in the recommended head, chest, and shoulder positions measure these effects at the mounting position on the surface of the body. Figure 8-11-Left shows that the peak overpressure and peak overpressure impulse measured by these sensors vary for subjects facing the blast, facing sideways, and facing away from the blast, despite being at the same standoff distance from the device.

As part of the Blast Load Assessment Sense and Test (BLAST) Program, Applied Research Associates (ARA) has already developed the Fast Algorithm for Signal Transformation (FAST) methodology, which provides a standardized approach, to research and operational communities, for interpreting pressure data from high-explosive blasts, in terms of actual force applied to the individual. As an example of the validity of the FAST algorithm, Figure 8-11-Right shows the results of running the body-worn surface pressure data through the FAST algorithms, with each box representing acceptable margins of error

FIGURE 8-10: Blast loads on the body can involve shock reflections, shock-shock interactions, and shielding by the body. Many historical blast injury correlations use incident overpressure.

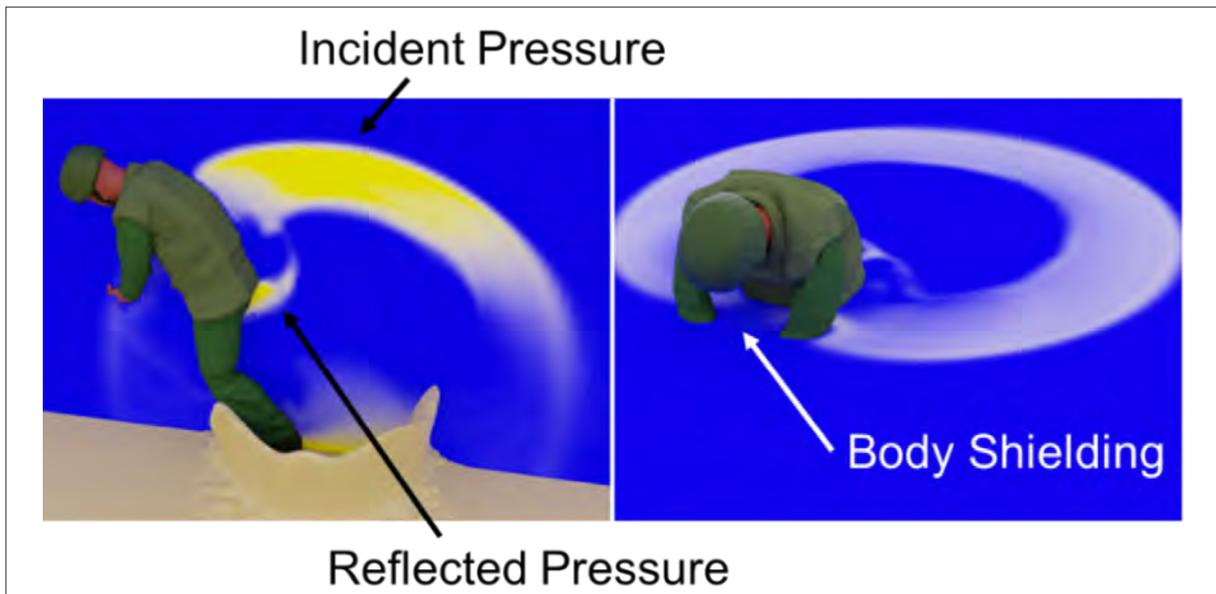
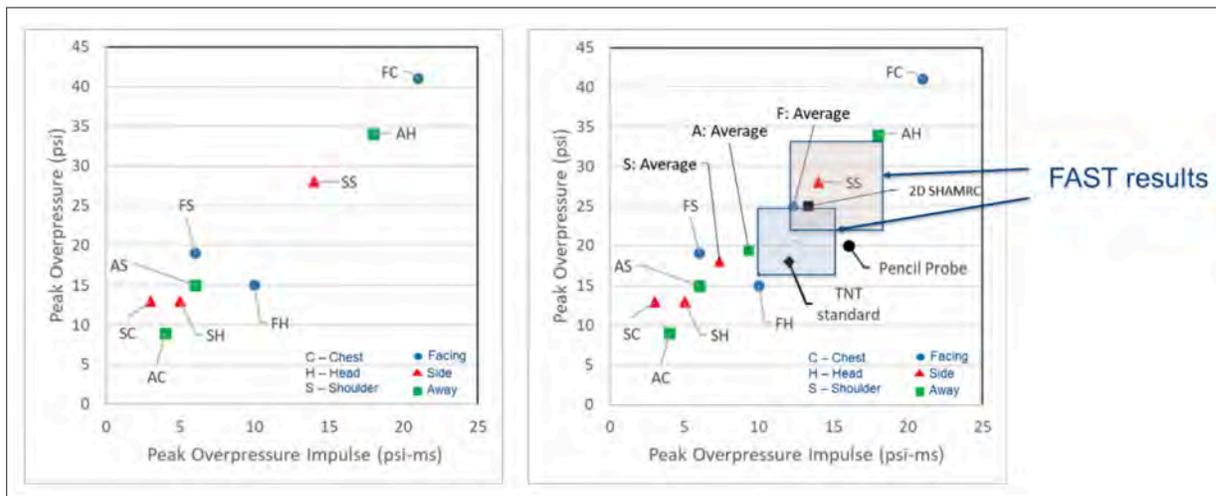


FIGURE 8-11: (Left) Peak overpressure and peak overpressure impulse data from blast gauges mounted on the body for three different orientations relative to the blast. The data shows there is significant variation in recorded blast loads for the same blast event. (Right) FAST estimates of incident blast conditions are shown for this event.



around the estimate. FAST outputs are almost identical for subjects facing sideways and facing away from the blast, as would be expected if the two individuals were standing at the same standoff distance from the explosive device. The FAST results for subjects facing the blast have slightly higher overpressure and overpressure impulse, but the margins of error overlap with the other subjects. All three cases are in good agreement with pencil probe data and simulation estimates

of incident blast conditions. Currently, the physics-based approach employed by the FAST algorithm provides an estimate of incident blast metrics for high-explosive charges.

It should be noted that blast exposures in training could be due to exposure from a wide range of weapon systems that have not been characterized under the BLAST Program. In many of these weapon systems, the blast source is from burning

propellant. The blast signature from these devices differs from detonation of high-explosive charges, commonly seen in breacher training or combat scenarios such as IED blasts. With FY20 funds obtained through the Defense Health Agency (DHA), ARA will apply the same physics-based approach to the waveforms generated by relevant weapons systems to expand FAST to include data collected in training as inputs, with the goal of yielding estimates of incident blast metrics for burning propellant.

This work was sponsored by DHA in support of the BLAST program, which has been developed and funded by ONR.

Evaluation of the BLAST and Future Naval Capabilities Concept Sensors in Blast Testing

The goal of this effort is to develop a custom low-power Warfighter-wearable sensing system, with a battery life exceeding five years, to detect and store overpressure and/or inertial shock signatures from blast events. This development platform intends to show the capability of developing extremely long-life sensing systems for Warfighter brain health monitoring for training and operations exercises and for combat theater use.

Naval Surface Warfare Center–Indian Head Division (NSWC-IHD) used initial funding from the ONR Warfighter Performance Department Blast Load Assessment Sense and Test (BLAST) Program to develop a sensing element utilizing microelectromechanical systems technology, custom hardware and software for data acquisition, and a compact blast overpressure measurement system. The U.S. Naval Research Laboratory (NRL) used initial ONR funding to develop a methodology for concept blast overpressure sensor prove-out using a shock tube in FY16–18, developed an algorithm to calculate peak overpressure and positive phase of the blast overpressure from sensor data, and proved the applicability of the methodology and the algorithm with currently available blast sensors being used by DOD.

In FY20, with U.S. Army Medical Materiel Development Activity (USAMMDA) funding, NSWC-IHD fabricated 35 custom sensor systems, within two months, using a reproducible, laboratory-based small-lot fabrication technology for both overpressure and acceleration measurement. These sensor systems were first evaluated in NRL-organized blast testing with peak incident overpressures up to 25 psi (172.37 kPa), using a sequence of 12 blast tests, with a total of 33 sensor systems in incident and reflected overpressure conditions. Laboratory grade pencil probe gauges were used as reference measurements to evaluate performance of the sensor systems. Data reduction and analysis are ongoing. Preliminary free-field blast testing of the sensors in September 2020 showed the feasibility and durability of the sensors and compared satisfactorily with laboratory grade sensor measurements. Results from additional free-field blast tests completed in November 2020 are being analyzed. Initial review suggests that sensor systems recorded data at multiple blast exposure levels for future evaluation and suggest improvements are needed for Warfighter brain health monitoring.

These sensor development and validation efforts support the Human Performance and Warfighter Brain Health areas of research by quantifying the insult using a wearable device. A key advantage is this sensor system’s ability to measure both overpressure insult and inertial effects (i.e., acceleration) on the Warfighter. The proposed sensor can provide a measure of severity and the number of blasts as separate datasets from a single incident. This is relevant to all Warfighters exposed to blast events (both in theater and in training), including door-breaching, explosives detonation, and firing of shoulder fire rockets (e.g., Shoulder-Launched Multipurpose Assault Weapon and Carl Gustaf).

This work was supported by USAMMDA.

Detonation Science Team's Evaluation of Wireless Wearable Blast Gauges

In October 2019, modification of Experimental Facility (EF)-17A, Aberdeen Proving Ground, was completed to enable explosive testing of commercially available off-the-shelf (COTS) wireless wearable blast gauges (WWBG). The range was set up to measure and visualize blast waves, from known explosive charges, as the blast waves encountered instrumented manikins outfitted with the Improved Outer Tactical Vest (IOTV) and helmets. Figure 8-12 shows a photograph of EF-17A with instrumented manikins (IOTV, helmet) and reference blast gauges arranged around a test explosive charge. Also shown is the reflective screen (lower right) used to image the shock wave as it encounters the manikins.

From November 2019 through January 2020, the Detonation Science Team evaluated COTS WWBG for accuracy and precision when exposed to explosive shock; using 53 shots in total. Figure 8-13 shows several images of a shock wave approaching and encountering test manikins during the test series. This was the first time that shock transit, including shock reflections, had been imaged for WWBG testing.

In September 2020, in collaboration with the U.S. Army Combat Capabilities Development Command (DEVCOM) Armaments Center, ARL assembled eight instrumented manikins, stands, IOTV and helmets; four hours of instructional videos; and WWBG for testing of shock produced by fielded systems (portable system designed and fabricated by R. Benjamin). Testing was completed in September 2020.

This study was sponsored by ARL.

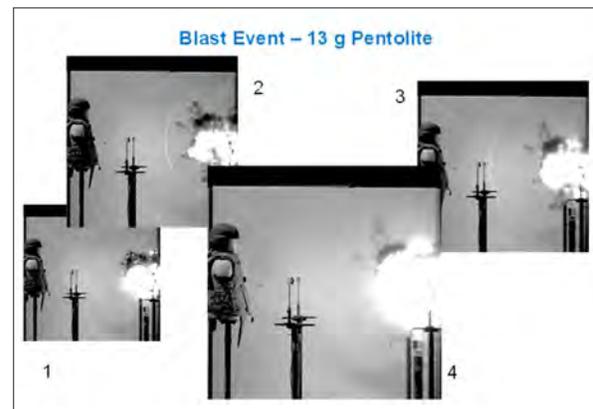


FIGURE 8-13: Individual frames from a series of Edgerton shadowgraphs showing the transit of an airborne explosive shock wave to a test manikin outfitted with WWBG.



FIGURE 8-12: A photograph of EF-17A with instrumented manikins (IOTV, helmet), and reference blast gauges in place arranged around a test explosive charge.

Environmental Sensors in Training and Human Exposure to Occupational Repetitive Blast: Immediate, Acute, and Longitudinal Effects

A growing body of literature suggests that repeated low-level blast exposures, such as those in some military training, coincide with measurable effects on the brain without an associated diagnosed injury. Researchers at WRAIR are conducting multiple studies in conjunction with routine training to support evidence-based decisions regarding blast exposure effects, monitoring feasibility, and health and performance risk assessment. The Environmental Sensors in Training (ESiT) program began as a U.S. Army Training and Doctrine Command-led initiative that later transitioned to a USAMRDC-led research program. ESiT epidemiological studies suggest that chronic blast exposure has associations with clinical outcomes of diagnosed tinnitus and vulnerability to post-concussion syndrome.

These studies characterize personnel exposure from a variety of weapons systems and environments, ranging from low overpressure (< 4 psi [27.5 kPa]) to moderate overpressure (4–8 psi [27.5–55 kPa]). These studies investigate neurocognitive performance, symptom reporting, hearing ability changes, and physiological responses, including eye tracking effects and blood-based proteomic and epigenetic biomarkers for neurotrauma. Data are collected within five minutes following blast exposure, at end of day, and where available, longitudinally across two to three years with instructor cadre.

Participation is active, with over 500 enrolled subjects at more than 20 sites, using weapons systems including heavy wall breaching, .50 caliber rifle, M2A1 machine gun, Carl Gustaf recoilless rifle, artillery, grenades, and flashbangs. Longitudinal data exist for over 60 subjects with 30 visits completed across a span of 36 months. The data revealed that current calculations for minimum safe distance can be inaccurate in complex environments. In addition

to blast overpressure, high-level sound pressure exposures, including infrasound, appear to be a key component of risk in these environments.

Changes in cognitive performance were associated with exposure dose. Changes in blood-based neurotrauma biomarker levels, eye tracking performance, and binaural hearing ability also have association to blast exposure, further suggesting a potential dose-response relationship. The ESiT program provides critical information for understanding occupational blast exposure and associated neurological and physiological effects. Program results are an asset for risk/benefit assessment and aid in developing detection and mitigation strategies for Service members in combat and training environments.

Studies are funded by MOMRP/JPC-5 and DHA.

Toward a Forcewide Blast Exposure Surveillance System for the U.S. Navy Explosive Ordnance Disposal Community

Naval Health Research Center (NHRC) has established a translational research program evaluating blast exposure and its health effects in Navy Explosive Ordnance Disposal (EOD) Operators. NHRC continues the process of transitioning this work to a Forcewide Blast Exposure Surveillance System. To date, blast exposure has been characterized in approximately 250 EOD operators across several studies. In a sample of 118 operators, 25.6 percent reported a vehicle crash or blast and 54.2 percent endorsed being within 50 meters of a blast.

In collaboration with the Neurotrauma Department at the Naval Medical Research Center (NMRC), the Blast Exposure Threshold Survey (BETS) was administered to 80 EOD operators. Development of this tool was published in the *Journal of Neurotrauma* (Modica et al., 2020). The unique and combined effects of blast exposure are being explored using data from BETS and genetic predisposition on behavioral health. This research was presented at the U.S. Special Operations

Command (USSOCOM) Brain Health Portfolio Review. The Office of the Assistant Secretary of Defense for Health Affairs, serving as the office of primary responsibility for the line of inquiry on surveillance in response to Section 734 BOS, has expressed interest in the current and planned activities. The next step is to validate BETS in a sample of military Service members at risk for blast exposure.

Previous work published in *Psychiatry Research* (Taylor et al., 2019) suggests that blast exposure interacts with a genetic variant of the serotonin system (5HTTLPR) to predict post-traumatic stress symptoms in EOD operators. Building on these results, diurnal patterns of salivary cortisol in EOD personnel were assessed, and results showed that cortisol patterns were similar to those reported in a prior study of Navy SEALs (Hernández et al., 2020; Taylor et al., 2016). In follow-on work, the investigators are 1) evaluating differences in cortisol trajectories between EOD technicians who endorsed blast exposure and those who did not and 2) characterizing the daily profiles of salivary dehydroepiandrosterone (DHEA), testosterone, and C-reactive protein to determine if blast exposure modulates these hormone patterns or has downstream effects on clinical outcomes.

Additional research indicates that blast exposure reduces the sympathetic response to acute exercise stress in EOD personnel. Individuals with blast exposure demonstrated blunted electrodermal response patterns—a surrogate marker of sympathetic nervous system activity—during exercise, in comparison to their low/non-exposed counterparts. This blunted response pattern may imply suboptimal sympathetic nervous system function in the exposed cohorts, which has implications for Service member resilience.

Lastly, researchers at NHRC are finalizing a manuscript examining the effects of combat and blast exposure on positive and negative behavioral health. The data reveal that, when controlling

for other military stressors, EOD operators with previous involvement in a vehicle crash or blast exposure endorsed greater anxiety symptoms and reported higher depressive symptoms than non-exposed cohorts, even when combat exposure was low.

This blast exposure research is currently informing the development and validation of blast exposure standards for military personnel and will inform systematic blast exposure monitoring in vulnerable military personnel.

This research is supported by MOMRP/JPC-5.

Assessment of Potential Long-Term Effects of Career Exposure to Repetitive Blast in Operational Communities: Experienced Breachers

Recent blast-injury research endeavors have sought to determine the extent of bodily changes in Service members experiencing repeated, low-level blast exposure in training. While these findings have allowed insights into physiological, psychological, and neurocognitive changes unique to acute blast overpressure exposure, career breachers who use explosives to gain (breach) entry to buildings warrant further study. A critical component of a research collaboration between the Center for Neuroscience and Regenerative Medicine (CNRM), NHRC, and University of Virginia was to determine if military and civilian law enforcement populations that experience hundreds of blast exposures demonstrate cumulative neurological effects in the latter part of their careers.

Described in a publication in the *Journal of Neurotrauma* (Stone, Avants, et al., 2020), the research team recruited 20 career breachers (14 military and 6 law enforcement) into the study and 14 controls (10 military and 4 law enforcement). A comprehensive data battery was collected from all participants including neuropsychological tests, blood-based biomarkers, and neuroimaging data.

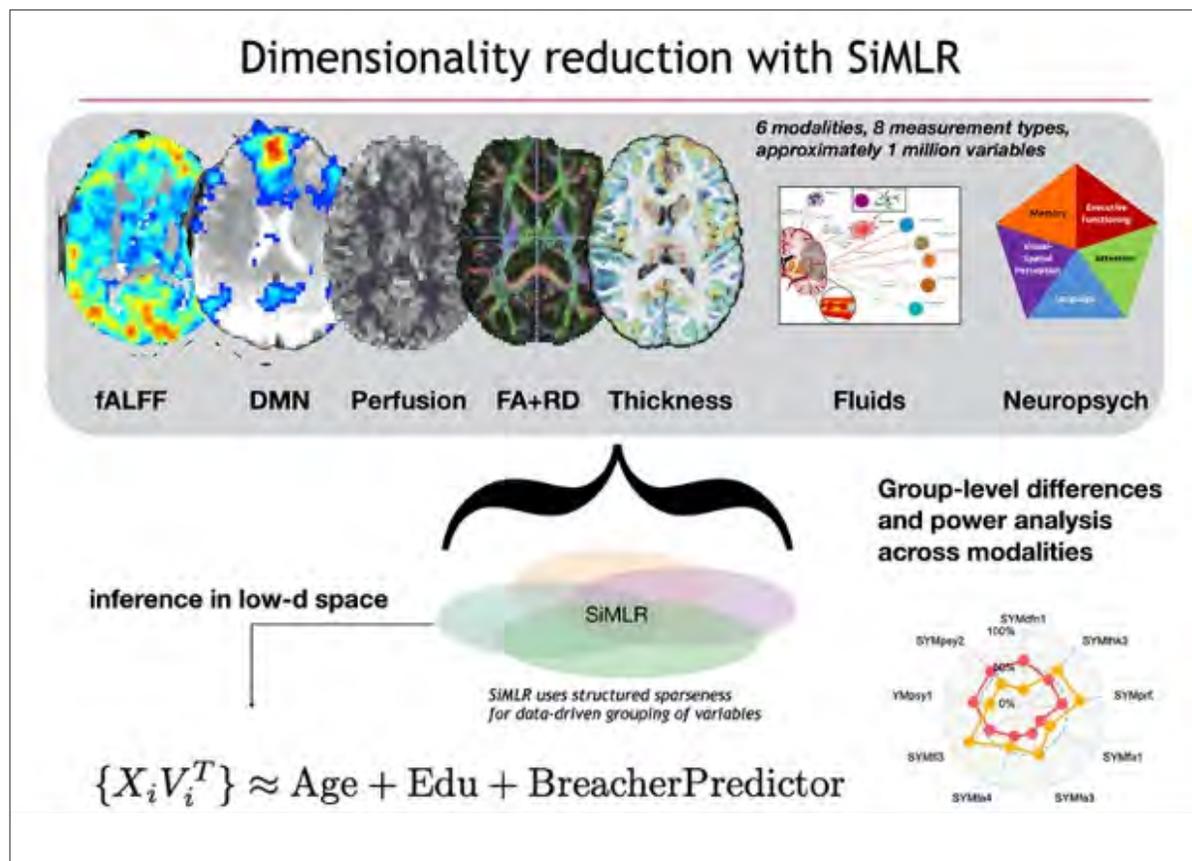
These data were analyzed using similarity-driven multi-view linear reconstruction (SiMLR), which is designed to integrate highly dimensional, yet sparse, data from multiple modalities (Figure 8-14). The differences between the career breacher and control groups included increases in neural inflammation, default mode network (DMN) connectivity, fractional anisotropy (FA), resting state activity, and cortical thickness in the breacher group.

Further research using more targeted sub-populations, such as grenade range trainers and explosive ordnance disposal units, will be required to reproduce the findings in the current study

and further investigate the observed neurological changes. The current findings support an emphasis on long-term assessment, monitoring, and prevention techniques for chronically blast-exposed Service members and suggest that bodily changes may present in a variety of ways and over long timescales.

This research was supported by the JPC-5 Development of Exposure Standards to Repeated Blast Exposure Program, ONR, CNRM, and the Clinical Neurosciences Program of the National Institute of Neurological Disorders and Stroke.

FIGURE 8-14: Illustration of inferential design using SiMLR. Multiple modalities are projected into a regularized, low-dimensional space for linear regression analysis. Fractional amplitude of low frequency fluctuations (fALFF), radial diffusivity (RD). Image originally featured in Stone, Avants, et al. (2020) and is licensed under [CC BY-NC 4.0](https://creativecommons.org/licenses/by-nc/4.0/).



Acute Deleterious Effects of Repeated Low-Level Blast Overpressure on the Brain

Exposure to repeated low-level blast overpressure, as experienced by military personnel in operational and training environments, can lead to deficits in behavior and cognition. FY18–20 NDAA Sections 734, 253, and 717 mandate that DOD monitor and characterize the effects of blast overpressure in training and operational environments. To identify the cumulative effects of repeated blast exposure, researchers at WRAIR published a study in *Frontiers in Neurology* (Heyburn et al., 2019) in which they used an Advanced Blast Simulator to closely mimic free-field blast. Rats were exposed to blast overpressure of varying intensities (8.5–19 psi [58.61–131 kPa]) and frequencies (1–14 days of single daily blast). At 24 hours after the final blast exposure, brain tissue was collected and analyzed for levels of inflammatory markers, astrocyte-specific glial fibrillary acidic protein (GFAP), blood-brain barrier (BBB)-related proteins (claudin-5, occludin, vascular endothelial growth factor [VEGF]), neurodegeneration-related proteins (amyloid beta [A β] 40/42, phosphorylated tau (pTau), transactive response DNA binding protein-43 [TDP-43]), and the mechanosensitive ion channel protein Piezo2. TDP-43 levels were differentially affected by the number and magnitude of blast exposures, with the levels increasing in rats exposed to 4 blasts at 19 psi (131 kPa) compared to rats exposed to 1 blast at 19 psi (131 kPa) or 14 blasts at 10 psi (68.95 kPa). A β 40/42 and pTau were decreased following repeated low-level blast exposure. Following repeated low-level blast exposure, (8.5 or 10 psi [58.61 or 10.95 kPa]), where no overt lung injury was observed, inflammatory markers were decreased, with interleukin (IL)-4 and IL-6 significantly decreased after 14 blasts of 10 psi (68.95 kPa). The BBB was disrupted following repeated blast, with claudin-5, occludin, VEGF, and GFAP levels significantly altered. Levels of Piezo2 increased with number and magnitude of blast exposures, suggesting that blast overpressure may render the brain vulnerable to injury from subsequent exposures. Overall, the cumulative

effects of repeated low-level blast overpressure exposure may increase the vulnerability to injury in the absence of any overt lung injury and cause disruption of neurovascular architecture, inflammatory responses, and neurodegeneration-related proteins, which may lead to downstream deleterious effects on behavior and cognition. This research will contribute to the development of injury risk thresholds which will serve as a potential health hazard tool for repeated blast exposure.

This study was sponsored by MOMRP/JPC-5.

The Impact of Concussion History on the Brain's Vulnerability to Blast Exposure

A history of repeated concussion is known to cause long-term neurological problems. Significant numbers of military Service members are reported to have a history of concussion before and/or after deployment. No systematic studies have been carried out to determine whether concussion history predicts the brain's vulnerability to blast exposure. Researchers at WRAIR have evaluated the effect of repeated concussive insults to the vulnerability of the brain to blast exposure using neurobehavioral functional assessments in rats.

Anesthetized rats were subjected to either repeated concussion (two concussive insults, one week apart using a modified Marmarou weight-drop model [Marmarou et al., 2009]; single blast exposure (19 psi [131 kPa] peak total pressure, 4–5 ms duration) using an Advanced Blast Simulator; or single blast exposure administered one day after the second weight-drop. Neurobehavioral changes were monitored at acute and sub-acute time points using rotating pole test for vestibulomotor function, open field exploration test for anxiety/depression, and novel object recognition test for short-term memory. Rotating pole test results indicated that vestibulomotor functions were worse in blast-exposed rats having prior concussive insults, compared to the sham controls or rats exposed to either repeated concussive insults or blast. The deficits were



Photo credit: U.S. Army

evident from day one post-blast and persisted for one month. Open field exploratory activity test results indicated that rats exposed to both concussive insults and blast develop more anxious and depressive-like behaviors than the other groups of rats at both acute and sub-acute time points. The novel object recognition test indicated short-term memory loss at one month post-blast in rats exposed to both repeated concussive insults and blast. These preclinical findings suggest that concussion history induces vulnerability of the brain to blast exposure.

The results indicate that Service members who have a history of concussion may be more vulnerable to blast exposure and that additional protective strategies should be considered.

This study was supported by MOMRP/JPC-5.

Low-Intensity Repetitive Blast Wave Exposure Leads to Visual System Damage in Rats

Multiple low-intensity blast exposures have been linked to impairment of neurosensory systems, prompting concern over the cumulative deleterious effects of blast and the need to define standards to mitigate this risk among U.S. military personnel. There are currently no set guidelines establishing cumulative limits for the number and intensity of blast exposures for training and combat missions. The eyes are at a high risk of being wounded by explosions, and although Service members are issued protective goggles, eye injuries nevertheless occur largely due to blast wave penetration. More than half of blast casualties present with vision deficits such as abnormal accommodation and photophobia. Researchers at WRAIR, in collaboration with the University of Maryland School of Medicine,

are conducting a comprehensive study, using a rodent model, to identify the threshold of the visual system (i.e., retina) to damage from training-relevant, repeated low-intensity blast exposures. Using an Advanced Blast Simulator, which closely mimics free-field explosions, adult male rats were subjected once daily to a 4–8 psi (27.58–55.16 kPa) shock wave for 1–30 total exposures. Rats were exposed to the shock wave in a frontal position, and the eyes and body were not shielded. Retinal signaling assessments were carried out via electroretinography (ERG) at 1–28 days following the last exposure event. Animals were euthanized and the eyes collected for histopathological evaluation of the retinas by morphological staining and protein biomarker immunohistochemistry (IHC), as confirmed by western blots. Cellular integrity of the retinas was further addressed using transmission electron microscopy of prepared sections to reveal disturbances to the ultrastructure of the neurons. As determined by ERG, significant reductions in retinal signaling were observed in rats subjected to a 6 psi (41.37 kPa) or greater blast after at least 14 exposures, and the loss of retinal function persists out to 28 days of recovery (Figure 8-15). These findings are supported by severe perturbations of neuronal cell layers and inflammation biomarker proteins in retina sections observed by histopathology (i.e., hematoxylin and eosin [H&E] stain and glial fibrillary acidic protein [GFAP] IHC, Figure 8-16) and western blot of GFAP levels. The results suggest the threshold for blast-induced retinal injury is at least four exposures at 4 psi (27.58 kPa). Western blots also show a stark reduction in the retina photoreceptor-specific light-signaling proteins, rhodopsin and transducin. Electron microscopy further reveals the underlying damage is largely due to marked disruption of retina photoreceptor outer segments, which may arise from the shear forces generated by intraocular translation of the blast shock waves.



Photo credit: Senior Airman Ethan Morgan/U.S. Air Force

By defining important neurobiological underpinnings of blast-induced injuries, these findings demonstrate that the eye is highly susceptible to repeated exposures of low-level blast, like that experienced by many Warfighters. This also provides a first step toward identifying tolerable thresholds of blast exposure as a means to prevent potential loss of sight.

This research was supported by MOMRP/JPC-5.

FIGURE 8-15: (Top four graphs) ERG waveforms and peak amplitudes (A- and B-waves) for left and right rat eyes of shams and those exposed to blasts of 4 and 6 psi (27.58 and 55.16 kPa) repeated once daily for 14 days, and then recovered 28 days. ERGs were recorded at a light flash stimulus of 10 cd/m². * p ≤ 0.05; significant difference between treatment groups. (Bottom two graphs) ERG flash curve responses of shams and those exposed to daily blast at 6 psi (41.37 kPa) for 14 days, and then recovered 28 days. ERGs were done over a light flash range of 3 log units (0.001–1 cd/m²). Peak amplitudes of B-waves are shown before and after normalization to their maximum levels (Vmax). ERG responses of blast-exposed animals are shifted right to higher light intensities, indicating a loss in peak amplitudes as well as in light sensitivity of nearly 1 log unit. Waveform shape changes and time delays suggest that sensitivity decrease is due to compromised photoreceptor (e.g., from shortened rod outer segments) while amplitude decline is due to photoreceptor losses. Flash curve graphs are courtesy of Dr. Mary Johnson at the University of Maryland School of Medicine, Department of Ophthalmology & Visual Sciences. Right eye (OD), left eye (OS).

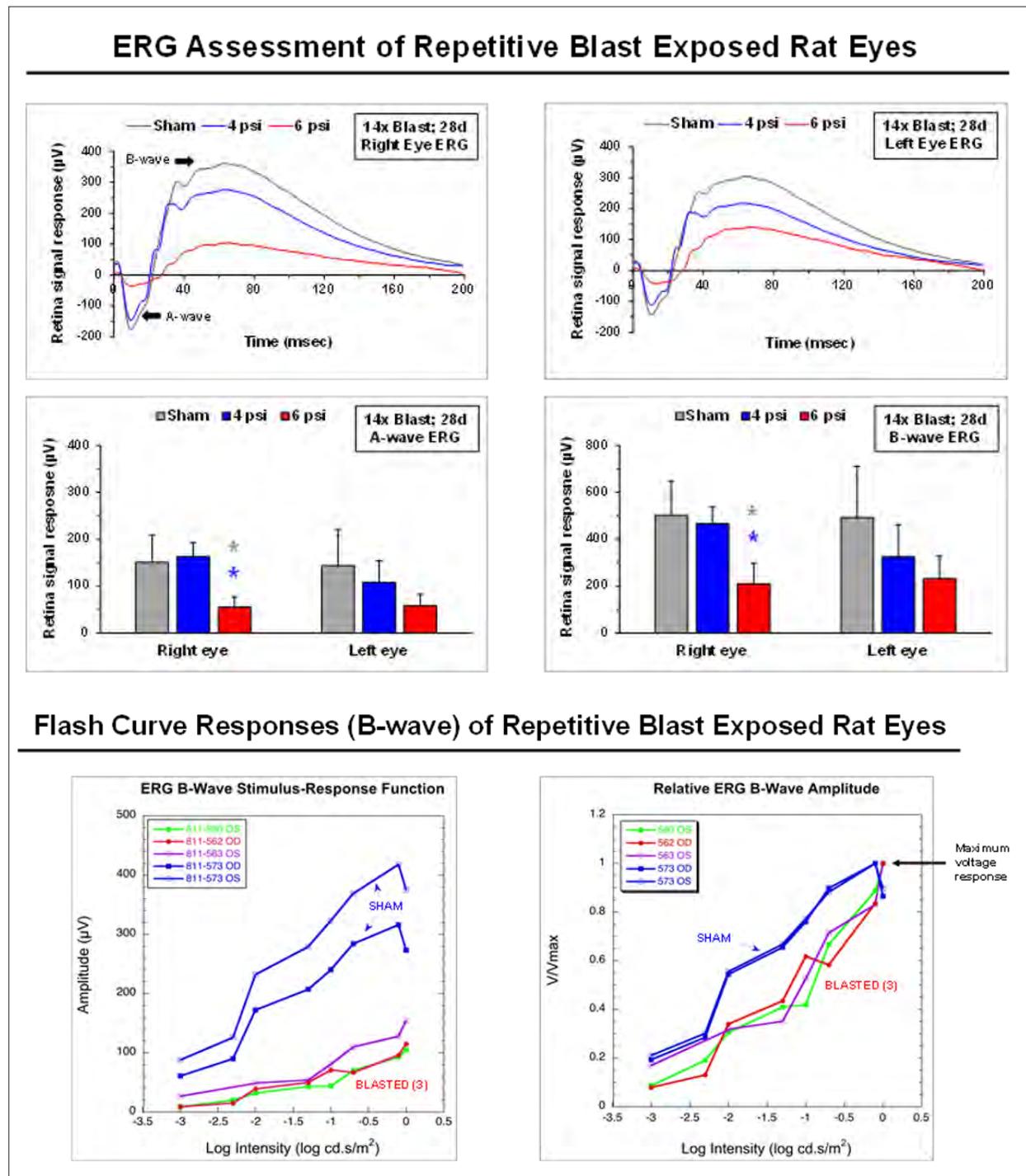
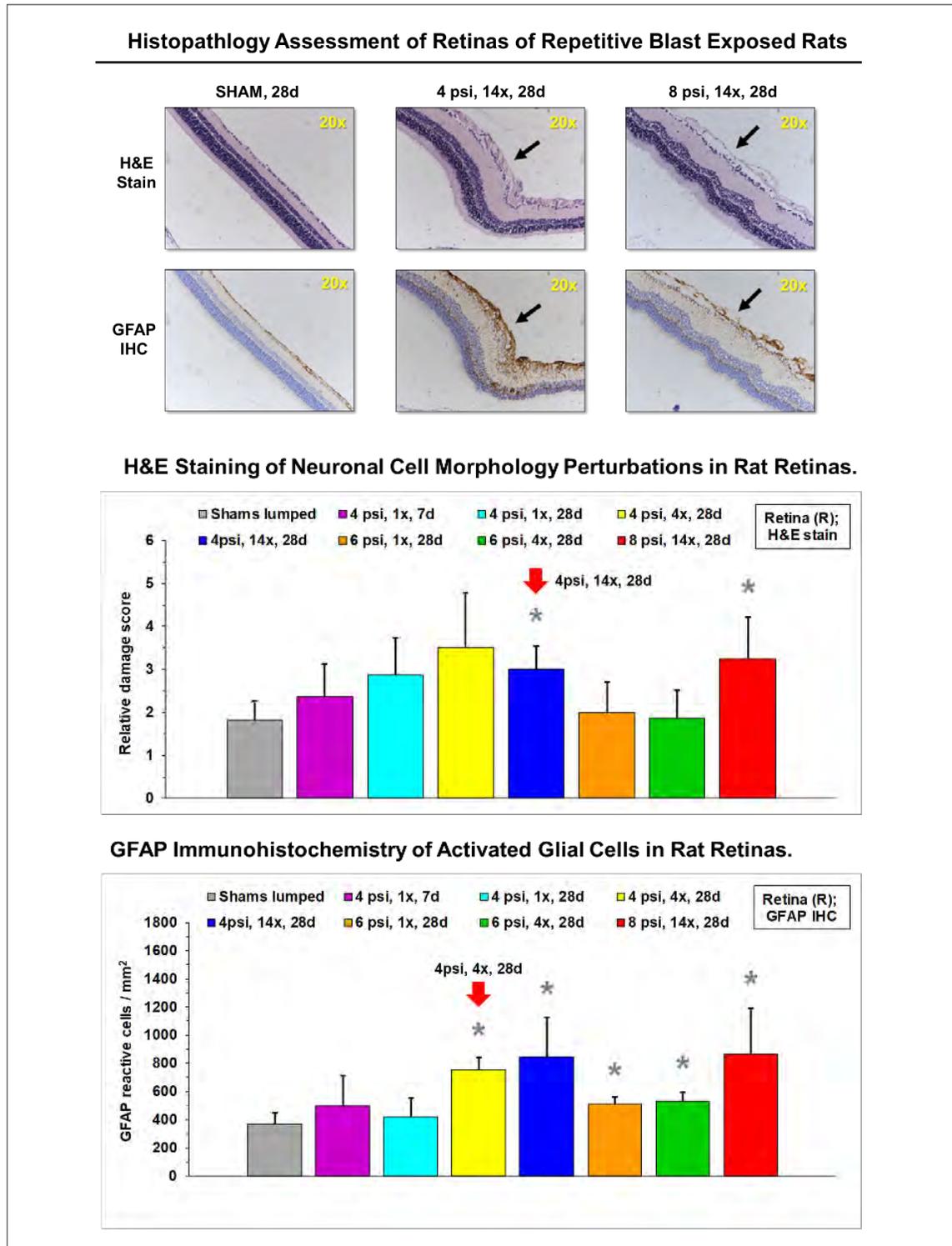


FIGURE 8-16: Representative light micrographs (20x magnification) of rat retinas from shams and those exposed to blasts of 4 and 8 psi (27.58 and 55.16 kPa) repeated once daily for 14 days, and then recovered 28 days. (Top panels) H&E stain histopathology was used to assess gross morphology of retinas. (Top graph) Retinas were assigned relative damage scores for the degree and extent of degenerative sites: 1 = none, 2 = mild, 3 = moderate, 4 = severe, and 5 = catastrophic. (Bottom panels and graph) IHC was performed on the same retinas for GFAP expression. This was quantified by counting the GFAP immunoreactive cells per area (number/mm²), as averaged across the entire retina (i.e., right + center + left zones, and throughout all neuronal layers). * $p \leq 0.05$; significant difference from shams. Black arrows point to examples of retinal perturbations (e.g., swelling and cell loss). Red arrows point to apparent thresholds causing significant blast-induced retinal injuries. Overall, these results confirm ERG findings that the retina has marked cellular disruptions following blast. Histological processing of rat eyes was done under contract by FD Neurotechnologies, Columbia, MD.



Lung Injury Risk Thresholds for Repeated Blast Exposure

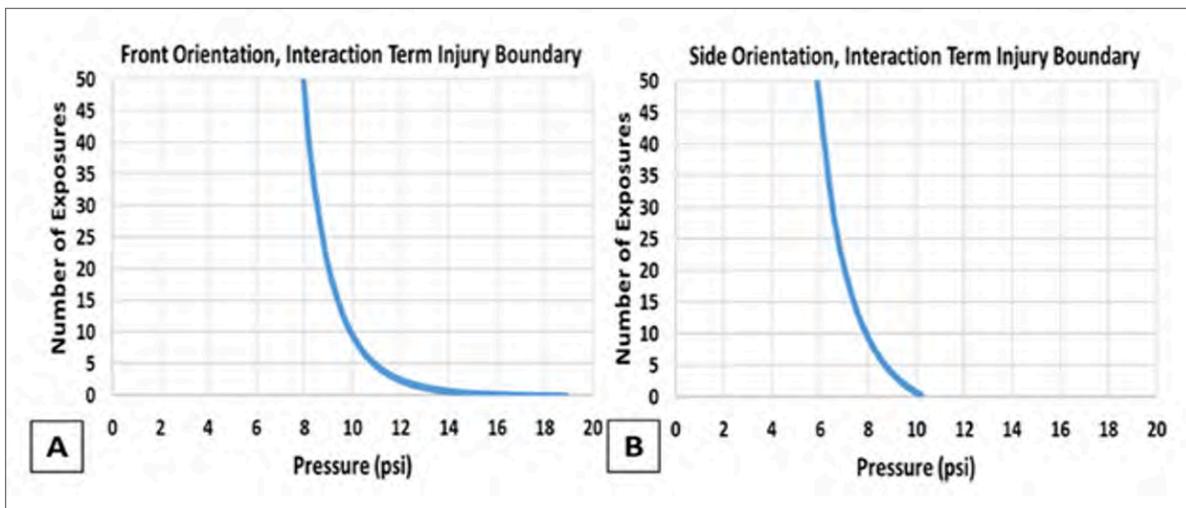
Service members may be exposed to blast overpressure in combat and/or when operating heavy weapon systems. Blast exposure may lead to numerous health consequences ranging in severity and chronicity, including organ injury and long-term disability. While injuries induced from a single sudden blast event may be more clinically apparent, blast overpressure exposure from heavy weapon systems used in training may have unique long-term deleterious effects. Currently, the military has not established non-auditory blast exposure limits for Service members due to repeated blasts. Furthermore, while several past and current studies have investigated the impact of blast exposure on the brain, the depth of research on blast-induced lung damage is less comprehensive.

Researchers at WRAIR, in partnership with NMRC, conducted a study to assess the pulmonary injury risk curves and behavioral outcomes of repeated low-level blast exposures (Sajja et al., 2020). Using an Advanced Blast Simulator, groups of rodents were exposed to blast overpressure once or repeatedly (up to 30 daily exposures), either frontally or from the side, at varying peak overpressure levels (8.5–19 psi [58.61–131 kPa]).

After each animal's final blast (or sham) exposure, they were assessed on the open field task, which revealed a significant reduction in exploratory behavior in rodents exposed to repeated blast overpressure at the highest overpressure level. However, no changes were observed after repeated blast overpressure exposures from 8.5–16 psi (58.61–110.32 kPa), nor any single blast overpressure exposure. Macroscopic lung assessments were performed, showing that single and repeated blast overpressure exposures at 16 psi (110.32 kPa) and 19 psi (131 kPa) caused lung injury, with contusions and hemorrhage more apparent in rodents in side orientation. Repeated, lower-level exposures did not cause comparable damage. Hematoxylin and eosin staining were then performed to ascertain cell morphology and inflammatory changes. Significant changes were observed at 10 psi (68.95 kPa) or higher, and orientation effects were seen at blast exposure levels higher than 13 psi (89.63 kPa).

Data modeling indicates that the injury threshold may be 50 exposures at 8 psi (55.16 kPa) for frontal exposure to blast and 6.5 psi (44.82 kPa) for side exposure, as illustrated in Figure 8-17. Further validation with experimental data will be needed to assess the effects of varying blast overpressure waveforms.

FIGURE 8-17: Boundary curves between not injured and injured based on number of blast overpressure exposures and peak pressure at (A) front orientation and (B) side orientation. Images originally featured in Sajja et al. (2020) and are licensed under [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).



Guidelines have been codified for the impact of noise on hearing and auditory functioning; however, it would also be beneficial to establish blast injury thresholds for lung injury, to protect and preserve the health of Service members.

This study was sponsored by MOMRP/JPC-5.

Development of Severity-Specific Human Spinal Column Injury Risk Curves from Accelerative Impacts

Mounted personnel in military vehicles sustain loads from the seat to the pelvis in combat events such as underbody blast. Human tolerances are needed to advance protection for this population. The objective of this study was to determine force-based lumbar spine injury criteria due to vertical impact, using post-mortem human surrogate experiments. Data were obtained from 43 thoracolumbar spinal column tests, conducted for ongoing studies. The spines were screened for pre-existing trauma, and bone mineral densities (BMD) were determined. Pre-test X-rays and computed tomography (CT) scans were taken. The spines were fixed at the superior and inferior levels, and load cells were attached to the ends of the fixation. The preparations were positioned on a custom vertical accelerator device based on a military seating posture and impacted at the caudal end. Post-test X-rays and CT scans were obtained and gross dissection was performed to confirm injuries, classified as single and multi-level injuries. The axial and resultant forces at the thoracolumbar and lumbosacral joints were used as response variables to develop lumbar spine injury risk curves (IRC) using parametric survival analysis. The Brier Score Metric was used to rank the variables. The age, BMD, column length, vertebral body, and intervertebral disc area parameters were covariates. The optimal metric describing the underlying spinal injury response was the resultant force at the lumbosacral joints, for the single-level spinal injuries, and the axial force at the thoracolumbar joint for the multi-level injuries. The force-BMD for the single level, and force-body area for the multi-level injuries, were

the best combinations that explained the two distinct injury patterns (single and multi-level). The respective single and multi-level IRCs were developed along with ± 95 percent confidence intervals for each injury type, and the quality of risk curves based on the confidence intervals. These risk curves serve as force-based spine injury criteria for single and multi-level injuries. They can be used to conduct matched pair tests to obtain dummy-based injury assessment risk curves, and injury assessment reference values to predict injury using dummy tests. They can also be used in the validation of human body and isolated spine finite element models to predict injuries. The relationship between the covariates of demographics, geometry, and material properties, and primary impact forces at the thoracolumbar and lumbosacral ends of the spinal column from this analysis contribute to a better understanding of the role of impact acceleration along the vertical direction. This research was published in the *Journal of the Mechanical Behavior of Biomedical Materials* (Yoganandan, Moore, et al., 2020) and the *Annals of Biomedical Engineering* (Yoganandan, DeVogel, et al., 2020). Spinal injury tolerances based on single and multi-level injuries under vertical accelerative loading can be used to predict injury, validate finite element models, and develop protective strategies for improving Soldier safety.

This effort was managed by CDMRP with support and programmatic oversight by MOMRP/JPC-5.

Pelvic Injury Risk Curves for Military Populations to Prevent Lateral Impact Injury Using Parametric Survival Analysis with the Inclusion of Demographic Covariates

During impact events, occupants in military vehicles may be exposed to types of impacts and directions or vectors that are different from the civilian automotive impact experience. These unique exposures have recently led to military-relevant studies that focus on vertical loading from underbody blast-type impacts. However, there is a

paucity of data in other loading directions that may modulate the overall response and injury criteria. The objective of this study, published in *Military Medicine* (Yoganandan et al., 2021), was to develop military-relevant injury risk curves (IRC) for the pelvis under lateral impacts, from a large human cadaver test conducted in the same laboratory using parametric survival analysis techniques, thereby minimizing cross-laboratory differences. Twenty-four whole-body human cadaver tests were conducted using an impactor to dynamically load the occupant in a seated posture. In the parametric survival analysis, the peak force was used as the response variable. Age, sex, stature, weight, and body mass index were treated as covariates. The survival analysis modeling was performed using R-software, and the lowest Brier Score Metric and its associated distribution were used to calculate the final IRCs. The maximum force associated with a specimen that underwent only one test and sustained pelvic injury was treated as a left-censored observation. In contrast, peak force from a non-injury test associated with a specimen that underwent testing without any pathology was considered a right-censored observation. Repeated tests on the same specimen that produced non-injury and injury outcomes were considered interval-censored data points. The cumulative density functions were the Weibull, log-normal, and log-logistic distributions.

Sex and total body mass were significant covariates. The IRCs were developed for males and females separately and developed for current military demographics (i.e., total body mass 83 kg and body mass index 25 kg/m²). The mid-size male body mass-specific IRCs can be used as baseline injury criteria for crashworthiness of future-generation military vehicles. The IRCs can also be used in computational human body models to predict injury in military environments and advance Soldier safety. Manikins specific to military anthropometry and body habitus may be designed/evaluated with these IRCs to assess/mitigate musculoskeletal injuries for this posture and impact.

This effort was managed by CDMRP with support and programmatic oversight by MOMRP/JPC-5.

Evaluating Personal Protective Equipment

Characterization of the Protective Capacity of Helmet Materials at Loading Conditions Relevant to Blast Injury Scenarios

Researchers at the Colorado School of Mines examined the protective capacity of open cell polyurethane foam, which is currently used in combat helmet liners (Koumlis & Lamberson, 2019). Data obtained from their research aids in better understanding the transfer of energy due to a blast, or impact, from the helmet to the skull-brain system. This is a critical step in connecting battlefield loading scenarios to the biomechanical response of the brain to prevent TBI. The enhanced understanding of this energy transfer resulting from the study can be utilized to improve helmet designs in two significant ways. First, the constitutive behavior of protective helmet materials is quantified, and can be readily implemented in high-fidelity numerical simulations of helmeted human head models. These simulations are used to more accurately predict the deformation of brain tissue due to realistic loading conditions (e.g., blast or blunt impact loading). The computed deformation levels can be correlated to biological injury thresholds of the brain tissue, in order to establish quantitative and realistic definitions of TBI. Second, the experiments shed light on the structure-property-performance relationships of the protective materials. Using an improved understanding of how specific liner material microstructures translate to protective performance, researchers are now able to aid in the design of next-generation protective helmets.

The research group probed combat helmet liner response across ten orders of magnitude in loading rate. Additionally, they developed and employed novel experimental methods and metrology to exceed current limitations of traditional high-rate methods and measurements, to obtain far richer

experimental datasets than those obtained previously. They achieved this by leveraging technological advancements in ultra-high-speed imaging and digital image processing algorithms, using hybrid analytical-experimental and numerical-experimental approaches.

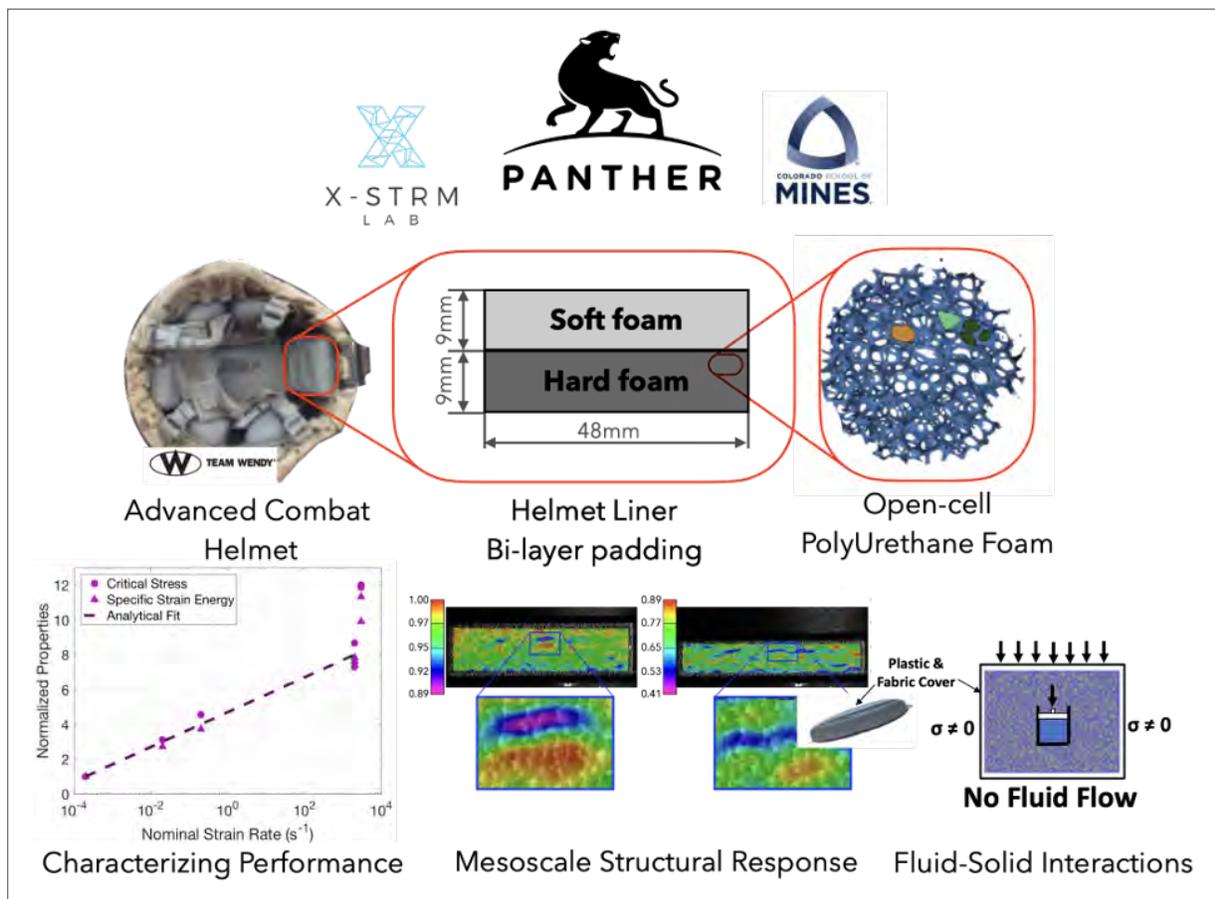
Thus far, the researchers have found that current combat helmet liners show a strongly rate-dependent response—meaning, their protective behavior dramatically changes depending on how fast they are ‘hit.’ Researchers determined that critical properties, such as helmet liner energy absorption vary logarithmically with the rate of loading. Moreover, researchers successfully probed liner structure-property relations, exploring and quantifying the mechanisms relating the interactions of the working medium in which the liners are used, depending on fabrication techniques, their mesoscale morphological

features, and how they influence bulk response under load, as well as their viscoelastic (time-dependent) properties.

This was the first successful attempt to obtain the bulk response of current combat helmet liners at high rates of loading, relevant to blast and blunt injuries. The research is summarized in Figure 8-18. By elucidating the different mechanisms and their relative contribution to the overall mechanical response under load, the researchers can tailor the liner mechanical properties. This enables them to design the next generation of protective materials that will have enhanced performance, optimized to protect and prevent military related TBI. Consequently, such advancements will improve the quality of life of Warfighters with such injuries returning from conflict.

This project was sponsored by ONR.

FIGURE 8-18: A summary of the work from researchers at the Colorado School of Mines on the protective capacity of open cell polyurethane foam used in combat helmet liners.



Approaches for Evaluating Helmet Performance and Advanced Materials of Helmets for Prevention of Mild TBI

Mild TBI can involve structural damage to cells in the brain, but the conditions that initiate structural damage have not been well defined. There is ongoing debate as to which kinematic inputs result in injury. Similarly, inertial loading during tertiary blast or during the blast wind (i.e., the negative pressure tail) phase of primary blast can generate significant accelerations on the head and brain. Through application of new cellular injury thresholds from collaborators in the PANTHER program, head motions that are likely to result in injury can be defined without relying on a neurosymptomatic diagnosis of injury. Head kinematics will be mapped to several injury modes to give a clear understanding of how head motion causes injury. The key application will be identification of the motions that are likely to result in injury, and the ability to evaluate helmets to determine if the equipment is likely to reduce injury. This will also aid in the design of helmet material to reduce the motion causing the injury. In this project, researchers at Brown University focus on approaches that measure the full field acceleration to evaluate helmet performance, and toughness enhancement mechanisms to improve the toughness of the helmet material.

In research published in the *Journal of the Mechanics and Physics of Solids* (Rahaman et al., 2020), the investigators propose an algorithm using only measurements from four tri-axial accelerometers to find the acceleration at any point of a rigid body. Rotation experiments were completed using a rectangular box attached with wireless accelerometers, demonstrating that the acceleration value predictions obtained from the accelerometer-only (AO) algorithm match closely with the values experimentally measured by the accelerometers (Figure 8-19). The proposed algorithm can be applied to measure a rigid body response to impact, and evaluate how effectively a helmet reduces the acceleration, and acceleration rate, of the head to prevent mTBI.

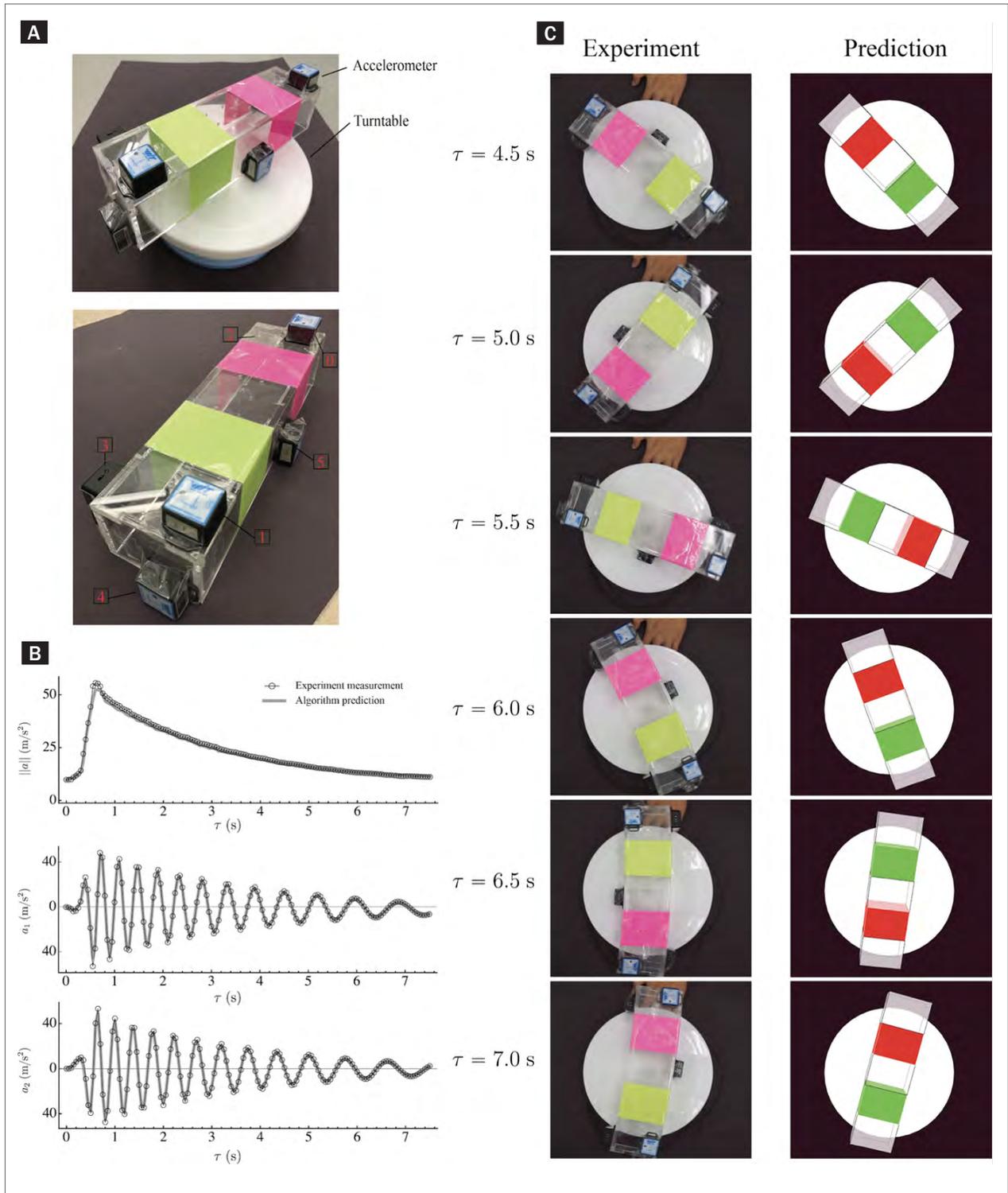


Photo credit: Tech. Sgt. Jason W. Edwards/U.S. Air Force

To build the foundation for the next generation of helmet materials of high toughness that provide superior protection against mTBI, the investigators researched the toughness mechanism of stiff structural biological materials (SSBM)—like shells, which are remarkably tough (Monn et al., 2020). The layered structure of these SSBMs is thought to be responsible for the toughness enhancement; however, it was determined that the layered spicules architecture of the marine sponge *Euplectella aspergillum* provides surprisingly small enhancements in toughness. It is therefore important that each SSBM's toughness properties are measured, rather than categorized as “tough” solely based on the existence of a layered architecture. The interaction between layers also plays an important role in toughness.

This project was sponsored by ONR.

FIGURE 8-19: Rotation experiment. (A) Rotation experiment configuration. Six tri-axial accelerometers are attached to the rectangular box and the box rotates using a turntable. Acceleration data were collected from accelerometers #1, #2, #4, and #5 to predict the acceleration of point where the accelerometer #0 is attached. (B) Comparison of the acceleration norm and components measured from the accelerometer #0 and those predicted from the AO algorithm. (C) Comparison of the motion of the box in the experiment and that which was predicted using the AO algorithm from 4.5 to 7 seconds.



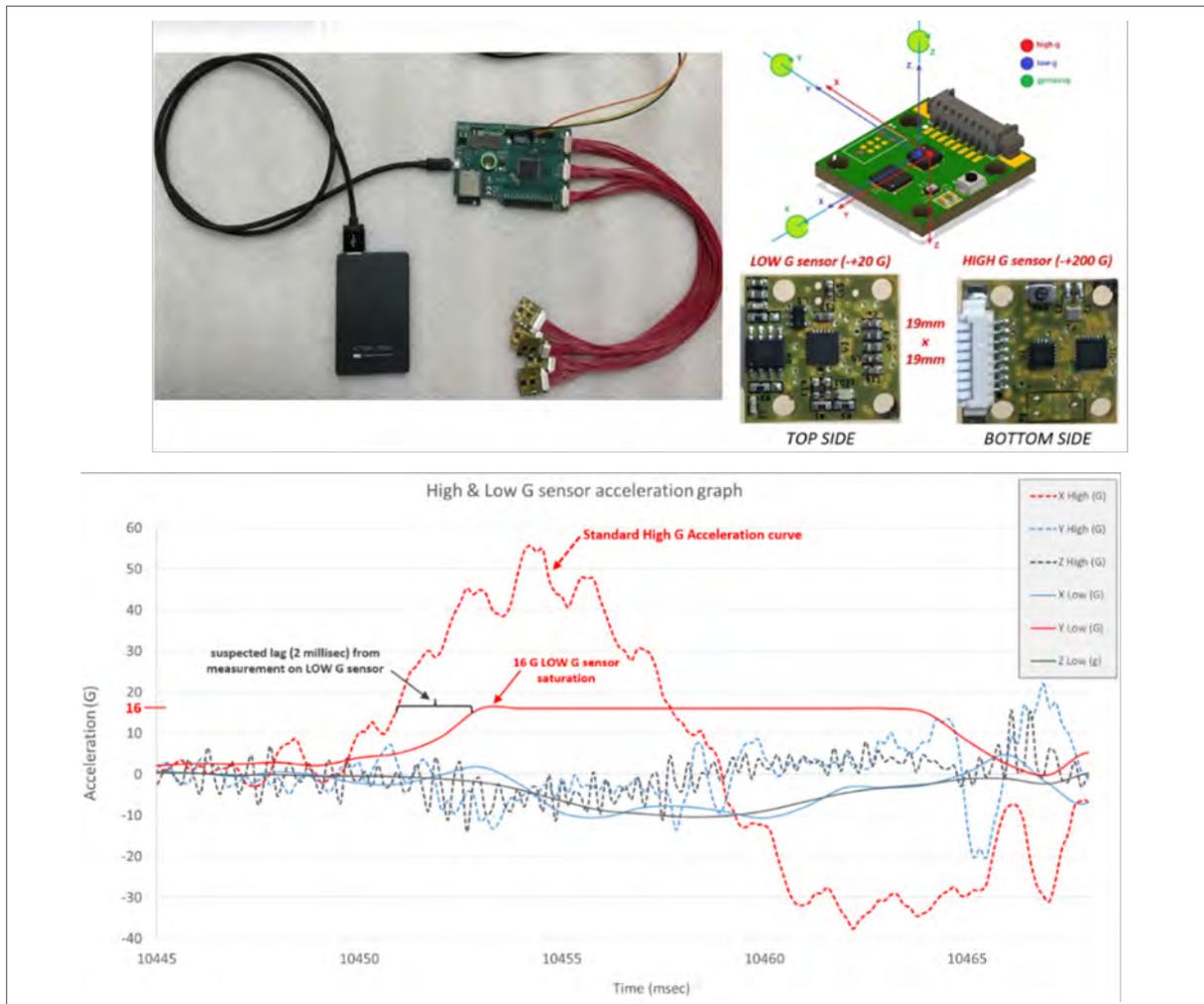
Measurement and Testing of Tertiary Blast Kinematics

Historically, head injury thresholds based on linear acceleration have been used to assess protective helmets and drive standardized performance requirements. Helmets have been shown to be largely effective at mitigating such linear forces. However, high rates of head injury, specifically mTBI, persist. The blunt impact requirements of military helmet specifications, such as AR/PD 10-02 (Advanced Combat Helmet) and AR/PD 17-02 (Integrated Head Protection System), require acceleration measurement at a single location on a magnesium alloy test headform, in a test that is constrained to linear motion. Previous modeling efforts at Sandia National Laboratories showed head rotation can also cause significant injury, and the brain appears significantly more

sensitive to such angular motions than linear ones. Thus, there is a need to consider such kinematics when assessing the protective capabilities of helmets. Further, there is an opportunity to utilize acceleration measurements to predict brain injury in the field.

Accomplishments under the current effort include the addition of low-G (16 G) accelerometers to a multi-sensor acceleration measurement system; previously developed and used to measure high-G (200 G) accelerations during blunt impact events, which includes head impacts that cause tertiary blast-related injuries, as the blast wind physically displaces personnel (Figure 8-20). The low-G accelerometers are used to collect pre-impact data, which can resolve acceleration due to gravity and thus provide an orientation of the system.

FIGURE 8-20: (Top) Recent High-G – Low-G sensor system. (Bottom) Acceleration graph of High-G – Low-G sensor system.



Additionally, ONR used the high-G sensor system for live blast testing. The sensor system was incorporated into a 3D printed lattice pad structure installed in enhanced combat helmet shells, and exposed to nominal overpressures of 17 and 25 psi (117.21 and 172.37 kPa) at different angles. The tested systems are currently being returned for data processing and analysis.

Lastly, a helmet testing fixture was developed to allow the implementation of the Hybrid III head and neck surrogate in military specification-equivalent blunt impact testing, across a variety of impact locations and head and neck angles (Figure 8-21). The fixturing system includes adjustable weights which can bring the total drop mass up to that of a Hybrid III 50th percentile male torso. The development of such test equipment is crucial to the advancement of test methodologies, which include a rotational component, in order to fully assess the brain tissue strains that occur during an impact event.

This project was sponsored by ONR.

Head Protection Against Ballistic and Blunt Impact

ARL carried out an investigation of load transfer and injury arising from ballistic and blunt impact to the head. ARL developed a transfer function approach utilizing a computational porcine model based on live experimental data, a human head model, and an Adaptable Testing and Load Assessment System (ATLAS) Headform model. Computational injury indicators assessed from the animal experiments were used to identify equivalent loading conditions for the human head and a surrogate test platform.

The ATLAS, a helmet test platform being developed by DEVCOM Soldier Center, in collaboration with the Johns Hopkins University Applied Physics Laboratory, was computationally analyzed to correlate with animal experimental data for development of a transfer function (Wozniak et al., 2020). A computational investigation was conducted to estimate response of the clay filled National Institute of Justice headform surrogate using ARL's Roma Plastilina No. 1 (RP1) clay model, and results were compared to human head response.

FIGURE 8-21: Newly developed rotational testing system.

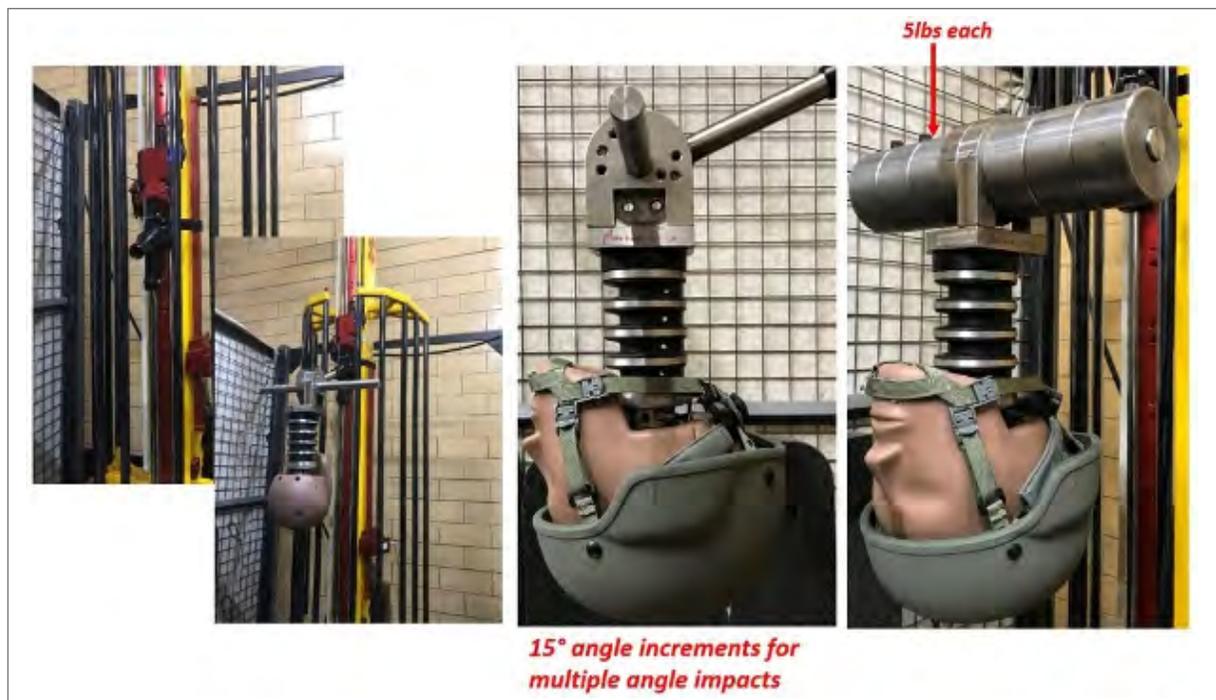




Photo credit: Lance Cpl. Nicholas Filca/U.S. Marine Corps

A study of potential injury mechanisms associated with TBI due to blunt impact was published in *Frontiers in Neurology* (Fagan et al., 2020). Researchers found elevated levels of shear strain, primarily focused near the bases of sulci, which corresponded well to previously reported microbleeds in collegiate athletes. Excessive tensile strains have been identified as the underlying injury mechanism of skull fracture from behind-helmet blunt trauma (BHBT) impacts in a previous analysis of post-mortem human subject skull fracture tests. The fractures from BHBT have also been associated with clinically and operationally relevant outcome measures by an expert medical panel that provided a link between the mechanics and medical risk of an event.

This study was sponsored by ARL.

Development of a Photonics Smart Helmet System for Early Detection of TBI Caused by Blunt Force Impacts and Blast Overpressure Effects

TBI and mTBI are insidious problems for Service members in training and operations. It is well established that mTBI is among the most difficult injuries to diagnose at the time of trauma. Additionally, the impact of mTBI is challenging to fully understand because Soldiers often retain active-duty status by failing to self-report events perceived as mild or innocuous. A shortage of early detection methods imposes severe limitations on clinicians' abilities to administer the most effective therapies within the first 60 minutes following traumatic injury (i.e., the "golden hour").

Researchers at the Lightwave Technology Laboratory at the Missouri University of Science and Technology are developing a Photonics Smart Helmet system for early detection and pre-clinical diagnosis of TBI and mTBI. The Photonics Smart Helmet combines a hair-like optical fiber, conventionally used for high-speed telecommunications, with a military-issue combat helmet's shell to create a composite sensor structure (Figure 8-22-Top). While optical fiber sensors conventionally measure strain, bonding them to the surface of a helmet enables accurate measurements of the initial shock waves, and the residual echoes of the impacts, as they propagate and reverberate throughout the helmet and the Soldier's head and neck.

The transient oscillatory signals from a single fiber were found to be so data-rich that machine learning algorithms demonstrated good predictive accuracies (> 70 percent) for magnitude, direction of impact, and striking implement used. An improved Photonics Smart Helmet, incorporating a second optical fiber, placed orthogonally to the first, is expected

to significantly improve the predictive algorithms' accuracy (> 95 percent) without requiring any changes to the current instrumentation (Figure 8-22-Bottom).

The Photonics Smart Helmet also responds to blast overpressure events. Explosion tests using a propane blast simulation device, Composition B explosives, and TexPak binary explosives were conducted at the Missouri University of Science and Technology Rock Mechanics & Explosives Research Center (Figure 8-23). In Phase II of the project, the Photonics Smart Helmet will incorporate additional optical fiber sensors to provide other kinematic data, such as head acceleration and rotation. The tailored machine learning algorithms will employ existing clinical data to generate preclinical mTBI treatment recommendations, in real-time, for Soldiers in the field.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

FIGURE 8-22: (Top Left) A wireless, fiber Bragg grating-equipped football helmet worn by a Humanetics Hybrid III 50th percentile male anthropomorphic test device. (Top Middle) Several pouch variants for mounting the transceiver on the helmet. (Top Right) Ops-Core helmet equipped with optical fiber and wireless module. (Bottom) Frames extracted from a video of the Biokinetics Linear Impactor apparatus striking a wireless, optical fiber-equipped football helmet and the real-time transient oscillatory signal generated by the impact.



FIGURE 8-23: (Left) Still image from a video of a preliminary test of the Explotrain X-OMG Large Battlefield Effects Blast Simulator (propane and oxygen mixture) generating a shock wave next to a wireless, optical fiber-equipped football helmet – and the real-time transient oscillatory signal generated by the blast. (Right) Still image from a video of a detonation of TexPak liquid binary explosive in the same experimental setup.



Thoracic Cavity Response to Blast Exposure with and without Soft-Armor Vest

The effectiveness of PPE in mitigating blast overpressure injuries has not been measured with reasonable certainty, leading to fundamental gaps that limit the development of mitigation and protective strategies. Researchers at WRAIR and the Michael E. DeBakey VA Medical Center have begun to address this shortcoming by seeking to establish the relationship between blast overpressure exposure and internal pressure responses. The investigators assessed the relationship between external flow conditions and internal pressure responses in the thoracic cavity, with and without Kevlar soft-armor protection. To study intrathoracic pressures, male Sprague Dawley rats were surgically instrumented with pressure sensors via the carotid artery and the esophagus/trachea and were exposed laterally to blast overpressure ranging 4–13 psi (25.58–89.63 kPa), with soft armor (SA) and without soft armor (woSA), in an Advanced Blast Simulator. For data analyses, all pressures were normalized to the static blast overpressure exposure. Normalized peak positive pressures and impulses were not altered when SA and woSA groups were compared. Notably, normalized peak pressures for both groups, and in both internal pressure sensors, were above blast overpressure exposure level, perhaps from a spalling effect. However, there were significant decreases in normalized rise time with both the carotid and esophagus/trachea pressures

in the SA group compared to the woSA group. Further analyses are underway to characterize each pressure group and additional pressure parameters. Overall, in addition to implications for better evaluation of PPE, the current data are crucial for scaling animal models, developing non-biological surrogates for PPE test and evaluation, and validating computational models.

This effort was supported by the Peer Reviewed Medical Research Program with program interest by CRM/RP/JPC-8.

Nanostructured Composite Fluids in Liquid Body Armor

Blast waves from explosive devices can result in TBI and behind-armor blunt trauma (BABT). Researchers at Missouri University of Science and Technology have been developing viscoelastic materials as highly efficient helmet liners to mitigate TBI and BABT. During an explosion, a high-pressure blast wave propagates radially outward, and a lower negative pressure phase follows. Pressure waves reflect between the helmet and head, resulting in overpressure torsional and rotational acceleration in the brain.

The strategy of the study is to maximize material performance by minimizing the weight and volume of the soft liner material added to the helmet itself. These studies include the effect of nanosized inorganic particles on the properties

of viscoelastic polymers and the development of multi-layer composites for highly efficient energy absorption. Various viscoelastic polymers based on polyurethane and silicone composites were prepared, and testing of the helmet liner materials was conducted under blast wave and blunt impact conditions to evaluate their energy absorption, redirection, and dissipation performance. Dielectric spectroscopy measurements were carried out to determine the energy dissipation factor (tan delta) of the helmet liner materials within a typical frequency range of shock waves (< 500 Hz). Viscoelastic polymer formulations with lower durometers revealed a higher dissipation factor and strain loss. Figure 8-24 shows the data for energy dissipation factor (tan delta ~10) and strain loss (~60 percent) for selected helmet liner materials.

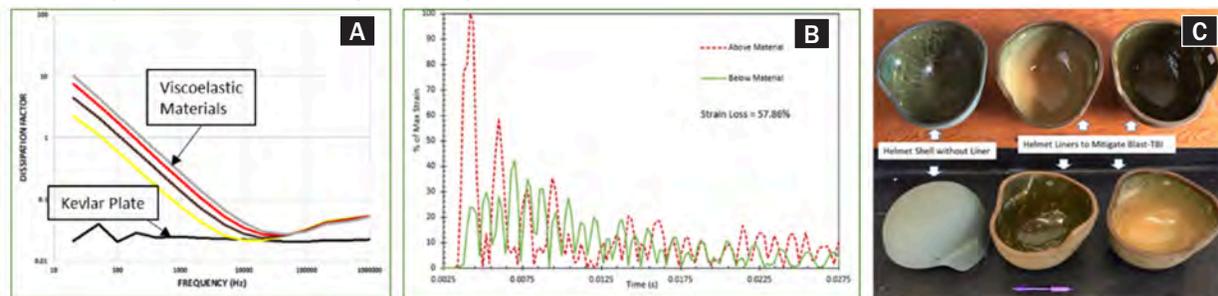
Additional tests were conducted using C4 explosives to determine differences between the incoming and outgoing velocities of shock waves from helmet liner materials. Velocity differences up to ~40 m/s were obtained for viscoelastic polymer formulations in comparison to ~3 m/s difference for a Kevlar plate. An invention disclosure has been submitted to the Missouri University of Science and Technology based on the promising results of helmet liner materials developed for blast wave absorption.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

Novel Armor Ceramics for Soldier Protection

Researchers at ARL are developing novel ceramic synthesis and processing methods, advanced characterization techniques, and improved simulation capabilities to push the state-of-the-art for ceramic armor materials, and mass-efficient armor designs, that are scalable against current and future threats. Current state-of-the-art materials from industrial partners were evaluated using novel, time-resolved ballistic experiments in the Dynamic Compression Sector (DCS) at Argonne National Laboratory. These results, combined with careful quantitative stereology analysis, Raman spectroscopy, and mechanical property characterization, have yielded insight into the characteristic dynamic behavior of these materials. The knowledge generated by ARL is being used to procure or develop non-commercial, super-hard materials and ceramic blends, such as polycrystalline chemical vapor deposition (P-CVD) diamond, silicon carbide (SiC)/diamond, boron suboxide (B_6O), and complex heterogeneous ceramics, such as graded and layered boron and silicon carbide (B_4C/SiC). The maturation of ceramic tape casting and additive manufacturing processes is enabling ARL to explore the role of ceramic structure on armor performance. An improved, third generation high voltage, in situ, diagnostic radiographic apparatus (HIDRA) has been developed and implemented at ARL to visualize ceramic structure/property relationships at larger temporal and spatial scales than DCS. The material synthesis and processing efforts, combined with

FIGURE 8-24: (A) Energy dissipation factor and (B) strain loss data for selected viscoelastic materials; (C) helmets coated with the developed liner materials to mitigate the amplitude of blast waves between helmet and head.



maturation of simulation tools and novel methods for time-resolved material characterization, will yield critical technical competencies. The research supporting this effort can be found in Magagnosc & Tonge (2020), Pelz et al. (2020), and Tonge (2020).

This study was sponsored by ARL.

Blast Protection for Dismounted Soldiers

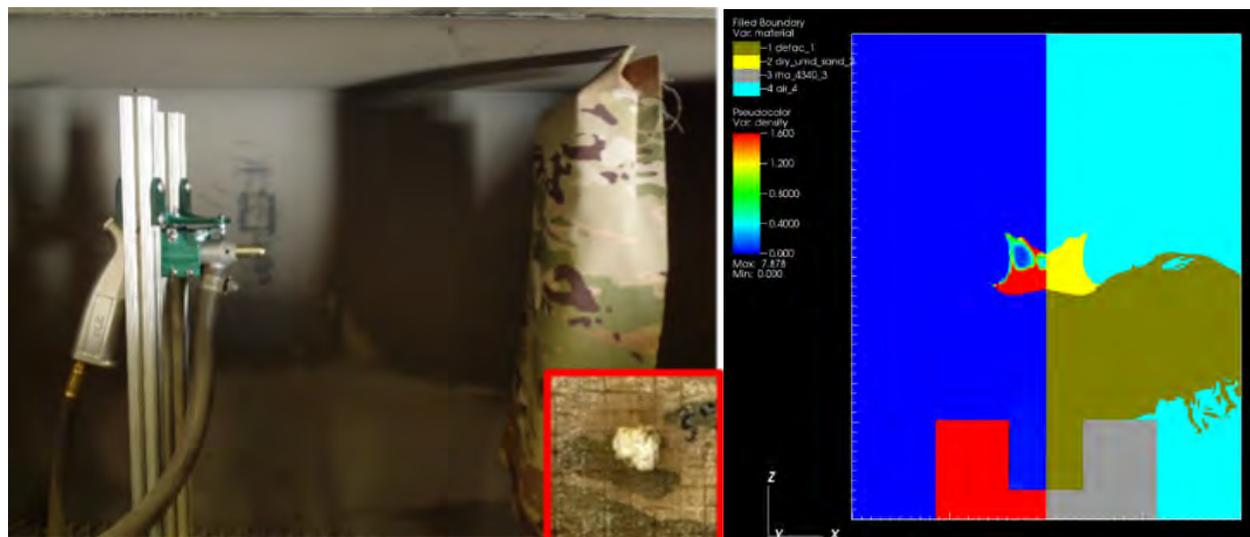
Experimental and modeling capabilities are being developed by ARL to characterize the blast environment relevant to injury of the dismounted Soldier, and allow for evaluation of armor performance against this threat. Full-scale arena experiments were performed, demonstrating that soil from blasts can be separated and displaced in two phases that occur at distinct time periods. The first is characterized by sparse, higher velocity particles that are likely to produce penetration upon impact and are observed in textiles after the event. The second phase is characterized by a lower velocity with a dense flow of soil that is likely responsible for tearing of the textile, which exposes larger areas of the backing material. These experiments also measured the mass of soil passing through a pre-defined area.

The current effort is focused on developing laboratory-scale methods to quickly evaluate the

Army Combat Uniform and other textile armors, while providing a correlation to full-scale damage mechanisms (McKee et al., 2020). Two approaches have been investigated. First, a media blaster (Figure 8-25-Left) was used to propel a stream of particles to damage textile samples. Initial results demonstrate that damage is varied based on textile proximity to the nozzle, and the particles produce damage in the form of textile tearing and abrasion. The second method makes use of sheet explosives and a device specially designed to propel particles at higher velocities, in a manner more directly comparable to blast (Figure 8-25-Right). Simulations have been performed to demonstrate the feasibility of the device to produce a spray of soil with an acceptable density of particles. Data collected from both methods will be used to validate and improve the predictive performance of an existing model of failure from soil impact on the Army Combat Uniform. The laboratory-scale methods will also be used to better understand how textile characteristics relate to performance. The increased pace of experiments using these laboratory-scale methods, combined with modeling capabilities, will enhance the ability to design textile armor and understand how it will perform when subject to buried blast loading.

This study was sponsored by ARL.

FIGURE 8-25: (Left) Media blaster method. (Right) Sheet explosive method.



Development of a Unified DOD Torso Model for Blast-Related Simulations

ARL has continued to collaborate with other government agencies in evaluating and improving existing finite element models of the human torso, to establish a unified inter-DOD agency model for evaluating blast-related threats to Service members. This collaboration enables multiple organizations to leverage the available resources and efforts being performed across the DOD. During FY20, evaluations of three new torso models were conducted: Corvid's Computational Anthropomorphic Virtual Experiment Man (CAVEMAN) model; ONR's iteration of the Advanced Total Body Model (ATMB), which models Service member injury primarily as a means for prevention; and the Joint Intermediate Force Capabilities Office (JIFCO)'s iteration of the ATMB, which models target injury primarily to assess the risk of significant injury from non-lethal kinetic energy weapons. These evaluations were added to the ten torso models that were evaluated during FY19. Included with ARL's evaluations were recommendations to pursue the ONR version of the ATMB as a government-owned model, CAVEMAN was recommended for possible adoption in the future. ARL has been evaluating both models under conditions relevant to behind-armor blunt trauma and is providing feedback to the model developers.

In addition to the evaluation and improvement of the overall model, ARL has been involved in developing a new lung constitutive model. The new lung model was embedded and evaluated in the ATMB for proof of transition, and initial results have been promising. It is expected that successful completion and validation of the lung model can be rapidly transitioned to the ATMB. ARL has also been collaborating with JIFCO in developing improved characterization for skin material, which will improve the collective understanding of how load is transferred through the outer layers of the torso. This is critically important to generating meaningful conditions for injury evaluation at the deeper organ level in the model.

This study was sponsored by ARL.

Acute Treatment

Research in acute treatment is intended to improve survivability and mitigate long-term disability for Service members across the full spectrum of injuries following blast events. Collaborations between DOD and partners in academia and the private sector are improving preclinical models, developing new diagnostic tools, and testing new pharmaceutical and surgical interventions to treat blast injury. The combined research efforts will improve our understanding of the capabilities and limitations of current technologies; design of new tools; methods to validate injury mitigation in the pre-hospital setting; and diagnostics and clinical guidelines for the acute treatment of blast injuries. Acute treatment accomplishments from FY20 are organized into four categories: anatomical and injury models; assessment and diagnosis; pharmaceutical interventions; and surgical interventions.

Anatomical and Injury Models

Hippocampus-Cerebellum Axis-Specific Transcriptomic Stratification to Discriminate Differential Degrees of Brain Injuries

The severity of a brain injury typically determines the degree of the psychological and physiological impacts and the associated long-term consequences among trauma survivors. The typical triphasic scaling method is used to score patients with mild, moderate, and severe forms of TBI. In a study published in *Experimental Neurology* (Chakraborty et al., 2021), researchers at WRAIR and U.S. Army Research Institute of Environmental Medicine anticipated that measuring and differentiating molecular markers could provide a more robust and effective method for the triage of TBI. To test this theory, they used a modified closed-head injury (CHI) weight-drop model with two impact heights (IH).

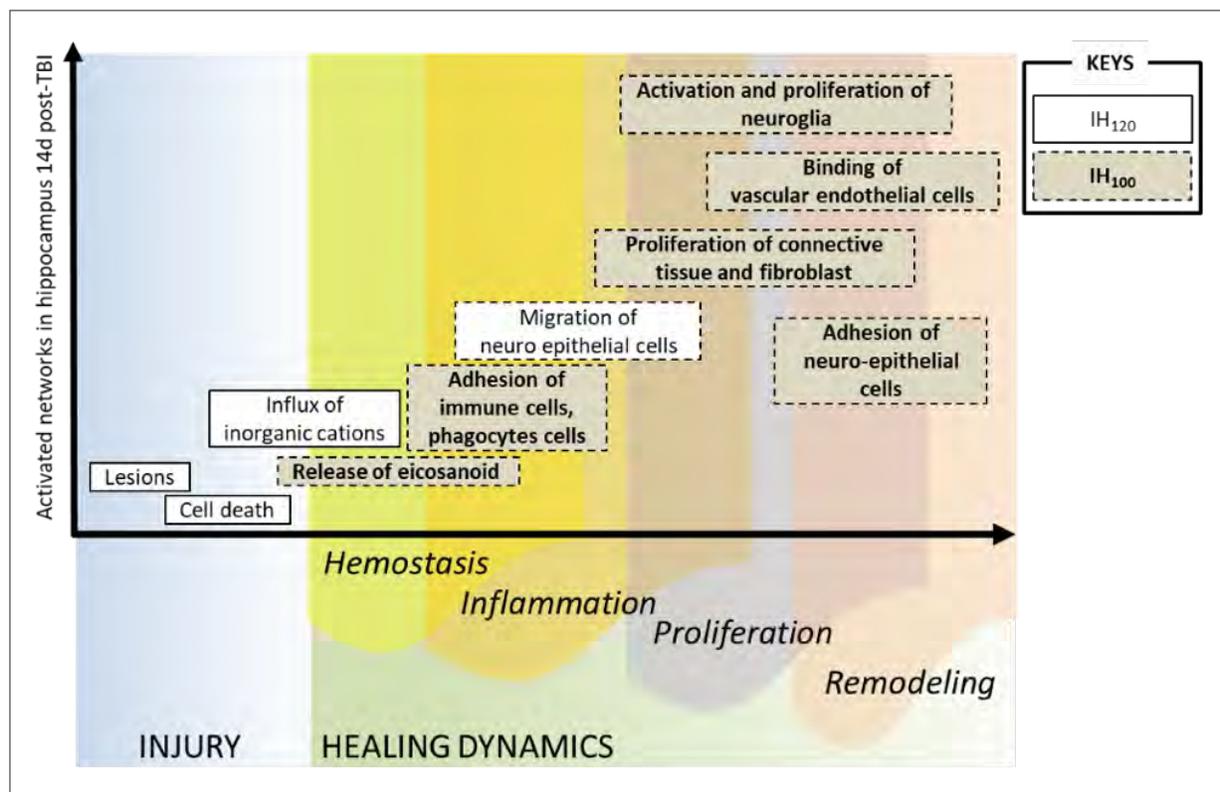
Differing IHs directly correlate with the impact of force causing head injury in rodent subjects. In the modified CHI model, diffuse axonal injury was

induced by fitting each rat skull with a helmet. The frontal cortex was the focal point of injury; however, the diffuse nature of the impact also intentionally affected adjacent brain regions, such as the hippocampus and cerebellum. At eight days post-injury, rats that were impacted by 120 cm IH (IH₁₂₀) showed reductions in visuomotor performance, as assessed by the Barnes maze behavioral paradigm, compared to those impacted by 100 cm IH (IH₁₀₀). Using a time-resolved interrogation of the transcriptomic landscape of hippocampus and cerebellum tissues, investigators mined genes with altered regulations based on IH. At 14 days post-TBI, all animals showed normal visuomotor behavior. Bio-functional analyses indicated that the hippocampus of IH₁₀₀ rats had undergone an advanced healing mechanism. This healing

mechanism was delayed in the IH₁₂₀ group, with evidence of active cell death networks, as illustrated in Figure 8-26.

The cornerstone of the finding was several remnants of TBI in the hippocampus transcriptomic landscape, even after 14 days post-injury, which co-occurred with the display of apparently normal visuomotor and visuospatial performances in rats with TBI. Based on their visuomotor performance, rats in the IH₁₂₀ group reached a potential asymptomatic state, while their hippocampal injuries were still lagging at the premature stage of healing. From a clinical perspective, these molecular perturbations are likely to be the driving force for long-term health risks. Dysfunctional hippocampal pathology after TBI has been associated with a risk for the

FIGURE 8-26: The status of the hippocampal injury at 14 days post-TBI in a rat exposed to a weight-drop paradigm with two different IHS. The functional networks significantly activated by either IH₁₀₀ or IH₁₂₀ TBI were aligned with the injury phase and subsequent steps of the healing cascade. The networks linked to IH₁₀₀ and IH₁₂₀ are inside the gray boxes with a broken border and white boxes with a solid border, respectively. Image is originally featured in Chakraborty et al. (2021) and is licensed under [CC BY-NC-ND 4.0](https://creativecommons.org/licenses/by-nc-nd/4.0/).



development of disorders later in life, including PTSD, chronic traumatic encephalopathy, epilepsy, and dementia. Hence, these findings underline a need for a hippocampus-cerebellum axis-specific intervention for long-term TBI management. Genomic microarrays, combined with behavioral analysis and assessment of symptomatology, could provide a new pathway for triage of TBI patients in the civilian or military setting.

This study was funded by MOMRP/JPC-5.

Models of Chronic Blast-Induced TBI Using the Advanced Blast Simulator and Closed-Head Impact Model of Engineered Rotational Acceleration

The CNRM conducts preclinical TBI studies that closely mirror human clinical studies under its Translational Research Division. This novel approach enhances CNRM's ability to translate preclinical treatments into successful future clinical trials that will improve outcomes for Service members with TBI. The Translational Research Division conducts a variety of complex injury models that closely replicate military-related TBI: a combination of blast exposure and/or impact and rotational forces with stress-inducing environmental stimuli. An additional focus is the assessment of symptomatology that is analogous to that measured in human trials: disruptions in mood (e.g., depression, anxiety), sleep, pain/headache, attention, impulsivity, and cognition (e.g., memory).

CNRM and the Uniformed Services University (USU) have access to rare, state-of-the-art machinery, such as the Advanced Blast Simulator and the Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA). The Advanced Blast Simulator is the only research equipment capable of producing the proper negative phase and secondary shock patterns of a free-field explosion in animal models. There are a limited number of Advanced Blast Simulator machines in the U.S. and the CNRM machine was custom-made to support blast models in mice, rats, and ferrets. The CHIMERA accurately replicates the rotational impact commonly involved

in TBI, and it, too, is designed for mouse, rat, and ferret models.

CNRM-funded investigators have developed two proof-of-concept, complex, chronic models of blast-induced TBI in mice and ferrets. Both models incorporate the combination of blast exposure, impact and/or rotational force, and stressful stimuli, analogous to the complex environment and TBI exposures experienced by Service members. The pathological features seen in these mice and ferret models reflect novel features seen in post-mortem human TBI cases. These two state-of-the-science paradigms are intended to act as an efficient pipeline that rapidly and effectively evaluates candidate interventions. These interventions will be designed to yield a decisive determination of the treatment's effect (e.g., success or failure) on the primary outcome measure, and will build in secondary outcome measures to improve future studies and clinical translation. CNRM-sponsored researchers recently published a review article in *Experimental Neurology* surveying the implementation of the CHIMERA, along with the associated pathological, imaging, neuropsychological, and behavioral observations (McNamara et al., 2020).

This research was supported by CNRM and DHA.

Blast Injury in Ferrets Mimics Many Features of Human Pathology

Blast injuries that impact the brain are a hallmark of combat in contemporary conflict. Improved preclinical models of blast-induced TBI are needed for more effective translation of pharmaceutical and therapeutic protocols. The ferret, as an animal with substantial sulci, gyri, white matter, and the hippocampus located in a ventral position (as in humans but not rodents), represents a valuable model for neurotrauma studies. In a study published in the *Journal of Neuropathology and Experimental Neurology* (Schwerin et al., 2021), researchers at USU exposed ferrets to an explosive blast delivered via the Advanced Blast Simulator, and evaluated their behavior during recovery, with the final

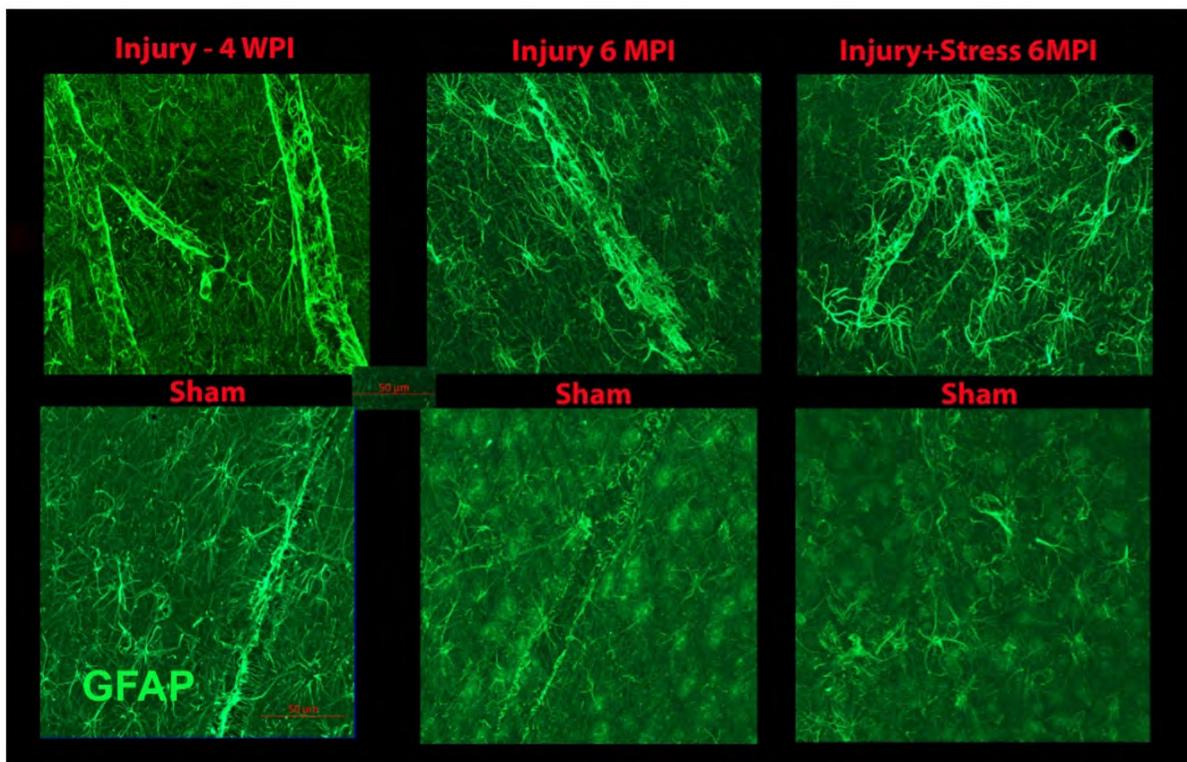
evaluation after 4- or 12-week survival. Using western blot analysis and immunohistochemistry, increases were observed in phosphorylated tau in multiple cortical areas in animals exposed to blast. Consistent changes were also observed in the expression of the tau isoforms 3R and 4R. Several human pathologies show substantial alterations in the expression ratio of these isoforms, which have been difficult to demonstrate in rodents. The current results indicate that the 3R and 4R isoforms occur in relatively equal amounts in the cerebral cortex of healthy ferrets, but significant changes in these markers occur in the frontal cortex after 12 weeks of survival post-blast injury. In addition, changes in the morphology of blood vessels were noted, which exacerbated after longer survival times. Patterns of gliosis were also observed, with many features comparable to human pathology of subjects experiencing blast injuries. These features include increased

subpial reactivity and gliosis at grey-white matter interfaces, at the fundus of sulci, and substantial increases in glial fibrillary acidic protein (GFAP) reactivity outlining blood vessels (Figure 8-27).

Further evaluation at longer survival times shows that many of these observations persist for at least six months post-injury. Intriguingly, ferrets surviving blast plus rotational injuries show alterations in sleep patterns that also persist for at least six months. These findings indicate that ferrets are a highly translatable model, in which to study blast injury of the brain, and may be suitable for testing and developing therapeutics.

This effort was managed by CDMRP with support from the Psychological Health/Traumatic Brain Injury Research Program (PH/TBIRP), with programmatic oversight by CCCRP/JPC-6, and CNRM.

FIGURE 8-27: (Top) Histologic images of blood vessels revealing that those in the injured cerebral cortex are heavily enveloped with astrocytes (GFAP). (Bottom) Lack of astrocytic envelopment in sham animals. Weeks post-injury (WPI), months post-injury (MPI).



Mathematical Model of Blood Volume Kinetics and Renal Function in Response to Burn Injury and Resuscitation

Burn injuries are a common consequence of blast exposure, particularly in combat. Fluid resuscitation is critical to burn injury treatment, but the timing, amount, and type of fluids to administer lacks clinical consensus. Considering there are substantial risks to insufficient or delayed fluid resuscitation (e.g., organ hypoperfusion, ischemia, death) and over-resuscitation (i.e., fluid creep), optimizing a resuscitation regimen may significantly contribute to reconciling the maintenance of organ function and minimizing adverse complications. A mathematical model published in the journal *Burns* (Arabidarrehdor et al., 2020) consists of an established multi-compartmental model of blood volume kinetics, a hybrid mechanistic-phenomenological model of renal function, and novel lumped-parameter models of burn-induced perturbations in volume kinetics and renal function equipped with contemporary knowledge of burn-related physiology and pathophysiology. This mathematical model was shown to be physiologically plausible in data collected from 16 sheep with induced full-thickness burn injuries. The model accurately predicted blood volume kinetics and renal function responses to burn injury and resuscitation. Future steps for this research include validation of the mathematical model in humans, which will serve to enhance researcher knowledge regarding burn-induced physiological changes and the development of burn resuscitation protocols and algorithms.

This effort was managed by CDMRP with support and programmatic oversight by Medical Simulation and Information Sciences Research Program (MSISRP)/JPC-1.

Age-Related Mechanical and Structural Changes of the Human Thoracic Aorta

While aortic changes are often studied in humans in relation to the cardiac cycle or by measuring velocity in vivo, some mechanical characteristics of basic aortic physiology cannot be readily

measured. This research project, published in *Acta Biomaterialia* (Jadidi et al., 2019), analyzed longitudinal and transverse histological sections of 76 thoracic aortas from seven age groups (13 to 78 years) to determine variations in wall thickness and elasticity in a non-stress and non-stretch state. Age-related changes in mechanical properties included increased thickness, circumferential compliance, and aortic vessel curve, as well as decreased elastin density, longitudinal compliance, and opening angle of the thoracic aorta.

The thoracic aorta is one of the most commonly repaired aortic segments in trauma patients, including those injured by blast. Characterization of mechanical, physiological, and structural features in human aortas of different ages can help researchers understand aortic pathology, inform the development of animal models that simulate human aging, and assist with designing devices for open and endovascular aortic repairs. Service members sustaining trauma to the aortic vessels may require open cardiothoracic or endovascular repair. Improved techniques and devices will result in improved outcomes and reduced morbidity/mortality.

This effort was managed by CDMRP with support and programmatic oversight by CCCRP/JPC-6.

Inner Ear Damage Contributes to Shock Wave-Induced Hearing Loss

To expand the current understanding of the etiology of blast-induced hearing loss, researchers at WRAIR and the National Institute on Deafness and Other Communication Disorders at the National Institutes of Health (NIH) evaluated the effects of a single (Bx1) and tightly-coupled triple (Bx3) 16 psi (110.32 kPa) blast exposure on ear structure and auditory function in mice. Of interest are the mechanosensory hair cells (HC), which are the first cells to neurally encode pressure waves in the auditory and vestibular pathways. All blast-exposed mice showed significant loss of outer hair cells (OHC) in the basal turn of the cochlear region, while middle turn HCs initially did not appear to

be affected (Figure 8-28). By 90- and 180-days post-blast, the number of surviving OHCs was lower in some triple-blast exposed cochleae. These low counts made the overall difference between control and triple-blast mice statistically significant. The delayed HC death observed in the middle turns of triple-blast cochleae may reflect greater damage to cochlear structures that support HCs (e.g., stria vascularis and supporting cells) and secondarily cause HC loss over an extended period. Although the number of inner hair cells (IHC) remained unchanged, the average number of IHC synapses was significantly decreased in blast-exposed mice.

To examine OHC function, distortion product otoacoustic emissions (DPOAE) were recorded. In all blast-exposed mice, DPOAEs were absent between 1- and 30-days post-exposure. Long-term tracking of a subset of mice showed that DPOAEs began to return at 30 days post-blast in mice exposed to a single blast, and at 180 days post-blast in triple-blasted mice (Figure 8-29). DPOAEs are the functional indicators of HCs and middle ear viability. Although tympanic membrane (TM) perforation was detected after blast exposure(s), TM healing presented at seven days post-injury. TM damage and healing did not differ in any obvious way between single- and triple-blasted mice. These findings indicate that shock waves can cause hair cell dysfunction rather than cell loss in the acute injury phase. Development of a therapeutic intervention after blast exposure is necessary to prevent permanent hearing loss.

This effort was managed by CDMRP with support and programmatic oversight by CRMRP/JPC-8.

Physics-Based Model of Tissue Trauma and Hemorrhage Based on Physical Properties of the Liver

Medical simulation has limited capability in accurately modeling liver tissue because of the organ's physical properties. Researchers at the University of California, Los Angeles, used a liver

FIGURE 8-28: Number of IHCs and OHCs.

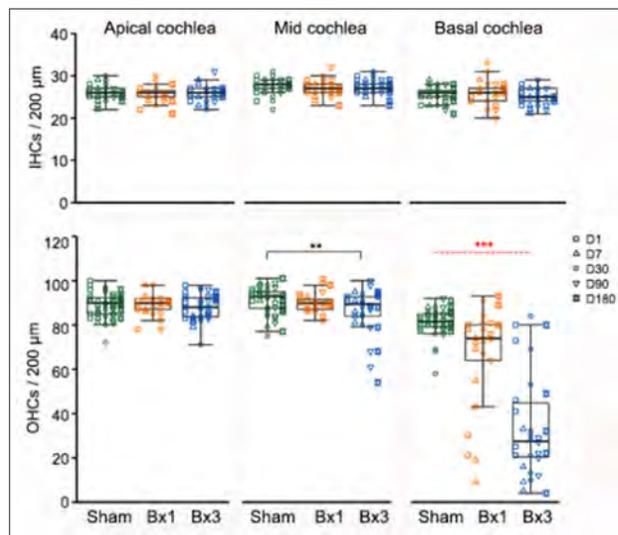
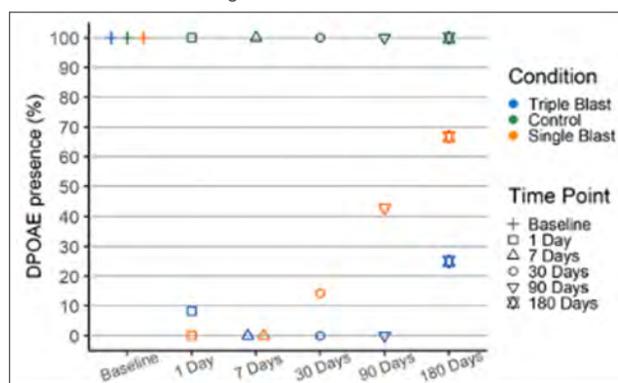


FIGURE 8-29: Percentage of mice with detectable DPOAEs.



perfusion system to develop a viscoelastic model of liver deformations paired with physiologic, high-fidelity simulations of the autonomic system. Using porcine livers, the team successfully demonstrated the model's interaction with external forces including shock wave and ballistic projectiles. This work was published in the *Journal of the Mechanical Behavior of Biomedical Materials* (Li, Maccabi, et al., 2019). Successful modeling of the liver will improve medical training for patient management in emergency combat injury scenarios. The model could also aid surgeons in planning for routine major surgery.

This effort was managed by CDMRP with support and programmatic oversight by MSISRP/JPC-1.

Assessment and Diagnosis

Burn Injuries in U.S. Service Members from 2001 to 2018

Burns account for 5 to 20 percent of battlefield wounds. While most burns are minimal and survivable, even minor burns can lead to significant morbidity and decreased quality of life, particularly those that affect the head and hands. Recent studies have only examined evacuated casualties and omitted the large proportion of mild burns that can be treated in theater. The present study leverages the Expeditionary Medical Encounter Database (EMED), a Navy-maintained health database describing all Service member medical encounters occurring during deployment, to capture, quantify, and characterize burn-injured Service members and all burn injuries, ranging from mild to severe, sustained while deployed in support of post-9/11 operations.

The EMED was queried for all surviving Service members with a burn injury, using injury-specific Abbreviated Injury Scale codes. Additional EMED data included demographic data, Injury Severity Score (ISS; battle/non-battle), injury mechanism, posture (mounted/dismounted), clinical information, and other injuries sustained in the same event.

From 2001 to 2018, 2,507 Service members sustained 5,551 deployment-related burn injuries. The population was male (97 percent), Army (69 percent) or Marine Corps (27 percent), lower- to mid-rank enlisted (89 percent), and active-duty (81 percent). The highest number of burn injuries occurred in 2006 ($n = 1,095$), with sustained high activity observed from 2004 to 2007. In the study population, 81 percent were in Operation Iraqi Freedom and 86 percent were combat injuries, with the remaining sustaining non-battle injuries. Blasts were responsible for 82 percent of injuries, and 65 percent of Service members were burned while driving or riding in a vehicle (i.e., mounted), with 23 percent injured while dismounted. Thirty percent of burn-injured Service members sustained concurrent TBI, and inhalation injury was observed

in 10 percent. The mean ISS was 8.4—categorized as “moderate” and “serious” injury severity overall. Overwhelmingly, burns were small (92 percent) and affected less than 20 percent total body surface area (TBSA): 85 percent of burns affected less than 10 percent TBSA. The head and hands were most commonly affected (48 percent); 80 percent of burn-injured Service members sustained at least one burn to the head or hands. The upper extremity—extending from the fingers to the shoulder—was the most impacted body region, accounting for 39 percent of all burns, with two-thirds sustaining at least one burn to the upper extremity.

Results of this research may be used to inform leadership of the scope and characteristics of Service members with burn injuries for the purpose of preparing for the future fight and developing care that can lead to optimal outcomes.

This research was sponsored by the DOD–Department of Veterans Affairs (VA) Extremity Trauma & Amputation Center of Excellence (EACE).

Identification and Description of a Relationship Between Burn Wound Location and Recovery Outcomes

Scientists from the U.S. Army Institute of Surgical Research published novel findings on a relationship between burn wound location and recovery (Liu et al., 2019). This correlation is important because it could be used in algorithms for triage and prehospital treatment decisions. This would be a critical addition to the traditional paradigm, which relies on burn care specialists, who are not present in the prehospital environment, and uses total body surface area and rudimentary tools for burn wound depth assessment. The finding of a relationship between burn wound location and recovery outcomes will contribute to advanced, simplified tools to support care decisions closer to the point of injury by non-specialist caregivers.

This research was supported by CCCRP.

Burn Wound Severity Classification to Support Care Decisions

Early burn injury assessments inform life-saving resuscitation and wound care strategies that optimize recovery outcomes following burn trauma. However, expert evaluation of burn wounds is not likely to be available close to the point of injury and casualty evacuation may be delayed in multi-domain operations, where burn wound prevalence may be high and injuries severe. Therefore, the absence of technologies to support clinical decision making for acute and ongoing burn wound management is a significant gap for prolonged field care scenarios. To address this gap, researchers from the U.S. Army Institute of Surgical Research published novel findings to enable prehospital strategies for objective assessment of burn wound depth, without evaluation by a burn care specialist (Ponticorvo et al., 2020; Kennedy et al., 2019). Using spatial frequency domain imaging (SFDI), the researchers measured spatial inhomogeneity in burn wounds and predicted heterogeneous healing. In addition, they visualized differences in healing rates, which depended on whether a wound was debrided and grafted, or not debrided and left to heal without intervention other than topical burn wound care. They also used SFDI to quantify the concentration of oxy- and deoxyhemoglobin, giving insight into hemodynamic changes occurring during healing. SFDI is one of several leading technology candidates for burn wound depth determination that may be amenable to forward deployment in multi-domain operations. Such technology is needed to support treatment decisions regarding the need for evacuation from combat environments.

This research was supported by CCCRP.

Commercialization and Clinical Use of a Portable MRI Device Developed from DOD-Funded Research

Conventional magnetic resonance imaging (MRI) requires high magnetic fields (1.5–3 tesla [T]), generated by superconducting magnets operating in vibration-sensitive environments. The associated equipment and material requirements (e.g., cryogenics) largely limits the use of MRI to specific locations in fixed hospital settings. Investigators at Harvard Medical School and the Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital were funded to develop a lightweight, open-access MRI instrument operating at 0.1 T and optimized for human brain imaging; along with development of hyperpolarization and Overhauser contrast mechanisms, based on nanoparticles and endogenous free radicals associated with TBI, to enable sensitive low-field MRI. The goal of this work was to advance MRI technology to support acquisition of magnetic resonance (MR) images closer to the point of injury. At the conclusion of the DOD funded research, two low-field MRI scanner systems (traditional electromagnetic and permanent magnet-based) were developed, capable of using the Overhauser effect to generate MR images at low magnetic field. The research team demonstrated high-speed imaging capabilities using a scanner with a room-temperature stable magnet, operating at 6.5 mT, to collect preliminary, low-resolution 3D brain imaging in vitro and in vivo. After the initial award ended in 2016, the researchers founded Hyperfine to further develop and commercialize the technology. In 2020, Hyperfine received U.S. Food and Drug Administration (FDA) clearances for a new mobile MRI device, Swoop™, operating at 20 times lower magnetic field than traditional MRI, and without high power or cryogenic support requirements. The Swoop™ (Figure 8-30) is marketed as a complement to conventional high-field MRI. The Swoop™ can be used in patients with imbedded metal fragments or devices and has been demonstrated in complex clinical

FIGURE 8-30: The portable MRI. (Left) Dr. Matthew Rosen. (Right) Dr. W. Taylor Kimberly. Photo courtesy of Dr. Matthew Rosen.



environments, including ventilated COVID-19 patients (Sheth et al., 2020). Availability of less expensive, portable, low-field MRI increases the availability of neuroimaging and expands its use outside of controlled hospital imaging facilities, into bedside- and field-based applications such as mobile stroke care, or field/deployed settings.

This effort was managed by CDMRP with support from PH/TBIRP with programmatic oversight by CCCRP/JPC-6.

Evaluation of the King-Devick Test, Salivary Non-Coding RNAs, and Resting State Neuroimaging as Predictive Biomarkers of Concussion

Researchers at Brooke Army Medical Center and the Geneva Foundation have been investigating how well the King-Devick (KD) Test can discriminate between individuals with and without a history of

concussion at baseline screening, and recently published the findings in *Brain Injury* (Dretsch et al., 2019). KD scores for those who sustained a concussion were significantly worse (slower) compared to baseline, but not for participants who finished the course with no concussion. However, the KD Test had poor discriminability when distinguishing between concussed and non-concussed participants. Described in a publication in *Clinical and Translational Medicine* (Hicks et al., 2020), the research team further examined other TBI biomarkers. The assessment of salivary non-coding RNA (ncRNA), a diagnostic biomarker adjunct for concussion, found 28 microRNAs (miRNA), 21 Refseq RNAs, and 1,378 “wiRNAs” (highly similar piwi-interacting RNA sequences reduced using a hierarchical clustering approach) to be significantly different between concussed and control groups. Of these, there were 16 miRNAs (57 percent), 12 Refseq RNAs (57 percent), and

675 miRNAs (49 percent) upregulated in the concussed group. A predictive model employing four of these miRNAs (miR-192-5p, miR-27a-5p, miR-30e-5p, miR-7-1-3p) differentiated 57/75 concussed and 71/97 non-concussed athletes (area under the curve [AUC] = 0.84; 95 percent confidence interval [CI] = 0.76–0.92). The study team found that a predictive model utilizing seven ratios, involving nine ncRNAs, along with participant age and chronic headache status, differentiated concussed and control participants with AUC of 0.86 (95 percent CI: 0.82–0.90). The model correctly identified 190/251 (76 percent) concussed participants and 232/287 (81 percent) control participants (positive predictive value = 81 percent, negative predictive value = 76 percent). Additionally, neuroimaging analyses were conducted to evaluate how resting state imaging analytic approaches could provide markers for acute concussion. These results revealed promising findings of a resting state imaging analytic approach that has modest sensitivity (75 percent), but high specificity (95.7 percent) for acute concussion. The current findings suggest novel mechanisms to detect minor TBI in Service members and inform earlier interventions.

This effort was managed by CDMRP with support and programmatic oversight by CCCRP/JPC-6.

Verification of Glycans as TBI Biomarkers

Brain damage from a TBI alters the function of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), a vital mitochondrial regulator that acts as a transcriptional coactivator, inducing genes involved in mitochondrial biogenesis and cellular respiration.

Researchers filed a patent application for TBI treatment based on an FDA-approved PGC-1 α agonist that does not reach the central nervous system (CNS) due to degradation in the liver. The patent covers a method to prevent degradation by the liver, allowing CNS protection against

TBI-related inflammation and mitochondrial dysfunction, primary problems associated with TBI.

Animal studies of TBI show that the drug developed by the study is neuroprotective through anti-inflammatory effects and enhanced mitochondrial function. The compound was developed in association with a panel of plasma biomarkers that accurately identified individuals with sports concussion, and Marines with a known history of TBI, from controls without a concussion or a history of TBI.

This effort was managed by CDMRP with support and programmatic oversight by CCCRP/JPC-6

Analyzing Blood-Based Biomarkers Associated with Blast-Related TBI

Much remains to be learned regarding changes to the body after exposure to blast overpressure. Complicating this research is the lack of pure blast overpressure exposures in human subjects, given that exposure to blast rarely results in primary blast injuries in the absence of secondary through quinary blast injuries. An exception, however, is the unique population of Service members who train on heavy weapons systems that exert blast forces onto the operators. Researchers at CNRM engaged in a blast-related TBI research study in FY20, which involved collaboration with NMRC and WRAIR. This study analyzed blood samples collected from 108 Service members during a 10-day blast-related training program, in which they were exposed to repeated blast. Based on data gathered from helmet-worn blast sensors, the 108 Service members experienced repeated, low-level blast exposures (≤ 2 psi [13.79 kPa]); however, 29 Service members were also exposed to instances of moderate blast overpressure (≥ 5 psi [34.47 kPa]).

The first publication, featured in *Brain Injury* (Edwards, Leete, et al., 2020), evaluated the extent to which moderate blast overpressure



Photo credit: Petty Officer 2nd Class Ryan Breeden/U.S. Navy

exposure changes peripheral biomarkers (i.e., amyloid beta [$A\beta$], neurofilament light [NFL], and tau) relative to either baseline or in those exposed to low-level blast. Within 24 hours, $A\beta_{42}$ in the moderate blast group was lower relative to the low-level blast-exposed group, and both $A\beta_{42}$ and NFL were lower than baseline. At the one-day mark, the moderate blast group had lower tau and NFL than both the low-level blast exposed group and baseline. Interestingly, this latter result reversed after measurements taken at 72 hours, such that the moderate blast exposed group exhibited higher tau levels than the low-level blast exposed group and baseline. This work demonstrates measurable alterations in biomarker concentrations after blast overpressure exposure, and that these biomarkers correlate with overpressure magnitude in the acute phase.

The second published outcome from this research endeavor is featured in *Frontiers in Neurology* (Edwards, Motamedi, et al., 2020). This work

focused exclusively on the 29 Service members exposed to moderate blast overpressure (≥ 5 psi [34.47 kPa]) during the training program. Three days after moderate blast exposure, blood-draws were taken, and RNA-sequencing was performed, to establish gene expression changes. Gene expression changes were observed in networks involved in cell death and survival, and cell structure, function, and metabolism.

These works offer insight into blast exposure pathology using data gathered directly from Service members performing military-relevant exercises. This and future work will further advance the field of diagnostic and prognostic TBI biomarkers and enhance the collective understanding of blast-induced TBI treatment methods.

This research was supported by the National Institute of Nursing Research Intramural Program, USAMRDC, the U.S. Navy Bureau of Medicine (BUMED), and JPC-5.



Photo credit: Petty Officer 1st Class Sean Mulligan/U.S. Navy

Laboratory Assay for TBI Point of Care Submitted for FDA Approval

The USAMMDA Warfighter Brain Health (WBH) Project Management Office (PMO) manages the Laboratory Assay for Traumatic Brain Injury (LATBI) product development effort and leads its Integrated Product Team (IPT). USAMMDA has partnered with Abbott, a leader in diagnostics development worldwide since 2014.

Through research started at WRAIR, and the advanced development acquisition strategy of the LATBI IPT, two potential biomarkers have been identified in individuals suspected to have a TBI: ubiquitin carboxy-terminal hydrolase [UCH-L1] and glial fibrillary acidic protein [GFAP].

The first increment of the LATBI benchtop,

developed with industry partner Banyan Biomarkers, was a completed pivotal trial of 2,000 TBI patients. It received FDA approval as the first-ever blood serum laboratory test which can help rule out the need for a CT scan of the head within 12 hours of TBI. Banyan did not commercialize the benchtop assay as it is a large hardware system with multiple peripheral components, has a sample processing and assay run-time of five hours, and has logistical challenges for fielding to military units.

The goal is to transition the same biomarkers from the Banyan benchtop system onto a cartridge-based assay that runs on the field-deployable LATBI Point of Care i-STAT blood analyzer system device, delivering results of the LATBI test within minutes. Leftover frozen samples from the benchtop trial were transferred to Abbott for a bridging comparison study, to deliver an initial incremental solution plasma assay on the i-STAT. The bridging validation study on i-STAT was completed, and Abbott submitted a regulatory packet to FDA in June 2020, with anticipated approval in early FY21. In parallel, Abbott also began enrollment, in July 2020, of the clinical trial for the whole blood point-of-care LATBI biomarker test with rapid turn-around time; anticipating trial completion in FY22.

A blood-based biomarker laboratory test for TBI will greatly enhance the ability of the DOD to objectively assess Service members who have suffered a suspected TBI. The goal of initial implementation will be to assist with management of patients with suspected TBI, with particular emphasis on implementation in areas where a Service member would otherwise require an evacuation from operational settings to obtain a CT scan of the head. LATBI has the potential to reduce unnecessary evacuations, solely for head CT scans, by about 30 percent.

This program is managed by the USAMMDA WBH PMO.

Advances in Exploring Blood-Based Biomarkers of TBI

The CNRM is supported by multiple core facilities—including the Biomarkers Core, which processes, receives, catalogs, analyzes, and stores biosamples (primarily blood) from researchers who collaborate with the Biospecimen Repository. The Biomarkers Core works with researchers who investigate military personnel and civilians with TBI and comparable controls. In addition to processing and storing study biosamples, the Biomarkers Core can also provide advanced analysis methods to evaluate epigenetic modifications; mRNA, circular and non-coding RNA expression; and high-sensitivity protein assays for various proteins including tau, neurofilament light (NFL), and glial fibrillary acidic protein (GFAP). The Repository currently holds approximately 111,000 specimens, but has the capability of holding over 200,000. In FY20, efforts by the Biomarkers Core, and biosamples from the Biospecimen Repository, have contributed to recent advances in exploring blood-based biomarkers of TBI. One such advance was published in the *Journal of Neurotrauma* (Devoto et al., 2020), in which exosomal microRNA (exomiR) from 153 participants enrolled in the Chronic Effects of Neurotrauma Consortium (CENC) study was evaluated. Participant groups were stratified based on the number of previously experienced mTBI events. Genetic expression analysis revealed that dysregulated exomiR correlated with inflammation, neurological deficits, and cell development in TBI patients. Differential microRNA expression patterns in TBI patients, and their associated neurobehavioral changes, may lead to a more nuanced understanding of chronic TBI pathophysiology and symptomatology.

Another study by CNRM's Biomarkers Core investigated return-to-play after sports-related concussion. In this *Journal of the American Medical Association Network Open* publication (Pattinson et al., 2020), National Collegiate Athletic Association (NCAA)–DOD Concussion Assessment, Research, and Education (CARE) Consortium researchers

collected blood samples from 127 college athletes at pre-season baseline, and multiple time points after sports-related concussion. They concluded that total tau and GFAP, but not NFL, may provide moderate ability to distinguish between athletes needing shorter or longer times to return to play.

Additional publications resulting from efforts of the Biomarkers Core (Stone, Avants, et al., 2020; Shahim et al., 2020a) are summarized on pages [148](#) and [212](#).

The Biomarkers Core infrastructure is supported by CNRM.

MicroRNA Biomarkers to Detect Mild Blast Overpressure-Related TBI in Service Members

In the absence of a sensitive diagnostic marker for blast overpressure injury, the diagnosis is determined primarily based on the patient's self-reported clinical symptoms. Therefore, there is an unmet, immediate need for more sensitive biomarkers for detecting mild blast overpressure-induced TBI. MicroRNAs (miRNA) are small, endogenous RNA molecules that regulate translation in eukaryotic cells. MiRNAs are considered excellent biomarkers because of their small size, resistance to degradation, and ease of sensitive detection. Researchers at USU have identified a panel of miRNA biomarkers that detect mild-to-severe TBI in civilian cases of impact TBI. This panel consisted of miR-151-5p, miR-195, miR-30d, miR-20a, miR-328, miR362-3p- miR-451, miR-486, miR-505-3p, miR-92a and miR-9-3p. This miRNA biomarker panel was able to distinguish patients with lesions on head CT from those who do not have lesions.

To evaluate whether the miRNA panel can be used to detect the effects of chronic low-level blast-induced TBI, the researchers performed animal studies with low-level repetitive blast overpressure exposures. Animals were exposed to three repetitive blast overpressure intensities

of 5.08 psi (35 kPa) to understand the chronic effects of blast-induced TBI. The data showed a significant increase in serum concentration of miR-151, miR-195, miR-20a, miR-328, miR-362-3p, miR-486, miR-505-3p, and miR-92a at 24 weeks following blast overpressure exposure. This suggests that the miRNA biomarker panel can be used as a potential indicator of neurobehavioral changes post-blast overpressure exposure. Researchers also evaluated these miRNA markers for their ability to detect low-intensity repetitive blast overpressure exposure in humans, at acute and chronic time points, following a repetitive low-level blast overpressure. Repetitive blast overpressure exposure is frequently experienced by Service members during training exercises. This study was conducted using samples from Service members undergoing heavy weapon fire training exercises, collected as part of the project titled “Investigating Training Associated Blasts.” Serum samples were drawn from these participants (n = 23 per group) at baseline (before training) and then serially at 6 hours, 24 hours, 72 hours, 2 weeks, and 3 months. The miRNA biomarker results show that the expression of miR-451, miR-151-5p, miR-362-3p, miR-328, and miR-9-3p were significantly elevated at 24 hours and

persisted until 3 months post-blast exposure. The representative data for miR-451 and miR-362-3p are shown in Figure 8-31. These miRNA biomarkers are either specifically expressed in the brain or highly enriched in the brain. Therefore, the results suggest a sustained release of these markers from the brain following a blast overpressure exposure event, which may be indicative of a subconcussive injury.

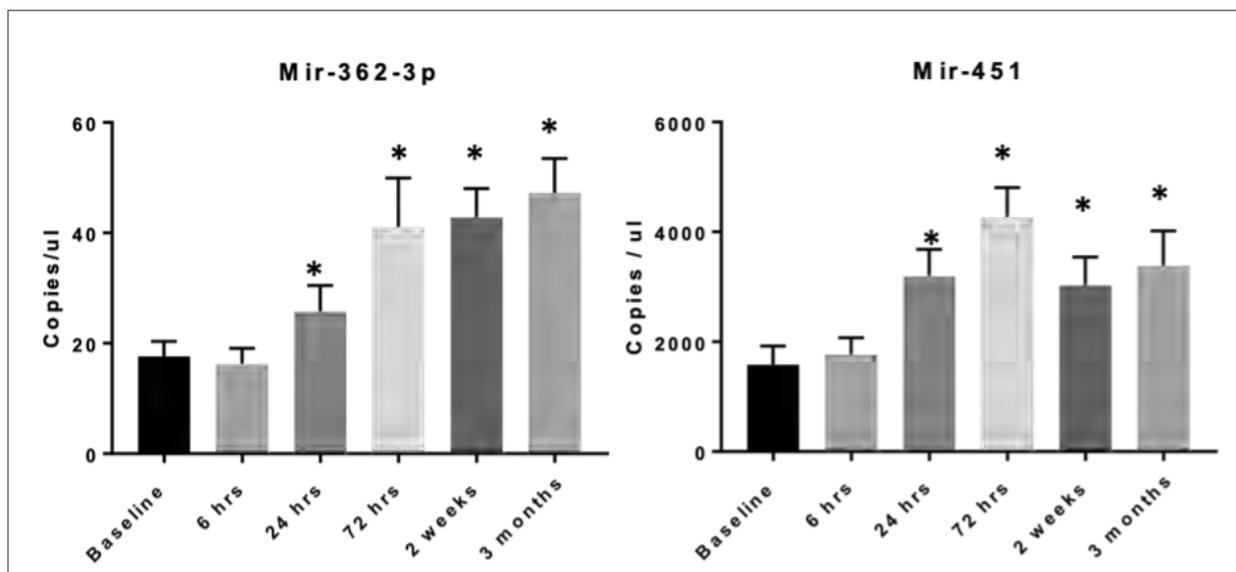
These markers can potentially be used as a tool to determine safe exposure limits during training. Additionally, these markers can provide information for the redeployment of personnel after they experience a blast exposure event.

This effort was supported by CCCRP/JPC-6.

Comprehensive Analysis of Neuroinflammatory Biomarkers in U.S. Army Soldiers with Acute Neurotrauma

Researchers at the University of Missouri School of Medicine, in partnership with the Leonard Wood Institute, are conducting studies aimed at comprehensive analysis of neuroinflammatory biomarkers in acute neurotrauma patients. The underlying rationale is that analyzing specific

FIGURE 8-31: MicroRNA biomarker expression in serum samples from Service members with low-level blast exposure during training exercises. Statistical significance was calculated using one-way analysis of variance (ANOVA) with the baseline as reference and corrected for multiple comparisons. Statistical significance was considered at $p < 0.05$.



changes in the pro/anti-inflammatory cytokines and chemokines will significantly improve the diagnosis of acute neurotrauma in Soldiers. Blood samples were collected from U.S. Army Soldiers with informed consent. Biomarkers were analyzed in the serum of Soldiers (n = 19) and control participants (n = 22) by enzyme-linked immunosorbent assay (ELISA). Findings from the analyses show that the levels of interleukin (IL)-37, ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), glia maturation factor (GMF), fibronectin, vascular endothelial growth factor (VEGF), and IL-8 are significantly increased in the serum of Soldiers compared to control participants (Figure 8-32).

These analyses will enable future work toward the development of a novel panel of neuroinflammation-associated biomarkers in acute neurotrauma, that will significantly improve diagnosis in the Service members, Veterans, and civilians. Additionally, targeted therapies focusing on these neuroinflammation biomarkers may

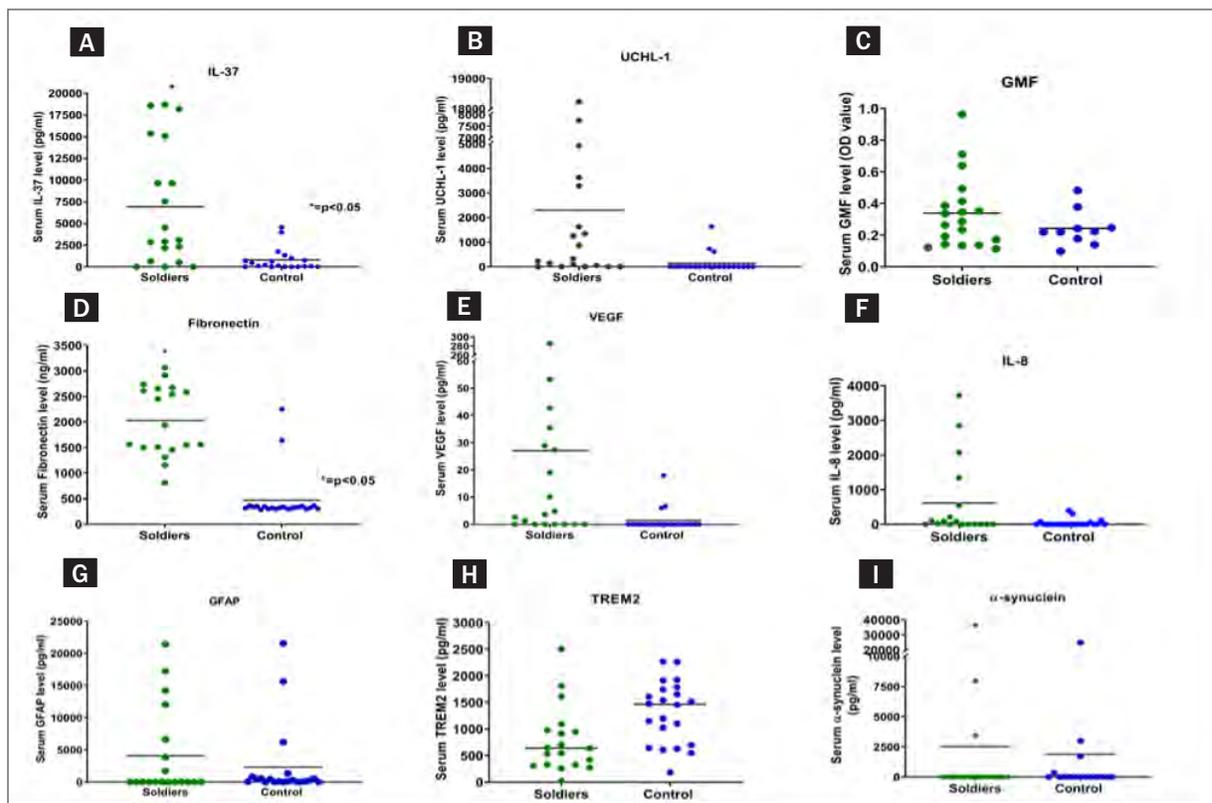
significantly reduce the acute neurotrauma-induced neuroinflammatory response, secondary damage, and improve cognitive function. Future studies will test the novel therapeutic potential of IL-37, cromolyn, and GMF antibody in mouse models of acute neurotrauma.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

Monitoring Acute Neurotrauma by Real-Time Non-Invasive Bioluminescence Imaging

Researchers at the University of Missouri School of Medicine, in partnership with the Leonard Wood Institute, are conducting studies aimed at deciphering molecular and cellular mechanisms underlying acute neurotrauma-induced neuropathology. In a study published in Cellular and Molecular Neurobiology (Raikwar et al., 2020), investigators tested the hypothesis that real-time, non-invasive, high-resolution

FIGURE 8-32: Serum biomarker levels in Soldiers and control participants. Biomarker levels were quantified in Soldier (n = 19) and control participant (n = 22) serum by ELISA.

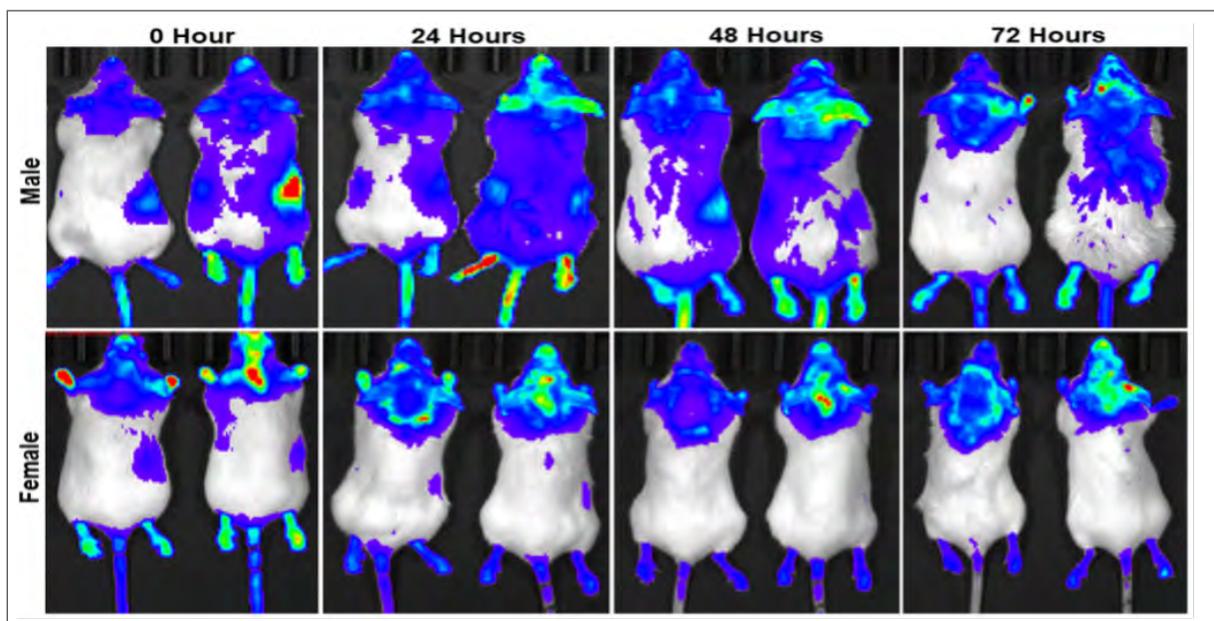


ultrasound and photoacoustic imaging allows rapid monitoring of acute neurotrauma dynamics, which can be used to develop neurotrauma patient-specific targeted precision therapy. The underlying rationale for these studies is that rapid diagnosis of acute neurotrauma by real-time, non-invasive, very high-resolution bioluminescence imaging (BLI) will enable accurate detection of the precise nature of neurotrauma, and the development of an appropriate medical treatment. To test this hypothesis and to gain novel mechanistic insights, nuclear factor-kappa B reporter luciferase (NFκB-RE-Luc) transgenic male and female mice were subjected to weight-drop-induced neurotrauma and real-time non-invasive BLI was performed at different time points. BLI data revealed that acute neurotrauma leads to an immediate and sustained activation of NFκB signaling in a gender-specific manner. In addition to the brain, there is widespread activation of NFκB signaling in multiple organs including heart and kidneys, especially in male NFκB-RE-Luc transgenic mice, indicative of shock wave progression. However, in female NFκB-RE-Luc transgenic mice, acute neurotrauma

induced a very specific and localized activation of NFκB signaling in the brain (Figure 8-33). Further, microRNA (miRNA) data suggest that acute neurotrauma induces significant upregulation of miR-9, miR-21, miR-34a-5p, miR-16-3p as well as miR-155p within 24 hours. Overall, these data suggest that acute neurotrauma-induced glia maturation factor expression causes activation of NFκB signaling, which leads to microglial activation, astrocytosis, and neuronal loss. This is one of the first studies to report immediate, and sustained, activation of NFκB signaling post-neurotrauma using real-time non-invasive BLI. These studies will prove beneficial to gaining novel mechanistic insights underlying acute neurotrauma, discovering novel therapeutic targets, and enabling real-time monitoring of therapeutic responses to neurotrauma-specific gene and stem cell-based precision medicine.

Future studies will be directed toward 1) the establishment of neurotrauma patient-specific, gene-edited induced pluripotent stem cell-based, disease-in-a-dish modeling; 2) NextGen

FIGURE 8-33: Acute neurotrauma induces rapid and sustained activation of NFκB signaling in a gender-specific manner. Real-time non-invasive BLI performed on NFκB-RE-Luc mice within 30 minutes post-neurotrauma revealed a rapid activation of NFκB signaling which was consistently sustained at 24, 48, and 72 hours post-neurotrauma. In male NFκB-RE-Luc mice, BLI signals could be detected in the heart, liver, and kidneys in addition to the brain. However, the BLI signals in female NFκB-RE-Luc mice remained very localized in the brain.



transcriptomic profiling and miRNA sequencing to identify differential gene and miRNA expression; and 3) testing therapeutic efficacy of novel gene editing- and stem cell-based regenerative therapies for acute neurotrauma.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

Analytical Methods to Determine Urinary Metabolites for the Non-Invasive Assessment of TBI

Researchers at Missouri University of Science and Technology, and Phelps Health, have been working in coordination with Fort Leonard Wood to develop and evaluate novel biomarker profiles, using urinary metabolites in relation to TBI severity, as well as individual and cumulative blast forces. The developed a metabolic biomarker panel based on the complex cascade of pathophysiological changes that accompanies TBI, including ionic flux, indiscriminate excitatory neurotransmitter release, increased glycolysis, and oxidative stress. The ultimate objective is to develop a high-throughput assay for the non-invasive assessment of TBI, to aid with detection, prognosis, and more accurate prediction of return-to-duty using measurable metabolic changes.

In FY20, the team of investigators developed several analytical methods using high-performance liquid chromatography–tandem mass spectrometry. The primary method is capable of simultaneously determining eight key metabolites in urine, including glutamic acid, homovanillic acid, 5-hydroxyindoleacetic acid, methionine sulfoxide, lactic acid, pyruvic acid, N-acetylaspartic acid, and F^{2α}-isoprostane, without intensive sample preparation or pre-concentration (Sigler et al., 2020). In addition, the research group developed separate methods for oxidative stress markers, such as linoleic acid and arachidonic acid, and validated enzyme-linked immunosorbent assay (ELISA) for the putative protein biomarkers S100β, glial fibrillary acidic protein (GFAP), neuron-specific

enolase, and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1). This multiplexed biomarker profile is being evaluated through two separate clinical research studies being conducted at the Fort Leonard Wood Urban Mobility Breacher Course and General Leonard Wood Army Community Hospital.

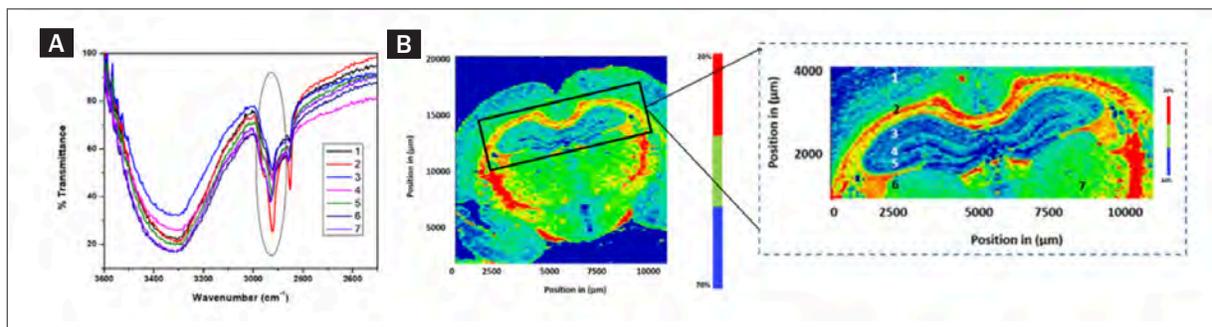
This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

Development of Vibrational Spectroscopic Imaging of Traumatic Brain and Spinal Cord Injury

Researchers at Missouri University of Science and Technology developed label-free vibrational spectroscopic imaging techniques to investigate myelin degradation and axonal degeneration in the open-field blast injury model of TBI, and to study the therapeutic potential of N-acetylcysteine amide (NACA) treatment in TBI processes with the possibility of improving cellular antioxidant defenses and remyelination. Figure 8-34 illustrates the spectroscopy and imaging capabilities to record spatial distributions of specific molecular vibrational fingerprints in brain tissues, such as myelin in the hippocampal formation and cerebellum regions; axons, collagen, fibrotic scar, and inflammatory cells at the lesion site. These recordings encode a large amount of injury information such as myelin degradation, axonal degeneration, inflammation, and scarring, which is potentially useful for diagnostic and therapeutic purposes.

Animals experiencing mild blast injury (induced by detonating 550 g of C4 explosive placed 40 cm above the ground at a distance of 3 m away, performed at Missouri University of Science and Technology's Experimental Mine Facility) were included in the study (n = 16 in the first run; n = 12 in the second run). The animals were divided into four groups for both histopathology evaluations and vibrational spectroscopic imaging studies: 1) control; 2) NACA-treated, no injury (sham); 3) blast-injured (no NACA treatment); and 4) NACA-treated,

FIGURE 8-34: Infrared spectroscopic imaging of unstained healthy rat brain coronal sections on CaF₂ slide at the frequency of 2,920cm⁻¹. Zoom-in scan around the hippocampal formation area and infrared spectra at seven representative locations are presented to show the details of lipid concentrations and myelin distribution.



blast-injured. Preliminary findings in the first run show that neuronal membranes are chemically disrupted via shock wave, and free radical-induced lipid peroxidation, for the blast-injured group samples; which leads to notable changes of vibrational absorptions at 2,924 cm⁻¹ (lipid), 2,849 cm⁻¹ (lipid) and 1,546 cm⁻¹ (Amide II) in particular regions of the cerebrum (hippocampus, cortex, hypothalamus) and cerebellum (granular/molecular layer).

Meanwhile, the NACA-treated, blast-injured group shows similar spectroscopic images as the control sample. An improved second run investigation is ongoing to further demonstrate how the researchers can utilize the developed techniques to study the myelin degradation and axonal degeneration during mild blast injury, and the possible NACA-treatment effects. The study will advance the fundamental knowledge in understanding the injury processes and underlying mechanisms of TBI.

This study was sponsored by the Leonard Wood Institute in cooperation with ARL.

Acute TBI-Induced Mast Cell Activation and Neuroinflammatory Responses

TBI has been shown to induce neuroinflammation, increased blood-brain barrier (BBB) permeability, and microvascular damage in the brain, which may predict future neurodegeneration, cognitive

decline, or psychological disorders. TBI causes immediate primary brain damage (direct damage) and late secondary brain damage (indirect) through neuroinflammatory mechanisms. However, the underlying molecular and structural neurovascular alterations involved in acute TBI pathogenesis are understudied and incompletely understood. Inflammatory mediators secreted from activated glial cells, neurons, and mast cells are implicated in the pathogenesis of TBI, through abnormalities or damage to the neurovascular unit, and may be indicators of secondary injuries in the brain after TBI. Mast cells are located near the blood vessels and implicated in BBB breach, neuroinflammation, stroke, and neurodegenerative diseases, and the FDA-approved mast cell-inhibitor drug, cromolyn, is known to protect neurons and inhibit cognitive decline in various neuroinflammatory conditions. Researchers at the University of Missouri School of Medicine are conducting studies to analyze mast cell activation, neuroinflammation, and microvascular abnormalities in mouse models of TBI, and the extent to which cromolyn can mitigate the pathogenesis of acute TBI and limit its long-term negative health outcomes.

In two recent publications (Kempuraj et al., 2020a; Kempuraj et al., 2020b), acute TBI was induced in mice via a closed-head weight-drop protocol. Neurovascular changes were assessed using immunofluorescence, and quantified by enzyme-linked immunosorbent assay (ELISA). Mast cell

activation, as detected by toluidine blue staining, increased in the brains of mice at 24 and 72 hours after TBI, as compared to mouse brains exposed to a sham procedure (Figure 8-35). Analysis of mouse brains after TBI, relative to sham control brains, showed increased expression of C-C motif chemokine 22, proteinase-activated receptor-2, and vascular endothelial growth factor receptor 2 expression, as well as derangement of tight junction proteins claudin 5 and zonula occludens-1 (ZO-1), which are associated with BBB permeability. At seven days after TBI induction, the researchers found decreased levels of pericyte marker platelet-derived growth factor receptor-beta (PDGFR- β), tight junction proteins junctional adhesion molecule-A (JAM-A), and ZO-1, relative to brains from sham control mice. Further, a group of mice was intraperitoneally administered cromolyn at one hour before, and two and four days after, the TBI protocol. Cromolyn significantly attenuated the acute TBI-associated decrease of PDGFR- β , JAM-A, and ZO-1.

Together, the results suggest that TBI causes BBB damage and that cromolyn-induced inhibition of mast cell activation can suppress the post-TBI

neuroimmune response, and possibly protect against acute TBI brain damage and the chronic pathology underlying neurodegeneration. Further research into this area will aid in the development of therapeutics to limit the pathophysiological consequences of TBI, and reduce the incidence of cognitive decline or psychiatric disorders.

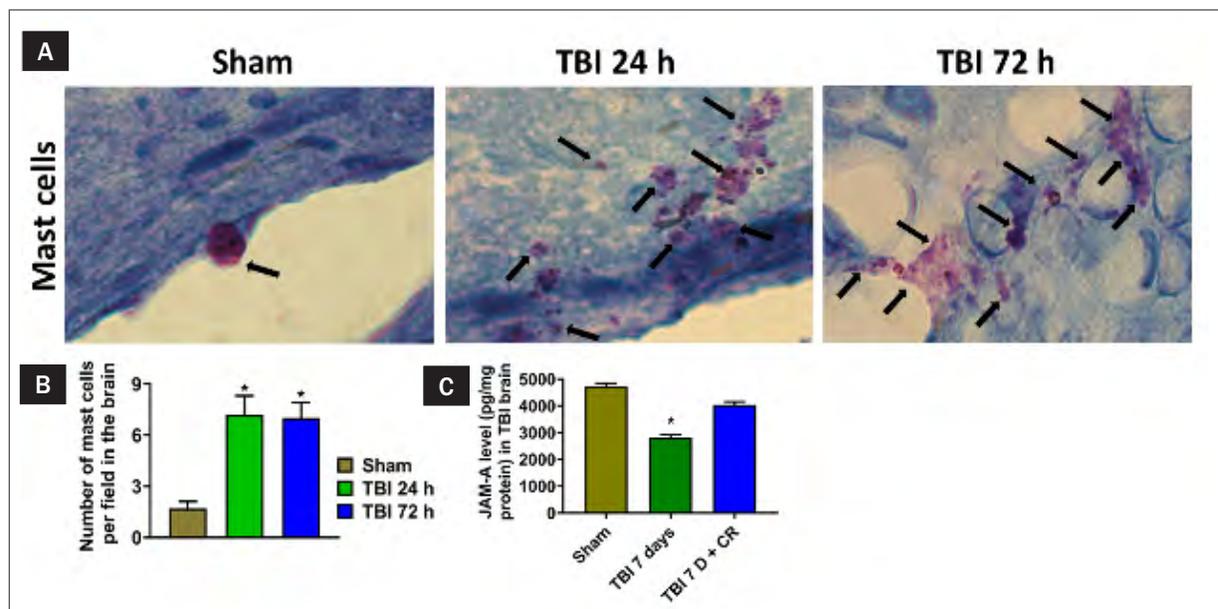
This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

TBI-Induced Neuroinflammation and the Dynamics of Cellular Regulation

TBI and its underreported mild form (mTBI) are prevalent injuries sustained by active-duty Service members, due to blast explosions from conventional weapons and IEDs. TBI causes various secondary molecular and cellular complications in the brain. Primary insults trigger secondary responses, leading to neuroinflammation that can progress to neurodegeneration.

Previous research has shown that, in response to TBI-induced inflammation, levels of the brain-specific, pro-inflammatory protein glia maturation

FIGURE 8-35: (A&B) Weight-drop-induced acute TBI increases mast cell number, degranulation (0.1 percent toluidine blue staining) and (C) decreases tight junction protein JAM-A in the mouse brain. Cromolyn (CR) administration prevents TBI-induced JAM-A decrease in the brain. * $p < 0.05$ versus sham control ($n = 5-6$ mice/group). This figure is originally featured in Kempuraj et al. (2020a) and is licensed under [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).

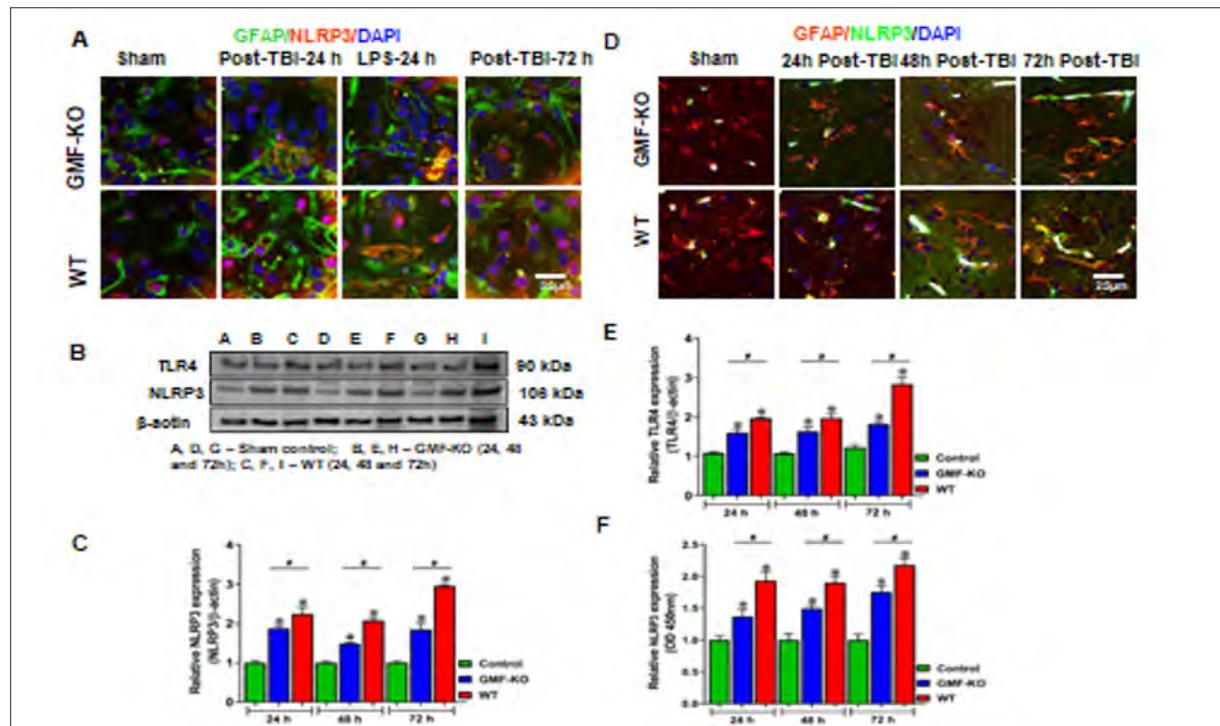


factor (GMF) are increased, with implications for glial cell activation and neurodegeneration. In recent studies conducted by University of Missouri School of Medicine researchers, two animal models of TBI—the weight-drop and controlled cortical impact (CCI) models—point to GMF as a regulator of neuroinflammation, and may serve as a novel blood-based biomarker of TBI.

The investigators induced TBI in both wildtype and GMF-deficient (i.e., GMF-knockout [GMF-KO]) mice. In response to the TBI protocol, reactive astrocytes and activated microglia were reduced in the absence of GMF. TBI induced inflammatory responses through microglial activation and polarization to an inflammatory phenotype, but the absence of GMF promoted the anti-inflammatory phenotype (Ahmed et al., 2020). One mechanism of cytokine production is activation of the nucleotide-binding domain leucine-rich repeat (NLR) family of inflammasomes leading to caspase-1 activation and processing of interleukin-1 β . These studies showed that GMF coordinately increases cellular endoplasmic reticulum stress and regulates

caspase-1 and NLR family pyrin domain containing 3 (NLRP3) activation in TBI (Figure 8-36). The absence of GMF ameliorates neuronal injury and behavioral impairments following TBI, brought about through significant improvement in substantia nigral tyrosine hydroxylase and dopamine transporter expression. There was significant reduction in neuroinflammation, as shown by decreased nuclear factor- κ B activation and reduced expression of inducible nitric oxide synthase and cyclooxygenase-2 (Selvakumar et al., 2020). Using the CCI model of TBI, the investigators found that lipocalin-2 (LCN2) could serve as a molecular link to the severity of TBI by potentiating the action of GMF. LCN2 is undetected in the normal brain or peripheral nerve; however, its expression increases in astrocytes, cortex, and hippocampus after TBI. Heme oxygenase 1 (HO-1) catalyzes the rate limiting step in heme oxidation and is a measure of cellular oxidative stress. Its function is closely associated with mitochondrial ferritin in controlling mitochondrial dynamics. After TBI, increased co-localization of LCN2 is seen with HO-1 (Figure 8-37-Top) and ferritin

FIGURE 8-36: GMF increases the priming of toll-like receptor 4 (TLR4)-mediated NLRP3 activation in TBI. Glial fibrillary acidic protein (GFAP), 4',6-diamidino-2-phenylindole (DAPI), wildtype (WT).



(Figure 8-37-Bottom), which are greatly reduced in the absence of GMF. Increased mitochondrial fragmentation was also found after TBI, with heightened expression of mitochondrial fission proteins (Drp1, Fis1) and decreased expression of fusion proteins (OPA1, Mfn1). In the absence of GMF, fission proteins were decreased, and fusion proteins increased, suggesting that the absence of GMF is neuroprotective in TBI. GMF could serve as a therapeutic target to improve secondary events after TBI, to reverse symptoms in the acute phase.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

Analysis and Comparison of Sports-Related and Blast-Induced TBI

TBI incurred during sports or sustained after exposure to explosive blast continue to burden athletes and Soldiers, and the majority of

sports-related and blast-induced TBI cases are clinically classified as mTBI. Therefore, the comparison of sports-related and blast-induced TBI is a valuable endeavor toward the diagnosis and treatment of mTBI. Researchers at University of Missouri-Kansas City carried out a comparative study on sports-related TBI and blast-induced TBI.

The investigators reviewed the literature; data on biomarkers, imaging studies, and neuropathology; and results from neuropsychiatric tests. Biomarkers for axonal injuries, brain-specific biomarkers, and those for inflammatory response were examined. While sports-related TBI shares many common biomarkers with blast-induced TBI, there are notable differences; for example, glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) levels are diminished in blast-induced TBI but elevated in sports-related TBI.

FIGURE 8-37: (Top) After TBI, increased co-localization of LCN2 is observed with HO-1 and (Bottom) ferritin, which are greatly reduced in the absence of GMF.

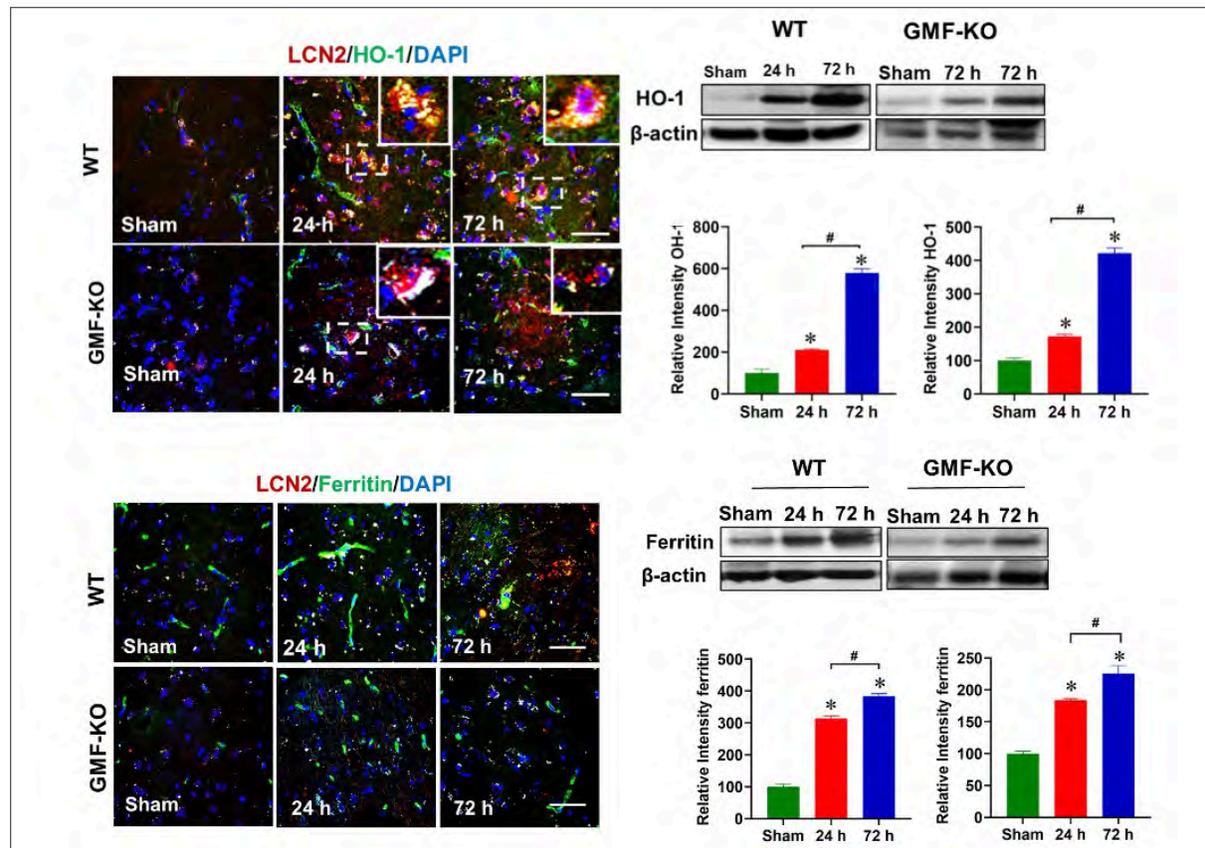




Photo credit: SSG Pablo N. Piedra/U.S. Army

Analyses of brain imaging data show similarities between sports-related and blast-induced TBI. Widespread reduction in cortical thickness has been reported in patients of both sports-related and blast-induced TBI; likewise, hypometabolism is observed via positron emission tomography (PET) scans in both groups. Electroencephalography studies showed reduced phase synchrony across frontal electrodes in both sports-related and blast-induced TBI, indicating reduced functional connectivity. Despite notable differences in individual studies, brain imaging results across several techniques indicate similar types of abnormalities over the same brain regions in both sports-related and blast-induced TBI.

When neuropsychological outcomes between TBI cases were analyzed, both patient groups experienced most of the neurological issues assessed. Interestingly, PTSD symptoms may not be as prevalent and long-lasting in TBI sustained during sports, suggesting that the environment in which the injury occurs is significant.

Because blast-induced TBI and sports-related TBI are likely fundamentally similar conditions, clinical management of blast-induced TBI in Soldiers will continue to benefit from knowledge gained in studying sports-related TBI.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

Predictive Modeling of Sports-Related Concussions Using Clinical Assessment Metrics

Concussion diagnosis can be challenging, particularly when relying on a physician's interpretation of varied clinical assessments (e.g., symptoms, balance, neurocognitive status) that lack universally accepted thresholds. Researchers at Missouri University of Science and Technology and Missouri State University have developed a predictive modeling framework, based on machine learning techniques (Figure 8-38), that utilizes clinical assessments at 24–48 hours post-injury, in a multi-factor model, to classify concussed and

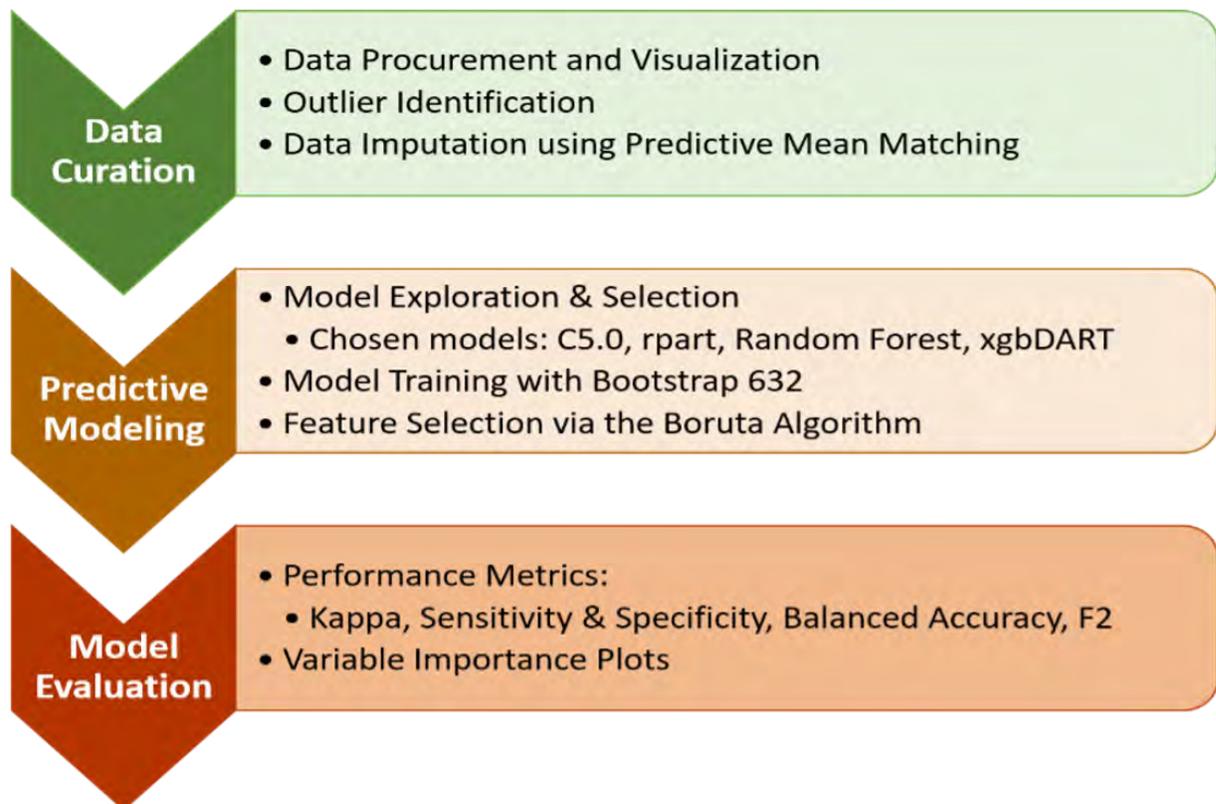
non-concussed individuals. These models could provide an automated means to flag concussed patients by having a trained proctor administer the assessments before a patient is seen by a physician. This can be especially useful in remote locations with limited access to doctors. Machine learning-based prognostics could provide initial flag recommendations and thus mitigate risk of further damage by underestimation of a Service member's concussion, or its severity.

After initial data curation steps to ensure robustness, a wide variety of classification models were initially explored and four models (C5.0, recursive partitioning [rpart], random forest, and xgbDART), were selected for detailed investigation on a dataset obtained from the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System. A total of 13 features from four widely used assessments, (Balance Error Scoring System [BESS], Standardized Assessment

of Concussion [SAC], Brief Symptom Inventory-18 [BSI-18], Immediate Post-Concussion Assessment and Cognitive Testing [ImPACT]), were considered as input features after feature selection with the Boruta algorithm. All models showed significantly better accuracy than the ZeroR classifier that assumes every patient has a concussion. The C5.0 and random forest models performed the best across different performance metrics. Variable importance plots for the different models revealed the importance of a few key variables, across the models, that may aid clinicians in interpreting which assessments are most useful in aiding concussion classification. While further work is needed, these initial results show promise for potential clinical use in concussion diagnosis protocol, especially in remote locations.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

FIGURE 8-38: Framework for predictive concussion diagnosis modeling.



Description of Sensorineural Hearing Loss Diagnoses Among Service Members in the Blast-Related Auditory Injury Database

Auditory injuries are common among military personnel and can severely impact communication and situational awareness. Individuals exposed to blast are at risk for sensorineural hearing loss (SNHL) due to auditory system damage from the blast wave or hazardous noise associated with the blast. SNHL is the most common type of permanent hearing loss and is the result of inner ear disease or damage. To better understand the burden of SNHL among U.S. military personnel, researchers at NHRC and Illinois State University examined the prevalence of SNHL diagnoses among male Service members, following a combat injury, and identified factors associated with the diagnosis of SNHL. The Blast-Related Auditory Injury Database was used to identify male Navy and Marine Corps military personnel who had hearing conservation audiograms within 12 months prior to, and following, combat injury and did not have pre-injury hearing loss. SNHL diagnoses were obtained from the Military Health System Data Repository using hearing loss relevant International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes.

The study population included 1,186 male Service members, of whom 7.5 percent had a diagnosis of SNHL following blast injury in their medical record. Of those with an SNHL diagnosis (n = 89), 60.7 percent were infantry and 55 percent were injured by a blast. Post-injury SNHL diagnoses were also associated with higher injury severity scores and older age. Tinnitus, diagnosed at a far-forward military treatment facility in theater, was reported in 22.5 percent of those with SNHL versus 11.8 percent of those without SNHL (p < 0.05). Additionally, 40.5 percent of those with SNHL diagnoses also had post-injury hearing loss,

according to audiometric data. These findings provide information on how operational injury characteristics relate to SNHL diagnoses and warrant further examination into the relationship between audiometric data and diagnoses. This disparity could result from cochlear damage that occurs without measurable audiometric hearing loss, but this needs to be further investigated.

The results described in this research could provide guidance as to who should receive prioritized audiology care, based on demographic and injury characteristics.

This research was supported by BUMED.

Development of the Smart Oxygenation System Prototype

Researchers at the University of Texas Medical Branch, Galveston, have developed and been granted a patent for a Smart Oxygenation System (SOS), which can assess and provide early warnings of pulmonary distress (Kinsky et al., 2020). The SOS device incorporates the ExSpiron and FreeO₂ systems in closed-loop oxygen control mode, along with a pulse oximeter. The SOS allows for ventilatory parameters, primarily from ExSpiron, and oxygenation parameters from the FreeO₂ pulse oximeter + flow sensor. Detailed warning alerts and alarms are incorporated into the SOS software. The SOS decision support for at-risk casualties will more rapidly assess and treat pulmonary injury through automated monitoring, that alerts of pulmonary distress and initiates life-saving interventions to reduce the severity of acute respiratory distress syndrome.

This effort was managed by CDMRP with support and programmatic oversight by CCCRP/JPC-6.

Technology Transition of Two Non-Invasive Device Prototypes to Measure Tissue Hemoglobin Oxygen Saturation and Dynamic Blood Volume

Researchers at the University of Michigan have developed two non-invasive monitoring devices that can be used for the management of polytrauma patients in prolonged field care settings. The first, a Resonance Raman Spectroscopy (RRS) device prototype, is designed to measure tissue hemoglobin oxygen saturation (StO₂) of the buccal mucosa, as a substitute for central or mixed venous hemoglobin oxygen saturation (ScvO₂) and, potentially, lactate. The intellectual property for this work has been successfully licensed to an industry partner, Pendar Technologies, to allow for continuous improvement and to develop regulatory approval and commercialization strategies (Ward et al., 2006).

The second device, the Dynamic Respiratory Impedance Volume Evaluation (DRIVE), is designed as a substitute for ultrasound of the inferior/superior vena cava and central venous pressure. The DRIVE works by passing a small amount of electricity through tissue, to measure blood volume moving in and out of the tissue during breathing, as opposed to RRS-StO₂, which uses a special wavelength of light to determine how much oxygen a tissue is receiving. The research has been successfully licensed to an industry partner, New Vital Signs, to allow for continuous improvement and to develop regulatory approval and commercialization strategies (Ward et al., 2014).

Both devices continue to be evaluated in clinical settings and are expected to improve survival and mitigate tissue injury and organ failure by better informing the use of supportive treatments, in a precision manner, for goal-directed therapy of severe hemodynamic compromise.

This effort was managed by CDMRP with support and programmatic oversight by CCCRP/JPC-6.

Development and Testing of a Transdural Sensor to Monitor Spinal Cord Oxygenation

Early management of acute spinal cord injury (SCI) can significantly impact patient outcomes; however, a major limitation in individualized management guidelines is the lack of a non-invasive, real-time mechanism for monitoring and tracking hemodynamic changes within the spinal cord. Researchers at the University of British Columbia developed a relatively non-invasive, implantable, near-infrared spectroscopy (NIRS) sensor (Figure 8-39 and Figure 8-40) with the goal of facilitating personalized acute SCI management. With funding from an FY15 Spinal Cord Injury Research Program (SCIRP) award, this research team demonstrated that the NIRS sensor can provide continuous oxygenation and hemodynamic measurements, over a seven-day post-SCI period, in a porcine model. This work was published in the *Journal of Neurotrauma* (Shadgan et al., 2019; Cheung et al., 2020). Furthermore, the NIRS measurements showed statistically significant correlations with each of the invasively collected intraparenchymal measures, confirming that the changes observed by the non-invasive NIRS sensor reflect what gold-standard invasive measurement methods would collect. The research team has recently received funding to continue this work through the Defense Advanced Research Projects Agency's (DARPA) Bridging the Gap Plus (BG+) Program. This multi-institutional, multi-national, multi-million-dollar effort will develop a system of systems that will utilize the NIRS sensor to develop a patient-specific, automated approach for SCI monitoring and stabilization. The non-invasive real-time monitoring by the NIRS system is a major step toward personalized acute SCI management and may have a real impact on improving long-term patient outcomes.

This effort was supported by SCIRP with program interest by CRMRP/JPC-8.

FIGURE 8-39: Schematic of NIRS sensor application on exposed dura after laminectomy is performed in cervical spine.

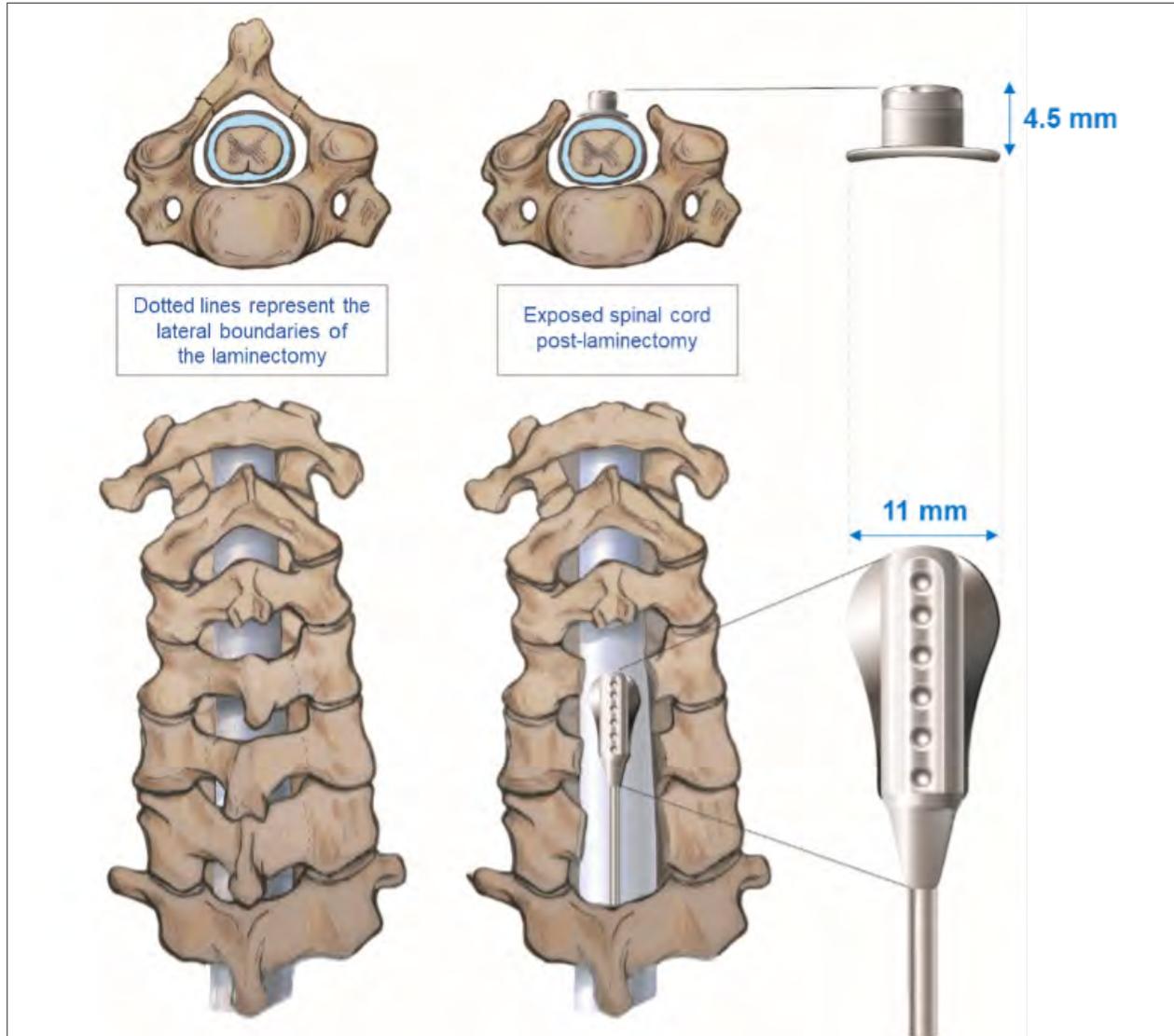
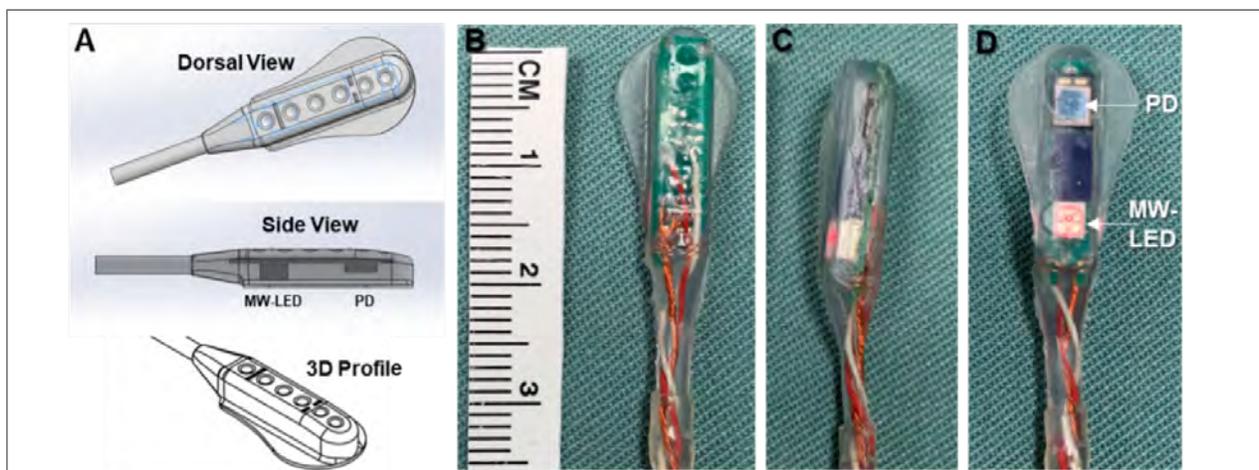


FIGURE 8-40: V4 NIRS Sensor. (A) The design drawings of the NIRS sensor with flaps widened only at the tip to facilitate removal. (B) Dorsal view of the sensor. Note that the “dimples” on the dorsal surface are to “dock” a lateral connector down onto the dorsal surface to provide stability and prevent the sensor from lifting off the dura. (C) Lateral view of the sensor. (D) Ventral view of sensor. Photodetector (PD), multi-wavelength LED emitter (MW-LED).



Pharmaceutical Interventions

Precision Medicine to Determine the Ideal Opioid for Pain Management Following Lower Extremity Surgery

Opioids are used for pain management following lower extremity surgery, and the need to sufficiently control pain is critical to avoiding adverse outcomes. It is known that individual patients metabolize opioids differently, leading to varying levels of analgesia. Researchers at the University of Louisville School of Medicine are studying patients' cytochrome P450 2D6 (CYP2D6) genotypes to determine how effectively each genotype converts hydrocodone to the active metabolite hydromorphone, and how plasma concentrations of hydromorphone correlate to analgesia.

In 271 patients undergoing lower extremity surgery, researchers found that groups of individuals metabolized hydrocodone differently, and only 15 percent had detectable plasma hydromorphone. In addition, they found that CYP2D6 inhibitors were commonly co-administered, which reduced the effectiveness of hydrocodone. These results suggest that an individual's genotype and drug-drug interactions can significantly affect pain control by opioids after surgery.

Further research is ongoing that may lead to precision medicine for CYP2D6 genotypes, and researchers plan to educate clinicians about the impact of CYP2D6 inhibitor co-administration. This research is needed to create clinical practices for sufficient, personalized pain management. Additionally, understanding individual patient genotypes and drug-drug interactions will lead to appropriate opioid pain management after surgery.

This effort was managed by CDMRP with support and programmatic oversight by CRM/RP/JPC-8.

Development of Adjunct Therapies to Enhance Functional Outcomes of Volumetric Muscle Loss Injuries

Service members who endure combat-related traumatic extremity injuries often experience volumetric muscle loss, which can contribute significantly to disability. Considerable efforts have been made toward developing therapeutics capable of promoting regeneration of functional skeletal muscle units within the affected musculature. Unfortunately, the heightened inflammatory and fibrogenic nature of the endogenous response to volumetric muscle loss has been a critical limiting factor to all such regenerative approaches to date.

To address this need, the EACE team at USU has been actively pursuing and evaluating a myriad of therapies aimed at modulating the local volumetric muscle loss wound environment, in a manner that unlocks greater efficacy of promising regenerative medicine therapies, towards the ultimate goal of restoring function to volumetric muscle loss affected areas (Goldman et al., 2020). Recent preclinical work has included the evaluation of anti-inflammatory drugs targeting the arachidonic acid pathway in concert with a biologic scaffolding. Results showed that the experimental interventions mildly influenced the local inflammatory response of the volumetric muscle loss wound bed, but ultimately did not alter wound healing or functional outcomes mediated by the primary intervention (i.e., biologic scaffolding).

Subsequent efforts have built on these foundational efforts and shifted focus to novel interventions targeting both inflammatory and fibrogenic mechanisms with the potential to exert greater control of the volumetric muscle loss wound environment and improving clinical outcomes for Service members.

This study was sponsored by EACE, USAMRDC, and the National Institute of Biomedical Imaging and Bioengineering.



Photo credit: Phil Sussman/ U.S. Army

Cardio-Centric Hemodynamic Management Improves Spinal Cord Oxygenation and Mitigates Hemorrhage in Acute Spinal Cord Injury in a Porcine Model

Current clinical standard of care for acute treatment immediately after an SCI includes vasopressor therapy to enhance blood flow to the spinal cord. This therapy carries risk of hemorrhage and lacks rigorous individual guidelines for timing and dosage. Therefore, there is a need for targeted pharmacological treatments that lack some of the side effects of acute SCI care. A team of researchers at Vancouver General Hospital is investigating the contribution and timing of cardiovascular dysfunction after SCI and how this may contribute to secondary injury. In a Nature Communications publication, Williams et al. (2020) assessed whether cardiovascular dysfunction occurs immediately after injury, and examined the effects of pharmacologically rescuing this dysfunction on spinal cord oxygenation (SCO₂)

and blood flow (SCBF) in pigs with high-thoracic SCI. High-thoracic SCI significantly impaired cardiovascular health and caused reductions in SCO₂ and SCBF within hours post-injury. These acute and chronic impairments were reversed using the β -agonist dobutamine, with higher effectiveness than vasopressor therapy. These results suggest that treatment focused on cardiovascular management is an advantageous alternative to vasopressor therapy in acute and chronic SCI treatment. Management of cardiovascular blood pressure and contractility represents a potentially safe method of acute SCI treatment with fewer negative side effects and increased protection, compared to current standards of vasopressor therapy.

This effort was supported by the SCIRP with program interest by CRM RP/JPC-8.

Acute Treatments to Prevent Tissue Loss and Chronic Pain and Increase Locomotor Recovery After Spinal Cord Injury

Following traumatic spinal cord injuries (often concomitant with polytrauma), damage to nervous tissue prevents incoming pain signals from being correctly regulated, resulting in hyperexcitable pain circuits. This can worsen spinal cord hemorrhage and activation of pro-inflammation pathways, exacerbates difficulties with rehabilitation, increases negative secondary health effects, and contributes to chronic pain symptoms. SCI pain is often severe and debilitating, and chronic pain critically impacts an individual's quality of life. There are very few safe and effective options for individuals to manage their pain. Early interventions that mitigate pain perception and reduce negative spinal cord pathology effects, while in a forward environment, are of critical importance to the Service member.

One such early intervention might be a pharmacological treatment immediately following an SCI. Researchers at Texas A&M University have determined that in a rat model of SCI, early reduction of hemorrhage and inhibition of pro-inflammatory pathways resulted in improved pain outcomes (Davis et al., 2020). Lidocaine administration after a spinal cord injury, but prior to shock, was very effective at attenuating hemorrhage and activation of pro-inflammatory pathways that lead to spinal cord tissue loss. This resulted in greater gains of locomotor function post-injury and decreased pain behaviors in the animals. Lidocaine may therefore hold promise as a far-forward, non-opioid intervention to prevent spinal cord damage, reduce chronic pain, and improve quality of life after an SCI.

This effort was supported by SCIRP with program interest by CRMRP/JPC-8.

TBI Drug Treatment Program Selects Drugs and Begins Platform Adaptive Clinical Trial Design for Moderate TBI Treatments

The USAMMDA WBH PMO manages the TBI Drug Treatment (TBI-DT) product development effort and leads its Integrated Product Team (IPT). USAMMDA has partnered with the University of California, San Francisco, and Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Network, since 2018, to test multiple TBI drug candidates in Phase 2 clinical trials. TRACK-TBI Network is a vertically integrated group of TBI subject matter experts, clinicians, academics, and clinical trial sites that leverages the advancements made by the TBI Endpoints Development Initiative (TED Initiative). The TRACK-TBI Network, along with the TBI-DT IPT, will assess TBI drug candidates that are ready for Phase 2 trials.

Currently, there are no FDA-approved drugs for the treatment of TBI. The goal of the first increment of the TBI-DT IPT is to deliver an FDA-approved drug to limit or reverse neurologic damage and/or slow progression of injury, decrease morbidity and mortality, improve cognitive outcomes, and restore brain function to Service members who have sustained a moderate TBI.

More than 30 clinical trials for TBI drugs have failed, despite decades of research by government and private industry drug sponsors. This has prompted a paradigm shift in the TBI-DT acquisition strategy for TBI drug pipeline development, towards risk reduction in Phase 2 clinical trials. Focused investment in Phase 2 trials will improve the quality and quantity of TBI drugs in the pipeline of development, fully characterize drug candidates prior to entering Phase 3 trials, and thereby de-risk further investment in continued development toward FDA regulatory clearance. The TRACK-TBI Network is partnering with an existing clinical trial network that has a proven capability to recruit individuals with TBI for clinical studies.

The drug selection evaluation included a request for TBI drug proposals, with selected proposals culminating in presentations at drug evaluation industry days. Risk analysis, compatibility of multiple drugs to be tested in adaptive platform trial design, and drug selection were key areas of focus in FY20. Several generic drugs are currently under evaluation for compatibility as multiple arms in a platform adaptive trial design. Testing generic drugs represents the lowest risk and fastest regulatory pathway for TBI drug development.

This program is sponsored by the USAMMDA WBH PMO.

Effect of Cannabinoid Type-2 Receptor Therapy on the Visual System Using the FDA-Approved Drug Raloxifene After TBI or Ocular Trauma

Visual impairments and deficits after traumatic brain or eye injury often result in the inability to return to duty, with additional life-long impairments. Both can occur as a direct result of blast overpressure, or as secondary effects stemming from blunt impact. Researchers at the University of Tennessee, Health Science Center have been testing an FDA-approved estrogen receptor drug, raloxifene (indicated for osteoporosis treatment), that has also been shown to exhibit inverse agonist effects on cannabinoid type-2 (CB2) receptors. The researchers have been evaluating the benefits of raloxifene for reducing visual deficits and retinal and optic nerve damage after mTBI, or closed-globe ocular injury, in standard mouse models of focal blast mTBI, impact mTBI, or ocular blast injury. In a study published in *Experimental Neurology* (Honig et al., 2019), two doses of raloxifene were evaluated in a blast-induced TBI mouse model and subjects were tested for contrast sensitivity, visual acuity, electroretinography (ERG), light aversion, and pupillometry. Histological analyses were also conducted.

Results from this study showed that, when administered within a 48-hour window, raloxifene can rescue functional deficits, including visual acuity

and contrast sensitivity loss; ERG deficits, increased light aversion, and pupillary constriction defects. Moreover, raloxifene administration also rescued the associated visual pathologies after mTBI, such as optic nerve axon loss. The drug benefit was found, by biochemical and histochemical analysis, to have its basis in a biasing of microglia from the harmful M1 phenotype toward the helpful M2 state. More recently, the researchers showed that raloxifene, delivered by the same post-trauma regimen used for blast-induced TBI, yields similar benefits following impact TBI or ocular blast injury; rescuing functional deficits such as visual acuity and contrast sensitivity loss; ERG deficits, increased light aversion, and pupillary constriction defects; and also rescuing visual system pathology, such as optic nerve axon loss. The researchers believe that these results could support Phase 2 testing of raloxifene as a therapy for mTBI and ocular blast injury. Following successful Phase 2 testing, raloxifene could be adopted as a treatment to speed recovery and lessen long-term deficits from visual system impairment caused by mTBI or closed-globe ocular injury.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CRM/RP/JPC-8.

Development of Blast-Induced TBI Models and Potential Therapeutics Using Nanodelivery of FDA-Approved Non-Biologics

Research at ONR has sought to determine the mechanisms mediating physiological effects arising from blast-induced TBI. In vitro brain endothelium models were developed to detect and quantify the extent of injury in response to simulated blasts. Tissue engineering approaches were utilized to construct biosystems that mimic the structure and function of the blood-brain barrier (BBB). In response to simulated blasts, the brain endothelium showed formation of a lesion (~0.2 mm diameter) devoid of brain endothelial cells that, if left untreated, may allow diffusion of macromolecules from circulating blood to the brain tissue. Notably, MRI resolution is typically ~1 mm, suggesting that

blast-induced sub-millimeter lesions in the brain are below the MRI resolution limit. Large tracers (i.e., 3–10 kDa dextran) were used to monitor diffusion and estimate permeability across the BBB (Figure 8-41). Unsurprisingly, the permeability of large molecules through the lesion was significantly increased. This work was published in Scientific Reports (Inyang, Abhyankar, et al., 2020).

As a potential therapeutic treatment to repair the damaged lesion, the investigators developed and applied a nanodelivery method for administration of FDA-approved triblock copolymer Poloxamer P188 and an antioxidant, N-acetylcysteine (NAC). The goal was to identify the injured cells only

(diagnostic), and to target-deliver therapeutic non-biologic compounds to restore the structure and function of the brain endothelium. This concept led to the development of theranostic repair of the injured brain tissue (Figure 8-42; Non-provisional U.S. patent application filed: “Target delivery of non-biologics through nanotechnology for tissue repair”). This work was published in American Chemical Society Omega (Inyang, Kuriakose, et al., 2020).

In summary, blast-induced mechanical injury is observed to modulate the organization and permeability of the endothelium. Because an injury to the brain endothelium typically induces a high expression of cell surface markers (i.e., E-selectins),

FIGURE 8-41: Schematics of blast chamber and a brief flow of experimental design from culture insert to blast chamber and diffusion chamber. (A) Cell culture insert; green cell tracker showing that the membrane supports endothelial cell culture monolayer. (B) Diagrammatic representation of the simulated blast chamber. (C) Schematic depiction of the diffusion chamber with a monolayer of cells on the luminal side of the membrane. (D) Permeability was measured by adding fluorescent dextran in the luminal chamber and measuring the time-dependent concentration in the abluminal chamber. Poloxamer P188 was shown to significantly reduce the permeability, suggesting the lesion induced by blast was at least partially repaired. Images originally appear in Inyang, Abhyankar, et al. (2020) and are licensed under [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).

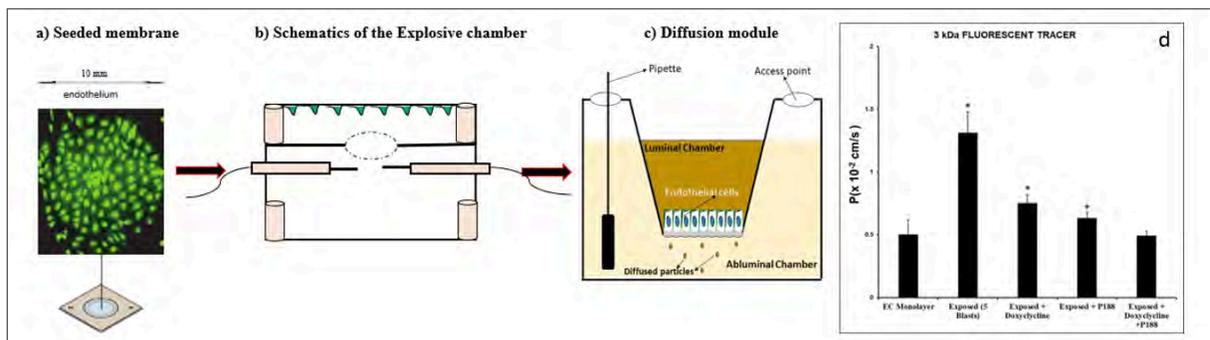
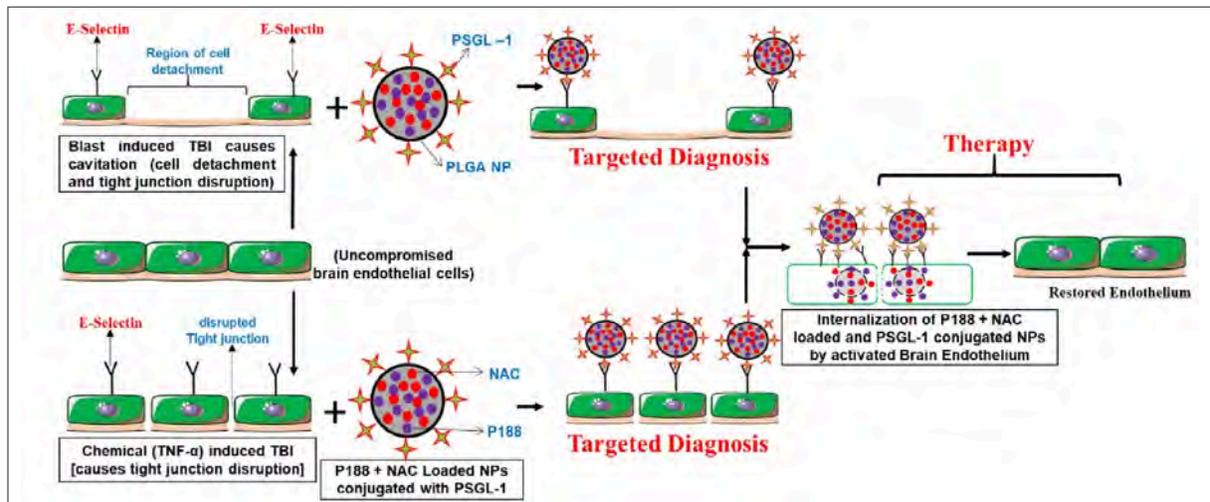


FIGURE 8-42: Illustration demonstrating the proposed theranostic approach. Injuries were simulated by either a mechanical trauma or using an inflammatory factor for comparison purposes. P-selectin glycoprotein ligand-1 (PSGL-1), tumor necrosis factor alpha (TNF- α). Image originally appears in Inyang, Kuriakose, et al. (2020) and is licensed under [ACS AuthorChoice](https://acs.org/authorchoice).



poly(lactic-co-glycolic acid) (PLGA) nanoparticles were engineered to encapsulate the two therapeutic non-biologics (P188 and NAC) and decorate them with ligands to specifically target the E-selectin. This theranostic approach was proven efficacious and demonstrated evidence of repair of the injury site and restoration of normal permeability in the brain endothelium. The tunable properties of PLGA nanoparticles were exploited to develop a targeted drug delivery strategy, combining the specificity of ligand/receptor interaction with therapeutic reagents. If built-upon in future work, this strategy may provide theranostic treatments for blast-related brain endothelium injuries.

This project was sponsored by ONR.

Development of Antioxidant Therapy and Oxidative Stress Biomarker Assay for Blast-Induced TBI in Rat Models

Interdisciplinary researchers at Missouri University of Science and Technology are evaluating the efficacy of an antioxidant therapy, in conjunction with an oxidative stress biomarker assay, for effective diagnosis, prognosis, and treatment of acute TBI. Blast exposure is one of the most common causes of TBI in active-duty Service members. After initial impact, the brain undergoes a delayed trauma—or secondary injury—where reduced cerebral blood flow results in hypoxia, a cascade of excitotoxic events, and generation of oxidative stress. Free radical-induced oxidative damage reactions, and membrane lipid peroxidation, are among the best-validated secondary injury mechanisms in TBI models. Therefore, the discovery of antioxidants that inhibit free radical-induced lipid peroxidation, and its neurotoxic consequences, has great potential as a pathway toward therapeutic drugs for the prevention and treatment of TBI.

Endogenous antioxidants, specifically glutathione (GSH), protect cells from oxidative stress after TBI. Accumulation of reactive oxygen species causes GSH to be oxidized to glutathione disulfide (GSSG), which alters the GSH/GSSG ratio, and leaves the

post-TBI brain relatively deficient in antioxidant defenses. Cysteine prodrugs, N-acetylcysteine and N-acetylcysteine amide (NACA), are GSH precursors and can increase GSH levels. NACA has comparatively higher permeability through the blood-brain barrier, and cellular and mitochondrial membranes. Therefore, the thiol-based antioxidant, NACA, was investigated as a potential candidate therapeutic agent for the prevention and treatment of TBI.

The preventative and therapeutic efficacy of NACA was examined in Sprague Dawley rats. Following seven days of oral administration with daily 250 mg/kg doses of NACA, rats were exposed to an explosive blast, and continued the treatment for another two days. The controlled open-field blast was conducted at the Rock Mechanics and Explosive Research Center at Missouri University of Science and Technology. Blast settings were controlled to generate shock waves simulating those in battlefield blasts. Two different distances were chosen to generate different resultant pressures, which should cause mild-to-moderate TBI. On day ten, rats were euthanized to collect the urine, blood, and brain samples for biomarker analysis. Oxidative stress biomarkers such as GSH, GSSG, N-acetylaspartic acid (NAA), 5-hydroxyindolacetic acid, F_{2a} -isoprostane, 4-hydroxynonenal, and malondialdehyde were analyzed using liquid chromatography-tandem mass spectrometry-based methods.

The effectiveness of antioxidant pre-treatment in reducing oxidative stress was indicated by the significantly lower levels of biomarkers, such as NAA, in urine from the rats that were treated with NACA antioxidant prior to the blast exposure. Additional work, such as analytical method optimization, treatment regimen and dose response studies, and blast parameter adjustment, is planned with the ultimate goal of developing therapeutic drugs.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.



Photo credit: Sgt. Luke Kuennen/ U.S. Marine Corps

Assessment of a Novel Non-Surgical Debridement Technology

Necrotic tissue from a burn injury is typically removed by surgical debridement. However, this procedure is commonly associated with blood loss and the removal of viable, healthy tissue. For some patients and contexts, such as extended care on the battlefield, it would be preferable to remove devitalized tissue with a nonsurgical debridement agent. Researchers from the U.S. Army Institute of Surgical Research demonstrated that a proprietary debridement gel (SN514) was effective at debriding both deep-partial thickness and full-thickness burn wounds using an established porcine thermal injury model (Stone, Jockheck-Clark, et al., 2020). SN514 gel treatment did not damage uninjured tissue, as demonstrated by a lack of edema, erythema, or inflammation of the intact skin surrounding the treated wounds. These data demonstrate that SN514 gel is capable of debriding necrotic tissue and suggest that SN514 gel could be a useful option for burn wound management in austere conditions, such as in multi-domain operations and prolonged field care scenarios.

This research was supported by CCCRP.

Non-invasive Fluid Resuscitation of Severe Burn Casualties in Forward Environments

High volumes of intravenous (IV) fluids are often given to patients with severe burns in order to maintain end organ perfusion. However, the use of IV fluids can lead to morbidities and even mortality associated with fluid overload. Additionally, the feasibility of access and the administration of IV fluids can be challenging in mass casualty situations, as well as in the prolonged field care environment. Researchers from the U.S. Army Institute of Surgical Research have identified enteral resuscitation as a promising strategy for fluid resuscitation of burn casualties (Gomez et al., 2018). After a 40 percent total body surface area burn, pigs were either water-restricted, given ad libitum access to water, or were given a volume-matched World Health Organization Oral Rehydration Salt solution (ORS). The use of ORS increased total urine output in this study, and led to similar hemodynamic recovery as is observed with IV fluid resuscitation in this model. The use of ORS versus IV resuscitation is currently

being studied in an observational, prospective clinical study in burned patients at the U.S. Army Burn Center. Methods for fluid resuscitation of after severe burn wounds, that are easy to use and reduce logistical burdens in the prehospital environment, could save lives and optimize recovery following potentially debilitating burn injuries.

This research was supported by CCCRP.

Surgical Interventions

Analysis of Medical Procedures Performed by Forward Surgical Teams to Determine the Cumulative Attributable Burden

A total of 27,251 medical procedures performed by Forward Surgical Teams (FST) in Afghanistan during 2008–2014 were ranked by frequency, mortality, and morbidity to determine the cumulative attributable burden. This study, published in *Military Medicine* by Staudt et al. (2020), identified 10 procedure groups that accounted for 75 percent of FST operative case burden, 4 of which were treatments for limb-threatening injuries. The study also identified infrequently conducted, high-risk procedures, the most commonly encountered morbidity findings in survivors, and the overall volume of fluids and blood products provided to casualties. Cumulatively, this information will prove helpful in establishing surgical benchmarks for care provided in similar environments and in identifying training and skillsets needed by FSTs. In addition, research and performance improvement activities can be targeted toward the most clinically relevant areas.

This effort was managed by CDMRP with support and programmatic oversight by CCCRP/JPC-6.

Development of a Distal Perfusion Stent for Portable Positioning and Hemodynamic Monitoring

Non-compressible torso hemorrhage often is a preventable cause of battlefield mortality. Researchers have been working to find hemorrhage control solutions that could be used in austere battlefield environments to stabilize injured Warfighters. In this study, a research team from the University of Pittsburgh developed the Rescue Stent, a distal perfusion stent. This device has branch perfusion and radiofrequency sensors for portable positioning and hemodynamic monitoring. In research published in the *Journal of Trauma and Acute Care Surgery*, Go et al. (2020) tested the device in an animal model of non-compressible hemorrhage by comparing the Rescue Stent to aortic balloon occlusion methods for damage control. Following vascular repair and recovery, the study team evaluated a number of outcomes, including hemodynamics, blood loss, and survival. Results showed that the Rescue Stent provided rapid hemorrhage control and favorable outcomes of blood flow, negligible organ injury, and improved survival over the course of the study. The stent has been optimized and redesigned for human anatomy ahead of future testing, and researchers have been granted a patent on this technology (Tillman et al., 2019).

Rather than occluding blood flow with Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA), an alternative approach, using a distal perfusion stent, permits successful control of hemorrhage while still allowing distal blood flow beyond the injury, resulting in superior clinical outcomes for major venous injuries.

This effort was managed by CDMRP with support and programmatic oversight by CCCRP/JPC-6.



Photo credit: Phil Sussman/ U.S. Army

Improved Guidelines for Use of Complete Resuscitative Endovascular Balloon Occlusion of the Aorta in Patients with Thoracic-Abdominal Trauma and Pulmonary Contusions

Hemorrhage on the battlefield, often resulting from blast trauma, is the leading cause of mortality in Service members with potentially survivable injuries. Critically injured Service members with thoraco-abdominal trauma, leading to hemorrhagic shock, have been successfully resuscitated with the use of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). While this technology offers many short-term advantages for survival, preliminary studies indicate longer-term cardiac dysfunction and distal ischemia, which may affect proximal organs such as the heart, lungs, and brain (Hoareau et al., 2019).

To investigate these repercussions of REBOA therapy, researchers are conducting a randomized

trial, in a swine model of polytrauma with TBI, pulmonary contusions, and hemorrhagic shock, to evaluate resuscitation with complete REBOA (c-REBOA) alongside their novel method of controlled partial endovascular aortic occlusion, referred to as Endovascular Variable Aortic Control (EVAC). In doing so, they aim to: 1) improve the previously developed swine polytrauma model to include TBI; 2) determine if c-REBOA leads to progression of TBI when compared to controls; 3) test if c-REBOA leads to progression of pulmonary contusions and development of acute respiratory distress syndrome (ARDS) when compared to control animals and animals undergoing EVAC; and 4) measure the cardiovascular effects of c-REBOA and EVAC in a swine model of polytrauma. Primary outcomes will be: the progression of TBI, progression of pulmonary contusion size, development of ARDS, and the development of cardiac dysfunction, as measured by cardiac pressure volume loops and conventional biomarkers. Previously identified physiologic and

inflammatory markers will be used to measure the effects of hemodynamic changes with each type of aortic balloon occlusive technology.

Work performed and presented this year, including a publication in the *European Journal of Trauma and Emergency Surgery* (Beyer et al., 2020), demonstrates the relationships between cardiac function, thoracic trauma, and endovascular occlusion of the aorta. These findings show that c-REBOA initiates myocardial injury; this injury can be followed longitudinally using the biomarker troponin; and a partial occlusion strategy, such as EVAC, may mitigate this injury. Furthermore, researchers have demonstrated that thoracic trauma with large pulmonary contusions may blunt the expected physiologic response to REBOA, which will have an immediate impact on providers caring for critically injured patients. Current guidelines recommend monitoring proximal blood pressure as the primary means for evaluating the proper deployment and inflation of REBOA, which may not be effective in the setting of blunt thoracic trauma. Additionally, pulmonary contusions did not worsen with c-REBOA, thus expanding the use of this life-saving technology to patients with polytrauma and thoracic injuries. Together, these findings provide a foundation for continued research on optimizing the acute resuscitation of blast and blunt polytrauma victims.

This effort was managed by CDMRP with support and programmatic oversight by CCCRP/JPC-6.

Critical Factors for Treatment in the Acute Phase After Spinal Cord Injury: Surgical Timing and Spinal Cord Perfusion Pressure Maintenance

In two separate studies across multiple clinical facilities, researchers from the University of California, San Francisco, examined the utility and timing parameters of surgical interventions after SCI. Burke et al. (2019) used a retrospective sample to demonstrate that early (< 12 hours post-injury) surgery and spinal decompression may lead to improved functional recovery, as compared to

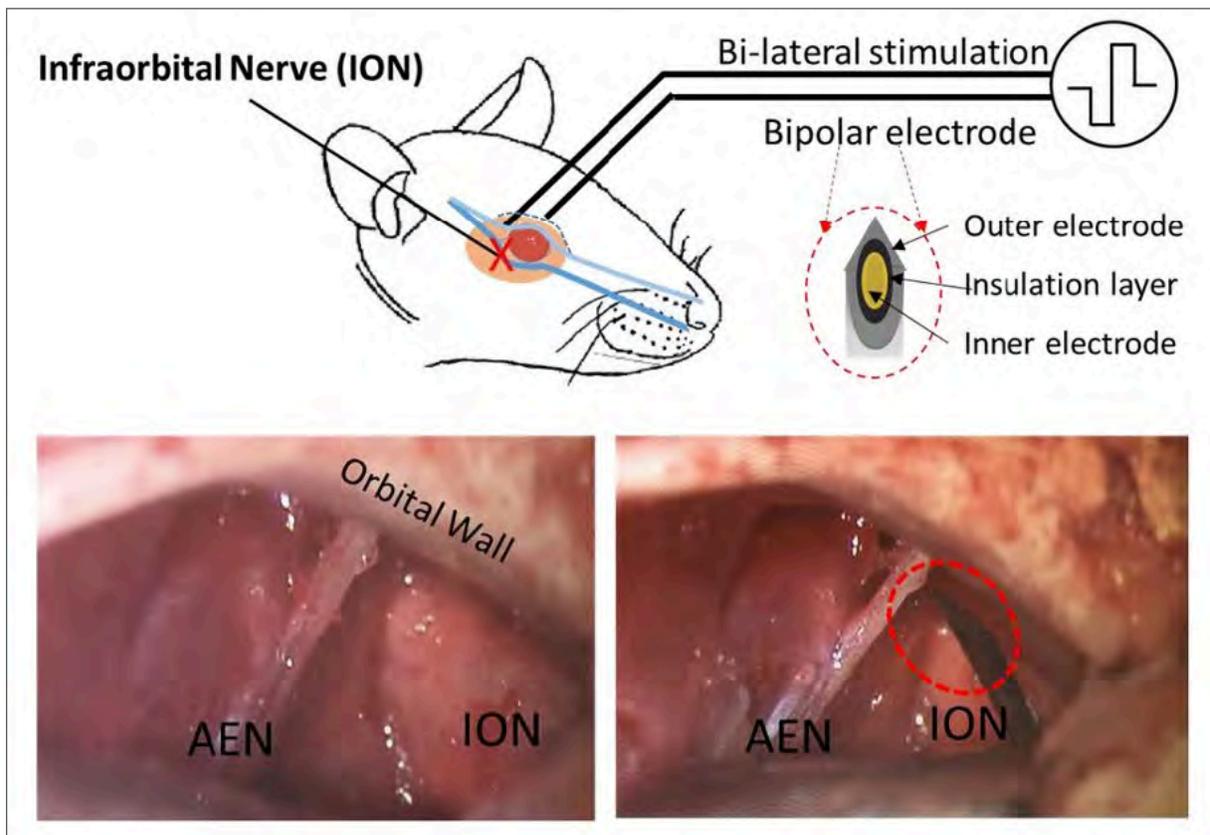
surgery that occurs outside of the 12-hour window. Improvements are based on the American Spinal Injury Association Impairment Scale or Abbreviated Injury Score grade-change from admission to discharge. In a separate study, Yue et al. (2020) demonstrated the efficacy and feasibility of maintaining spinal cord perfusion pressure in the days post-injury to improve functional and sensory recovery after SCI. This treatment has significant advantages over current standards of care for SCI using vasopressor therapy. This work is highly important due to the critical decisions physicians must make to coordinate care in the first hours-to-days following injury, as the spinal cord is vulnerable to further damage. These studies reveal the outstanding potential of early surgical and spinal pressure interventions in acutely enhancing functional recovery after SCI.

This effort was supported by SCIRP with program interest by CCCRP/JPC-6 and CRM RP/JPC-8.

Automated Closed-Loop Resuscitation of Hemorrhagic Shock and TBI with Trigeminal Nerve Stimulation

The standard of care for treating hemorrhagic shock includes intravenous fluid administration and blood transfusion, but unique circumstances under which combat-related injuries take place makes application of these interventions logistically difficult. As an alternative, researchers at the Feinstein Institutes for Medical Research are pursuing the use of neuromodulation to mitigate the deleterious effects of hemorrhagic shock, by using trigeminal nerve stimulation as a resuscitation technology to maintain adequate hemodynamic stability, and control blood pressure, during pre-hospital trauma care. The researchers established a novel surgical approach for the electrical stimulation of the trigeminal nerve branches of the infraorbital nerve, anterior ethmoidal nerve, and supraorbital nerve in rats (Figure 8-43). They also designed a hardware and software algorithm to conduct a closed-loop stimulation of the trigeminal nerve based on the measured blood pressure, and demonstrated it

FIGURE 8-43: Percutaneous electrical stimulation of the infraorbital branch of trigeminal nerve in a rat model. Anterior ethmoidal nerve (AEN), infraorbital nerve (ION).



in rat models of hemorrhagic shock (Li, Chilawal, et al., 2019) and TBI. In addition, a surgical procedure to stimulate either the infraorbital or supraorbital nerve of trigeminal nerve branches was established in a swine model.

The inventors filed a patent application (Li & Narayan, 2019), which covers the fundamental concept of using trigeminal nerve stimulation for the treatment of shock and TBI. In addition, the researchers published a review, in *Bioelectronic Medicine*, covering the use of neuromodulation for resuscitation in hemorrhagic shock (Powell et al., 2019).

This effort was managed by CDMRP with support and programmatic oversight by MSISRP/JPC-1.

Prolonged Field Care Drill and Detection Device

In collaboration with experts from the Johns Hopkins University Applied Physics Laboratory, CNRM developed prototypes of two devices that can provide field-based diagnosis and care of traumatic epidural or subdural hemorrhage in austere environments. The first device is designed to detect hemorrhage via ultrasound and near-infrared spectroscopy (NIRS). A narrative review of this work was published in *Frontiers in Neurology* (Whiting et al., 2020). The second device was developed to provide safe and sterile intracranial access. When used together, these devices can provide treatment and management of an injury that is frequently life-threatening in the prolonged field care environment.

This research was supported by CNRM.

Use of Human Acellular Vessels on Veterans at Risk for Limb Loss

The current standard of care for blood vessel repair in casualties at risk of limb loss requires a specialized vascular surgeon to remove a healthy native vessel from the patient's body to be used as a repair graft. A retired Veteran at Walter Reed National Military Medicine Center (WRNMMC) was at risk for limb loss, requiring arterial bypass, and did not have adequate native vessels to accommodate the standard of care procedure. Under an expanded access use Investigational New Drug application approved by the FDA, surgeons implanted a Human Acellular Vessel (HAV) in the retired Veteran, saving their limb. Humacyte, Inc., the inventor of the HAV, is currently studying the product in an ongoing clinical trial to establish efficacy and safety data to support FDA submission. If approved by the FDA, the HAV will replace the current standard of care for blood vessel repair. Advantages include infection resistance, availability for use off-the-shelf, reduction in surgery time, and ease of use providing non-specialized general surgeons the ability to perform the blood vessel repair procedure. To date, the use of the HAVs has saved the limbs of three Veterans who would have otherwise required amputations.

This study was sponsored by USAMMDA.

Reset

Reset describes a concept that extends beyond rehabilitation, to include all activities necessary for injured Service members to return to duty or to productive civilian life. Reset includes research to advance strategies for reducing recovery time, improving rehabilitation programs, maximizing opportunities for return-to-duty and reintegration into the civilian workforce, and improving the quality of life for Service members who have experienced blast-related injuries. Reset accomplishments from FY20 are organized into four categories: secondary injury and

comorbidities; reconstruction and prosthetics; long-term care; and consortium studies.

Secondary Injury and Comorbidities

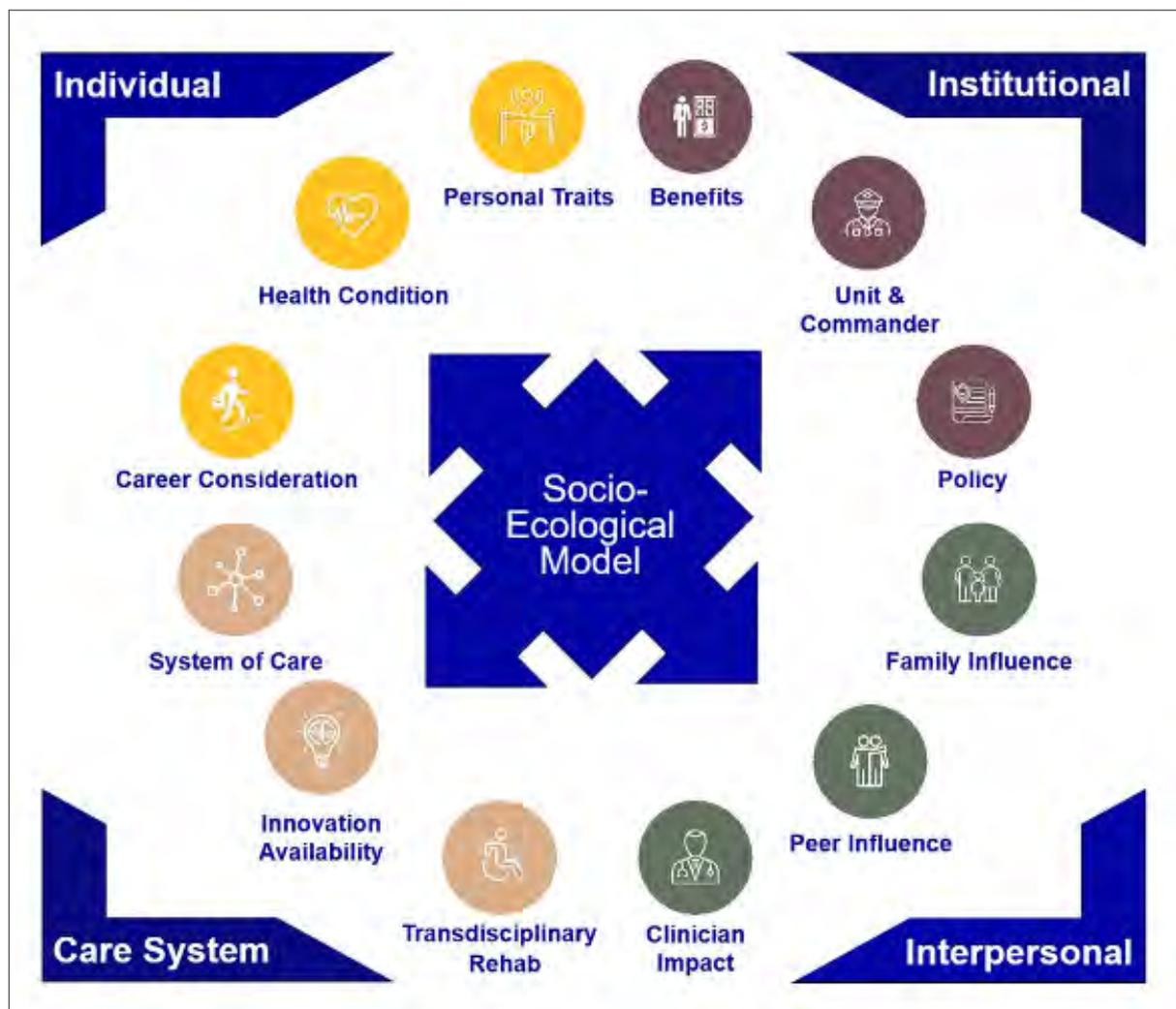
The Decision to Return to Duty Following Severe Lower Extremity Trauma

Rehabilitation research of wounded Service members commonly focuses on the physical ability to return to duty as a measure of successful recovery. However, numerous factors or barriers may influence the ability and/or desire to return to duty after lower extremity musculoskeletal trauma. Service members, and the clinical care team working with them on a daily basis, offer unique perspectives on the influential factors that weigh into decisions to return to duty. In a series of clinician-based and patient-based focus groups, EACE led a team of researchers at Joint Base San Antonio and VA Puget Sound, who sought to identify the intrinsic and extrinsic factors that patients and clinicians identified as influencing the decision to return to duty after a severe lower extremity trauma. Four themes emerged among Service member patients and clinicians when deciding when to return to duty; they are summarized in Figure 8-44.

A few of the expected themes common to both groups, patients and clinicians, were the influence of the team and family unit, and career trajectory options after a severe injury. An unexpected theme was acknowledgement of, and dissatisfaction with, the recent dismantling of institutional systems that support severely injured Service members. Patients placed less emphasis on severity of injury, and greater emphasis on system and policy barriers, than clinicians did.

Classification of factors that influence the decision to return to duty after severe lower extremity trauma is expected to improve the efficacy of future rehabilitation efforts and clinical practice guidelines by providing the

FIGURE 8-44: Factors that influence the decision to return to duty after lower extremity trauma.



clinical team with the knowledge necessary to recognize modifiable barriers to patient success. A better understanding of factors influencing this decision-making may support policies for mitigating return-to-duty barriers, better monitoring of the changing landscape of return-to-duty after lower extremity trauma, improving systems of healthcare, and/or reducing turnover and facilitating force readiness.

This study was sponsored by EACE and the Center for Rehabilitation Sciences Research (CRSR) within USU.

The Influence of Tobacco Use, Alcohol Consumption, and Weight Gain on Development of Secondary Musculoskeletal Injury After Lower Limb Amputation

To date, there is limited research identifying modifiable risk factors associated with the development of secondary musculoskeletal injuries following traumatic lower limb amputation. However, well-established research has associated tobacco use, alcohol consumption, and greater body mass with the development and chronicity of musculoskeletal injuries in able-bodied individuals. The EACE team at Naval Medical Center San Diego, in collaboration with NHRC, conducted a study to evaluate whether tobacco use, alcohol

consumption, and weight gain are associated with the diagnosis of overuse musculoskeletal injuries within the first 12 months following deployment-related lower limb amputation. The study was published in the Archives of Physical Medicine and Rehabilitation (Yepson et al., 2020).

A total of 681 Service members with a deployment-related lower limb amputation were included in this retrospective cohort study. Tobacco use, alcohol consumption, and body weight, recorded as part of clinical care received at a DOD facility, were extracted for all time points available in the patients' electronic medical records. Tobacco use and alcohol consumption were self-reported. Using the last recorded weight within 12 months prior to lower limb amputation, and the maximum weight recorded within the first three months after lower limb amputation, the change in weight was calculated. Overuse musculoskeletal injury data within 1 year prior to, and 4–12 months after, injury were ascertained from the DOD Military Health System Medical Data Repository. Codes were used to identify the diagnosed overuse musculoskeletal injuries and to categorize these injuries into the following anatomical regions: lower limb, upper limb, and lower back.

In the 3-month period following lower limb amputation, 55.7 percent and 72 percent of the studied Service members reported tobacco and alcohol use, respectively, and weight changed by an average of 22.9 ± 23.6 pounds. Overuse injuries within 4–12 months after amputation of the lower limb were found in 57 percent of the study sample. These injuries involved the lower limb (28.3 percent), upper limb (21.7 percent), and low back pain (21.1 percent). While neither maximum weight, nor weight change, after lower limb amputation were associated with overuse musculoskeletal injury diagnosis, the interaction between overuse injury and substance use was notable. The likelihood of a Service member being diagnosed with a lower limb overuse injury within 4–12 months after lower limb amputation nearly

doubled if tobacco use was reported in the first 3 months after amputation. Likewise, alcohol consumption within the first 3 months after lower limb amputation more than doubled the risk of being diagnosed with any overuse injury in 4–12 months after amputation.

Identifying modifiable risk factors associated with secondary musculoskeletal injuries, following a deployment-related amputation, allows for implementation of interventions that could prevent long-term deleterious effects.

This study is sponsored by EACE.

Characterizing and Understanding the Low Back Pain Experience Among People with Lower Limb Loss

Traditional biomechanical models do not accurately describe the initial diagnosis and subsequent treatment of chronic low back pain. As a result, support for a biopsychosocial model has increased, particularly in clinical populations with concurrent musculoskeletal disorders, such as people with lower limb loss. While the relationship between lower limb loss and the role of altered mechanics in the development of low back pain is well defined, the multi-factorial nature of low back pain etiology suggests psychological (e.g., anxiety, depression) and social factors (e.g., employment status) may contribute to the progression of the disorder, or result from the disorder. To explore the moderating effects of psychosocial factors on the persistence of low back pain among persons with lower limb loss, EACE teams at WRNMMC and Naval Medical Center San Diego, in collaboration with investigators at the University of South Carolina, investigated whether these factors were able to discriminate between people with lower limb loss with, versus without, low back pain. The team also explored those factors in the context of self-reported functional disability (Butowicz et al., 2020).

Thirty-three males with lower limb loss, with and without chronic low back pain, participated. Psychosocial factors and low back pain-related functional disability were measured using common self-report questionnaires. There were no differences among psychosocial factors between those with, versus without, low back pain. Employment status, anxiety, and fear of movement were associated with low back pain-related disability. Despite the increased prevalence of low back pain among people with lower limb loss, the self-reported disability scores of people with lower limb loss and low back pain were lower than those reported in non-lower limb amputation populations with low back pain. Considering that low back pain is secondary to severe lower limb trauma, the reduced self-reported functional disability scores may not be surprising when functional impairments are considered in the context of traumatic lower limb loss. Moreover, reported levels of anxiety, depression, catastrophizing, and fear of movement were all below clinically relevant thresholds.

The relatively low levels of these psychosocial factors in both those with, and without, low back pain, in the current cohort, may be related to the traumatic etiology of lower limb loss and/or the unique personality characteristics associated with military service. The current findings suggest that traditional measures of self-reported, perceived functional disability are not moderated by psychological constructs among persons with lower limb loss, but rather by social constructs (e.g., employment status). Psychological (e.g., anxiety) and social (e.g., military culture) factors appear to moderate functional disability associated with low back pain within this population, and highlight the interdependence among biological, psychological, and social factors in determining appropriate treatment interventions.

This research was supported by the Peer Reviewed Orthopaedic Research Program (PRORP), CRSR within USU, and EACE.

Single-Leg Forward Hopping Exposures Adversely Affect Knee Joint Health Among People with Lower Limb Loss

Many Service members who have suffered a single-leg amputation use single-leg hopping as a convenient ambulation method, despite the practice being discouraged by their therapists. The potential deleterious effects of frequent hopping on knee joint health remains unclear. To investigate, the EACE team at WRNMMC, in collaboration with researchers at the University of Maryland, conducted a study to compare knee joint mechanics, between single-leg hopping and walking, at self-selected paces (Wasser et al., 2020).

Full-body biomechanical data were obtained from 32 individuals with unilateral lower limb loss (22 transtibial, 10 transfemoral). Peak knee moments were computed and input to a phenomenological model to estimate the damage and long-term failure probability of the medial knee cartilage when hopping versus walking. Results indicated that each hop accumulates as much damage as at least eight strides of walking, and each meter of hopping accumulates as much damage as 12 meters of walking. Hopping more than 100 times per day is a potential risk factor for future knee osteoarthritis, if performed chronically. The failure probability of the medial knee cartilage exceeded 50 percent when 197 hops per day were performed.

A large population of lower limb loss individuals will develop knee osteoarthritis during their lifetime. Understanding the impact of single-leg hopping is vital for informing clinical guidelines and reducing future damage of articular cartilage.

This study was sponsored by EACE and CRSR within USU.



Photo credit: Seaman Luke Cunningham/ U.S. Navy

Wearable Sensors for Determination of Persistent Gait Symptoms After Mild TBI

Although gait deficits are common in the acute phase after an mTBI, subtle defects in gait may persist chronically, although solid data in this area is lacking. As gait dysfunction is linked to many other mTBI symptoms, including depression, cognitive dysfunction, sleep disturbance, headache, dizziness, and motor deficits, thorough and careful assessment of gait, after mTBI, would benefit Service members and Veterans struggling with the aftereffects of TBI. Investigators at the Oregon Health and Science University report findings from single- and dual-task gait evaluations utilizing wearable sensors, demonstrating that individuals with chronic mTBI have deficits across multiple gait domains. This includes slower pace and turning, as well as less rhythm, under

dual-task gait, compared to healthy controls. Further, more severe symptoms related to increased gait variability, and decreased pace and turning, were found in the chronic mTBI group. Overall, the results suggest that individuals with mTBI may have a decreased ability to complete gait without directing their entire attention specifically to the task. The work was published in the *Journal of Neurotrauma* (Martini et al., 2020). Assessing gait, under single- and dual-task conditions, allows researchers to determine the amount of attention that gait task completion requires, which may serve as a secondary identifier of global cognitive deficits that can be addressed during recovery.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CRM/RP/JPC-8.

Trunk Postural Control Strategies Among People with Lower Limb Amputation While Walking and Performing a Concurrent Task

Altered trunk movements during walking, in people with lower limb amputation, are often associated with an increased risk for secondary health conditions; however, the postural control strategies underlying such alterations remain unclear. People with, versus without, lower limb amputation walk with more lateral trunk movement and out-of-phase trunk-pelvic coordination that, with repeated exposure, likely contribute to conditions such as low back pain. Notably, people with lower limb amputation often report feeling compelled to consciously focus on every step, and pay more attention to walking than people without lower limb amputation. In a secondary analysis, the EACE team at WRNMMC evaluated the influence of a concurrent cognitive task on trunk stability and gait mechanics, to explore if competition for neuromuscular processing resources can assist in identifying unique strategies to control kinematic variability.

The study included 16 males with lower limb amputation and eight uninjured males (controls) walking on a treadmill, at their self-selected speed, in five experimental conditions—four while performing a concurrent task (two walking, two seated), and one without a concurrent task. Individuals with lower limb amputation demonstrated more trunk kinematic variability, in the presence of wider strides, compared to individuals without lower limb amputation, and it appears that performing a concurrent cognitive task while walking did not change trunk or gait mechanics. The study found that there were no differences between task performances while sitting, compared to walking, in any group, suggesting that task performance did not suffer due to the demands of walking, particularly among individuals with lower limb amputation.

Additionally, the lack of differences in perceived cognitive workload between groups among the

tasks, both when seated and walking, suggests that individuals with lower limb amputation did not perceive walking while performing a concurrent cognitive task (regardless of task demand) as more demanding than individuals without lower limb amputation. The ability to control the trunk during gait requires attentional resources and environments that challenge the neuromuscular system to divide attention between these resources, potentially adversely affecting trunk control. Notably, the concurrent tasks did not appear to influence gait mechanics or trunk kinematic variability in any group. The decreased ability to resist kinematic perturbations through the trunk and spine, particularly in the presence of increased motion, is a potential mechanistic pathway underlying the recurrence of secondary musculoskeletal conditions such as lower back pain. These results may assist in understanding how people with lower limb amputation adapt to kinematic perturbations over cyclical/repetitive exposures, due to neuromuscular noise, associated with increases in neural processing demands.

This study was sponsored by EACE and CRSR within USU.

Noise Outcomes in Servicemembers Epidemiology (NOISE) Study

Researchers from the National Center for Rehabilitative Auditory Research, Oregon Health and Science University, and HCE are collaborating on a longitudinal epidemiological study that evaluates lifetime noise exposures, chemical and blast exposures, TBI, physical and psychiatric comorbidities, and other exposures and outcomes that can affect auditory function. The team developed a seven-page TBI and blast exposure questionnaire for this study, and recently published baseline findings for the first 690 study participants (Henry et al., 2020). The prevalence of hearing loss in the sample was 8 percent for low frequencies (0.25 to 2 kHz), 20 percent for high frequencies (3 to 8 kHz), and 39 percent for extended high frequencies (9 to 16 kHz). The

prevalence of tinnitus was 53 percent, and was most prevalent among those who serve/served in the U.S. Army, relative to the other military branches. The prevalence of both hearing loss and tinnitus was higher among those who were older, had more years of military service, had a greater degree of noise exposure, or had exposures to blasts or TBI in the military. Many additional analyses are planned to take full advantage of the unique opportunities offered by this rich dataset. Read more about continuing NOISE studies on [page 255](#).

This effort was supported by the DOD's Peer-Reviewed Medical Research Program and Joint Warfighter Medical Research Program, as well as a VA Rehabilitation Research and Development Research Career Scientist Award.

Long Term Clinical Correlates of TBI: Imaging, Biomarkers, and Clinical Phenotyping Parameters

A natural history study is being conducted at the NIH Clinical Center in coordination with CNRM. The study follows a cohort of participants with a clinical diagnosis of non-penetrating TBI. Participation in the TBI cohort study includes up to nine evaluation sessions (at 30, 90, 180, and 365 days after injury), then once per year until year five. Evaluations included neuroimaging via non-contrast MRI, neuropsychological evaluations, other functional evaluations, blood and urine collection; and auditory, vestibular, and oculomotor assessments. Healthy volunteers and TBI patients are scheduled, as needed, to match assessments. Healthy volunteers were also studied to provide multiple CNRM investigators with hematological, cognitive, and functional outcome measures and neuroimaging parameters to compare to participants with TBI.

Several notable publications have resulted from this dataset in FY20. The first is a study published in *Physical Medicine and Rehabilitation* (Joseph, Lippa, et al., 2020), focusing on a subset of

chronic TBI patients with subjective balance problems, relative to TBI patients who did not endorse such issues. Using measures including the Dual-Task test and Sensory Organization Test, chronic TBI patients with subjective balance issues showed deficits in the dual-task assessments and the automaticity of gait. These findings may help modify vestibular therapy in chronic TBI patients.

A second study, published in *Brain Injury* (Rizk et al., 2020), tracked microbleeds in TBI patients for five years after injury. The population consisted of 30 patients, all of whom received an initial post-TBI MRI within 48 hours of their injury, and continued in the longitudinal study for five years. Through the course of the study, 83 percent of the acutely observed traumatic microbleeds persisted after one year post-TBI, and all such microbleeds persisted in patients receiving serial 2–5-year MRI follow-ups. This contrasts with findings from the other neuroimaging measures, including diffusion weighted imaging lesions, extra-axial and intraventricular hemorrhage, hematoma, traumatic meningeal enhancement, fluid-attenuated inversion recovery hyperintensities, and encephalomalacia; the majority of which resolved within one-year post injury. This finding suggests that traumatic microbleeds may be a uniquely persistent indicator of TBI and should be correlated with long-term neurobehavioral deficits.

The third study recruited Swedish and American ice hockey players (and controls) along with the NIH Clinical Center cohort described above. All participants underwent blood-based biomarker, functional outcome, and imaging assessments at short- and long-term time points. Neurofilament light (NFL) in the serum and cerebrospinal fluid of the athletes predicted persistent, post-concussive symptomatology at one year relative to preseason baseline. In the clinic cohort, NFL was elevated over time in TBI patients relative to controls, and NFL levels discriminated between mTBI patients and those with moderate-to-severe TBI. Lastly,

serum NFL correlated with Glasgow Outcome Scale-Extended measures as well as neuroimaging findings of brain atrophy and traumatic axonal injury. This work was published in *Neurology* (Shahim et al., 2020a). Further work with this clinic cohort was also published in *Neurology* (Shahim et al., 2020b), expanding on the diagnostic and prognostic results using serum NFL, while also reporting that glial fibrillary acidic protein (GFAP) differs in acute TBI patients, relative to controls, with moderate discriminability at 30 days post-injury. Tau and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) levels showed weak stratified predictions of TBI severity and low correlations with neuroimaging findings.

This longitudinal study has provided unique insights into the correlation of many behavioral, physiological, and cognitive factors associated with TBI. Additional analyses from this patient cohort will expand on these associations and inform future research in the prevention and treatment of TBI.

This research was funded by the Intramural Research Program at NIH and CNRM.

Distinguishing the Impact of TBI and PTSD on Cognitive Function

The Recruitment Core at CNRM published a recent paper in *Cyberpsychology, Behavior, and Social Networking* (Dunbar et al., 2019), delineating the interplay between TBI and PTSD on cognitive function. The researchers examined questionnaire data from 326 active-duty or retired Service members, or their families, using the NIH Toolbox Cognitive Battery, an iPad-based cognitive assessment. They demonstrated that a military population has above average cognition and that this is sustained even after multiple TBIs, either on deployment or elsewhere. However, if one has also developed PTSD, cognition is significantly impaired and falls below normal. This indicates that if TBI has a significant impact on the brain, it may overwhelm the ability of the brain to be resilient, resulting in PTSD and cognitive impairment.

This research was supported by CNRM.

Clinical Utility of PTSD, Sleep, Resilience, and Blast Exposure as Risk Factors to Predict Self-Reported Neurobehavioral Outcome Following TBI

Neurobehavioral outcome following TBI, of all severities, is variable, complex, and multi-factorial. Past research has found an association between neurobehavioral outcome and PTSD, sleep, resilience, and lifetime blast exposure following TBI. The purpose of this study was to examine the clinical utility of these four variables as potential risk factors for identifying and predicting poor neurobehavioral outcome following TBI.

In a study performed at WRNMMC, Camp Pendleton, and Naval Medical Center San Diego, 993 Service member and Veteran participants were evaluated following an mTBI with no trauma-related intracranial abnormality evident on CT or MRI scan, moderate-to-severe TBI, or orthopedic injury without brain injury. The TBI groups included those with blast overpressure exposure, blunt impact, or both. Participants were divided into three cohorts based on time since injury: cohort 1 (less than 12 months, $n = 237$), cohort 2 (3 years, $n = 370$), and cohort 3 (10 years, $n = 386$). Participants completed a two-hour neurobehavioral test battery that included the Neurobehavioral Symptom Inventory (NSI), PTSD-Checklist (PCLC), and six scales from the TBI-Quality of Life (TBI-QOL) measurement system. Risk factors were dichotomized as sleep (good versus poor [NSI/PCLC sleep items]), resilience (high versus low [TBI-QOL Resilience scale]), PTSD (present versus absent [PCLC]), and lifetime blast exposure (0–10 events versus 11+ events). Poor neurobehavioral outcome was defined as three or more low scores (< 1 standard deviation) on five TBI-QOL scales (i.e., Anger, Fatigue, Headaches, Depression, and Cognitive Complaints). Sixteen risk factor combinations were examined that included each of the four risk factors separately and all two-, three-, and four-factor combinations.

In all three cohorts, the majority of risk factor combinations (12 of 16) resulted in odds ratios (OR) considered to be clinically meaningful (ORs > 3.00). Risk factor combinations with the highest ORs in each cohort were PTSD (cohorts 1 and 2; ORs = 17.76 and 25.31), PTSD + sleep (cohorts 1 and 2; ORs = 18.44 and 21.18), PTSD + sleep + resilience (cohorts 1, 2, and 3; ORs = 13.56, 14.04, and 20.08), resilience (cohort 3; OR = 32.63), and PTSD + resilience (cohort 3; OR = 24.74). Overall, any risk factor combination that included PTSD consistently yielded high ORs in all three cohorts. Lifetime blast exposure resulted in the lowest ORs in all three cohorts (OR range = 0.79 to 1.57).

This study demonstrated, that in comparison to risk factors such as sleep, resilience, and PTSD, lifetime blast exposure resulted in the lowest risk of poor clinical outcome following TBI of any severity.

This study was supported by the Defense and Veterans Brain Injury Center (DVBIC), now called the TBI Center of Excellence (TBICoE).

Cognitive Performance Amongst Service Members with a History of Mild TBI and Exposure to Blast in Close Range

Mild TBI affects approximately 15–23 percent of U.S. Service members who have deployed, of whom 35–67 percent report persistent post-concussive symptoms. The rate of persistent post-concussive symptoms in this population is higher than rates in the general population (10–15 percent), potentially due to varying mechanisms of injury (e.g., blast exposure) between military and general populations. When comparing published literature on blast- versus non-blast-induced mTBI, there is generally no difference in objective cognitive sequelae; however, most studies do not report detailed injury characteristics, such as distance from blast exposure, which may affect outcomes. It has been reported that exposure to a close blast

(< 10 meters) was associated with increased risk of memory impairment, compared to no exposure to close blast. The current study aimed to evaluate the effects of close blast on cognitive performance amongst deployed Service members and Veterans with a history of mTBI.

This prospective study recruited Service members and Veterans (primarily Army; 39 ± 8 years), with a history of deployment, from Joint Base San Antonio's Fort Sam Houston. Participants with a history of mTBI, as defined by VA/DOD criteria, were grouped into close blast mTBI (< 30 feet from blast; n = 18) or mTBI (> 30 feet from blast or no blast; n = 9). Controls with deployment history, but no mTBI (n = 24), were also recruited. All participants completed a study-specific TBI interview and the following neuropsychological measures: Auditory Consonant Trigrams (ACT), Paced Auditory Serial Addition Test (PASAT), Verbal Selective Reminding Test (VSRT), Symbol Digit Modality Test (SDMT), Trailmaking Test (Trails), and Test of Non-Verbal Intelligence (TONI). There were no differences between close blast mTBI and mTBI groups on demographic variables. On neuropsychological measures, the groups differed on working memory (ACT 18 second delay versus 36 second delay), mental flexibility (Trails B time), and visual reasoning. In all instances, the mTBI group performed worse than the control group, and there was no statistically significant difference between the close blast mTBI and mTBI groups, nor between the close blast mTBI and controls. There were no group differences on the measure of verbal learning and memory (VSRT Total Recall; VSRT Delayed Recall), measures of processing speed (SDMT Written; SDMT Oral; Trails A time), or on a measure of working memory that had higher demands for processing speed (PASAT Trial 1; PASAT Trial 2).

While the mTBI group did demonstrate cognitive inefficiencies (i.e., domains of working memory, mental flexibility, and visual reasoning) compared



Photo credit: Pfc. Erik Warren/ U.S. Army

to controls, the close blast mTBI group did not demonstrate the same cognitive deficits. These data support that close blast mTBI (< 30 feet) is not associated with worse neuropsychological performance when compared to controls, nor compared to those with a history of mTBI without close exposure to blast. Continued investigation into other blast exposure variables, or individual comorbidities that may affect clinical presentation, are warranted.

This research was supported by DVBIC (now called TBICoE).

Epidemiological Approach to Identifying Health Sequelae of High- and Low-Level Blast Exposure

Members of the U.S. Armed Forces may be subject to blast overpressure exposure over the course of their service. This overpressure exposure comes in two forms: acute, high-level blast and repetitive low-level blast exposure (e.g., from firing heavy-caliber weapons). The former is more frequent in combat and operational environments, while the latter is common in both training and operational environments. Ongoing epidemiological research at NHRC examines both types of overpressure exposure simultaneously with large samples. NHRC uses an epidemiological approach that leverages archival medical and career records to investigate the long-term health implications of both high- and low-level overpressure exposure.

Recent work has been published in the Journal of Neurotrauma (Belding et al., 2020a) and Military Medicine (Belding et al., 2020b), as well as a recent comprehensive report from NHRC (Belding, Jackson, et al., 2020).

Findings to date support several conclusions regarding the health sequelae of low-level blast exposure. Marines working in high- (versus low-) risk occupations (e.g., Infantrymen, Artillerymen) were significantly more likely to sustain a probable concussion after blast exposure during deployment, suggesting that low-level blast exposure increases susceptibility to concussion and may prime Service members for subsequent injury. Additionally, Marines working in high-risk occupations reported significantly more neurological symptoms than those in low-risk occupations, in both the presence and absence of a concussion. In fact, during deployment, Marines with concussions due to either blast, or working in high-risk occupations, reported neurological symptoms at the same level as musculoskeletal symptom reporting, the leading cause of hospitalizations for active-duty Service members. Both high- and low-level blast exposure are associated with neurological symptoms that persist for six months or more following deployment. Ongoing work will determine whether Service members working in occupations with high- (versus low-) risk of low-level blast exposure across all branches of service are significantly more likely to be diagnosed with TBI, post-concussive syndrome, cognitive issues, tinnitus, and hearing issues.

The investigators also sought to determine the impact of the mechanism of injury (i.e., blast- versus impact-induced) on concussion sustained during deployment. The recruited population included over 5,800 enlisted Marines who completed the Post Deployment Health Assessment between 2005 and 2012, and sustained a probable concussion. Of this group, 66 percent of concussions were blast-induced, and blast-induced (versus impact-induced) concussions were associated with significantly

more self-reported neurological symptoms. Regarding symptom chronicity, symptom reporting decreased at statistically equivalent rates for blast- and impact-induced concussions; however, because blast-induced concussions are associated with more symptoms initially, these symptoms were still elevated six months later.

There is little research on the combined and overlapping sequelae of high- and low-level blast injuries. This ongoing and future work characterizes, with large sample sizes, the individual and combined sequelae of occupation and low-level blast injury, with that of high-level blast injury, to inform policies and practices regarding risk mitigation and short- and long-term clinical and behavioral management.

This research was sponsored by BUMED and NHRC.

Impact of Lifetime Repetitive Blast Overpressure Exposure on Quality of Life After TBI

Researchers at Camp Pendleton and WRNMMC embarked on a study to 1) address the impact that repetitive blast exposure (RBE) has on recovery from TBI, in Service members and Veterans, 2) determine if the relative amount of blast exposure in a career changes this effect, and 3) determine if any effects of blast exposure are different than known pre-existing neurotrauma, such as pre-injury TBI history (piTBIHx), defined as previous TBI that occurred before the index injury for the study.

Participants were 341 Service members and Veterans who were evaluated following an uncomplicated mild (n = 253), or a complicated mild, moderate, or severe TBI (n = 101). piTBIHx was based on a structured interview, and RBE was based on self-report. Participants were divided into six cohorts based on RBE. The cohort characteristics are depicted in Figure 8-45. Participants completed a two-hour neurobehavioral test battery that included 13 scales from the TBI-Quality of Life (TBI-QOL) measurement system.

	RBE Severity	piTBIHx	n
Cohort 1	None	No	72
Cohort 2	None	Yes	20
Cohort 3	Moderate	No	115
Cohort 4	Moderate	Yes	34
Cohort 5	Heavy	No	59
Cohort 6	Heavy	Yes	40

FIGURE 8-45: Characteristics of the six study cohorts. RBE severity determined to be “None,” “Moderate” (1–11 exposures lifetime), or “Heavy” (> 11 exposures lifetime). piTBIHx defined as previous TBI that occurred before the studied TBI. Column 4, “n”, is number of Service members and Veterans in each cohort.

The cohorts did not differ on injury severity or years of education, but they did differ on time since injury, age, gender, and ethnicity, which were all entered as covariates.

Heavy RBE, in the absence of piTBIHx (cohort 5), was found to be associated with worse QOL on measures of anger, anxiety, emotional and behavioral dyscontrol, headache, pain, cognitive complaints—executive functioning, and cognitive complaints—general. There were no differences on measures of depression, grief, fatigue, or any TBI-QOL scales in the positive QOL domain (e.g., resilience). Moderate RBE, in the absence of piTBIHx (cohort 3), did not differ from cohort 1 on any of the TBI-QOL scales, except cognitive complaints—executive function. The effect of RBE frequency (heavy versus moderate) was examined by comparing RBE groups, controlling for piTBIHx. No differences in the TBI-QOL scale were found for these comparisons. Potential cumulative effects of RBE and piTBIHx were examined by comparing participants with known piTBIHx but no RBE (cohort 2), to participants with both RBE and piTBIHx (cohorts 4 and 6). No differences were found on any of the QOL scales.

The clinical impact of this study is that heavy RBE may be an indicator of pre-injury vulnerability and may portend diminished quality of life after TBI.

This research was supported and sponsored by DVBIC (now called TBICoE).

Systematic Collection of Lifetime Blast Exposure Histories via the Blast Ordnance and Occupational Measure Project

In the absence of real-time blast gauge data, carefully crafted inventories are needed to catalog and characterize lifetime histories of potential blast exposures in Service members and Veterans. Blast gauges have contributed significantly to the understanding of blast exposure, and its immediate physical effects, and has allowed for the refinement of computational models. However, such models remain in the developmental stages and have yet to be satisfactorily incorporated into combat or training arenas. The National Intrepid Center of Excellence (NICoE) provides care for Service members with persistent symptoms associated with TBI and behavioral health conditions. Many of these Service members present with complex histories, including multiple deployments, head injuries, and exposure to varying levels of blast overpressure within both operational and training settings. To improve characterization of the patient population, NICoE internally funded a quality improvement project to develop a comprehensive, military occupational exposure inventory to systematically collect lifetime exposure histories from patients and research participants. The NICoE Blast Ordnance and Occupational Exposure Measure (BOOM) project will include three phases of feedback groups, to iteratively collect stakeholder input on a draft military exposure inventory developed by the project team. The document will be revised after the completion of each phase.

Within FY20, researchers completed Phase 1, incorporating input from research and operational blast subject matter experts at WRAIR, MOMRP,

VA, USSOCOM, and DHA into a revised draft inventory. The draft inventory will continue to be revised following Phase 2 (NICoE clinicians) and Phase 3 (NICoE active-duty Service member patients), to be completed in early FY21. After completion of the three phases, the inventory will be incorporated into clinical practice or developed into a comprehensive research study. The project consists of systematic, iterative activities that will leverage subject matter expert and stakeholder input to create an extensive military blast exposure inventory that will ultimately improve the ability to collect lifetime exposure information in a standardized manner.

This research was sponsored by NICoE.

Analysis of Concussion Recovery Trajectories Using Multi-Modal Assessments and Serum Biomarkers

For the military, concussions affect the ability of Service members to perform their duties at the highest level, physically and/or mentally. The knowledge of when return-to-duty is appropriate is critical to the care of Service members and their ability to optimally perform their job. One of the project goals of a group of Missouri University of Science and Technology researchers is to develop a concussion recovery timeline model. The study published by Roy et al. (2020) provides an assessment of concussion recovery trajectories, while incorporating heterogeneity of individual responses. Recovery trajectories of up to seven discrete time points were analyzed from baseline to six months post-injury using three multi-modal clinical assessment tools (Standardized Assessment of Concussion [SAC], Balance Error Scoring System [BESS], and Immediate Post-Concussion Assessment and Cognitive Testing [ImPACT]), and four blood-based biomarkers (glial fibrillary acidic protein [GFAP], ubiquitin carboxy-terminal hydrolase L1 [UCH-L1], microtubule-associated protein tau [MAPT], and neurofilament light [NF-L]) that have not yet been fully investigated. The data, obtained from the Federal Interagency Traumatic Brain Injury



Photo credit: Justin Smelley/ U.S. Navy

Research (FITBIR) Informatics System, includes concussed subjects and a matched control group, to allow for comparison in prognostic assessment.

The trajectories show that GFAP is significantly elevated in the case group at < 6 hours post-injury, but is not significantly different from the control group at later times. Men have a significantly higher mean GFAP level at < 6 hours than women. Measures related to balance, memory, orientation, and concentration were also significantly different than controls early after concussion. These results show promise in better understanding the pattern of how different assessments and serum biomarkers change over time after concussion, which could aid clinicians, who are treating military personnel, in supporting return-to-duty decisions.

To build on this work, a model to cluster the recovery trajectory of the concussed participants, per biomarker, was developed to further sort out the different levels of heterogeneity. The

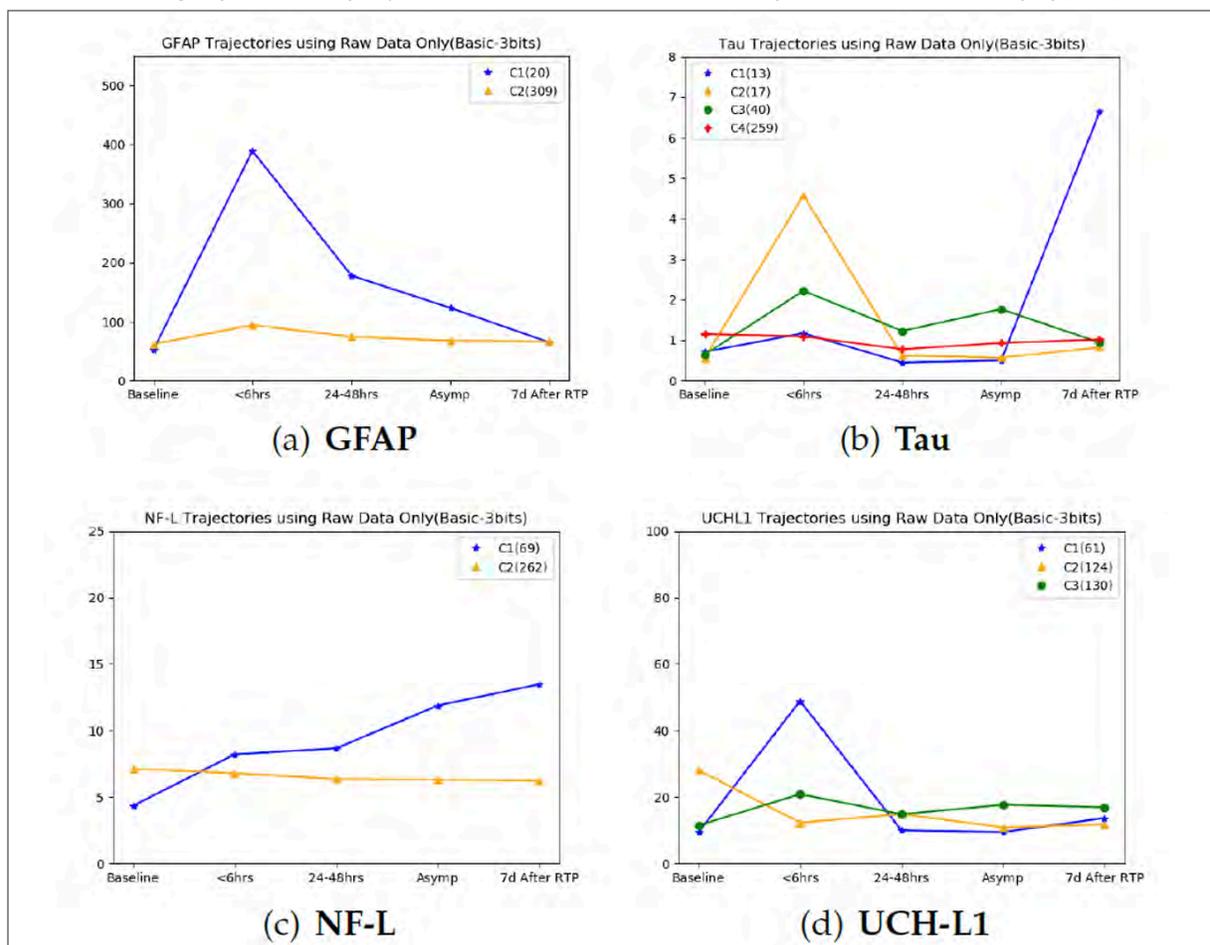
investigators first tested for multi-modality in blood-based biomarker levels at multiple time points using the Silverman test, which revealed promise for the clustering approach. The outcome of the clustering model revealed concussion subjects could be grouped into meaningful clusters according to their blood biomarker trajectories. For each biomarker (Figure 8-46), there was a large group with a minimal rise in blood biomarkers and a smaller group with a large rise in blood biomarkers. These results suggest that rises in blood biomarker levels in concussed subjects are increased in a bimodal or trimodal fashion with subgroups showing larger rises in biomarker levels.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

Construction of Kinetic Models of Biomarker Levels After Mild TBI

A defined mathematical model is essential to understand the mechanisms of mTBI. Depending on the severity of an mTBI, a portion of the released biomarkers crosses the blood-brain barrier and can be measured in the blood. The biomarkers diffused into the blood are eventually excreted out of the body. A mathematical model was designed by researchers at the Missouri University of Science and Technology, and Missouri State University, to describe the kinetic behavior of the blood biomarkers based on pharmacokinetic modeling. The blood biomarker measurements are utilized to estimate the model parameters based on the least squares method. Prior to estimation, a sensitivity analysis was performed to reduce the number of parameters required to be estimated.

FIGURE 8-46: Subgroups of recovery trajectories of concussed contact athletes per biomarker. Return-to-play (RTP).



When blood biomarker levels are sampled at multiple times after a concussion, time-concentration curves can be modeled by kinetic models that identify kinetic parameters such as half-life, time to maximum concentration, and maximum concentration. Some kinetic parameters can be estimated, such as volume of distribution; whereas, other kinetic parameters can be calculated, such as rate of absorption and rate of elimination. Initial results, gathered from NCAA-DOD Concussion Assessment, Research, and Education (CARE) data in the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System from a patient sample that includes military cadets, show significant differences in the kinetic parameters between blood biomarkers (Figure 8-47).

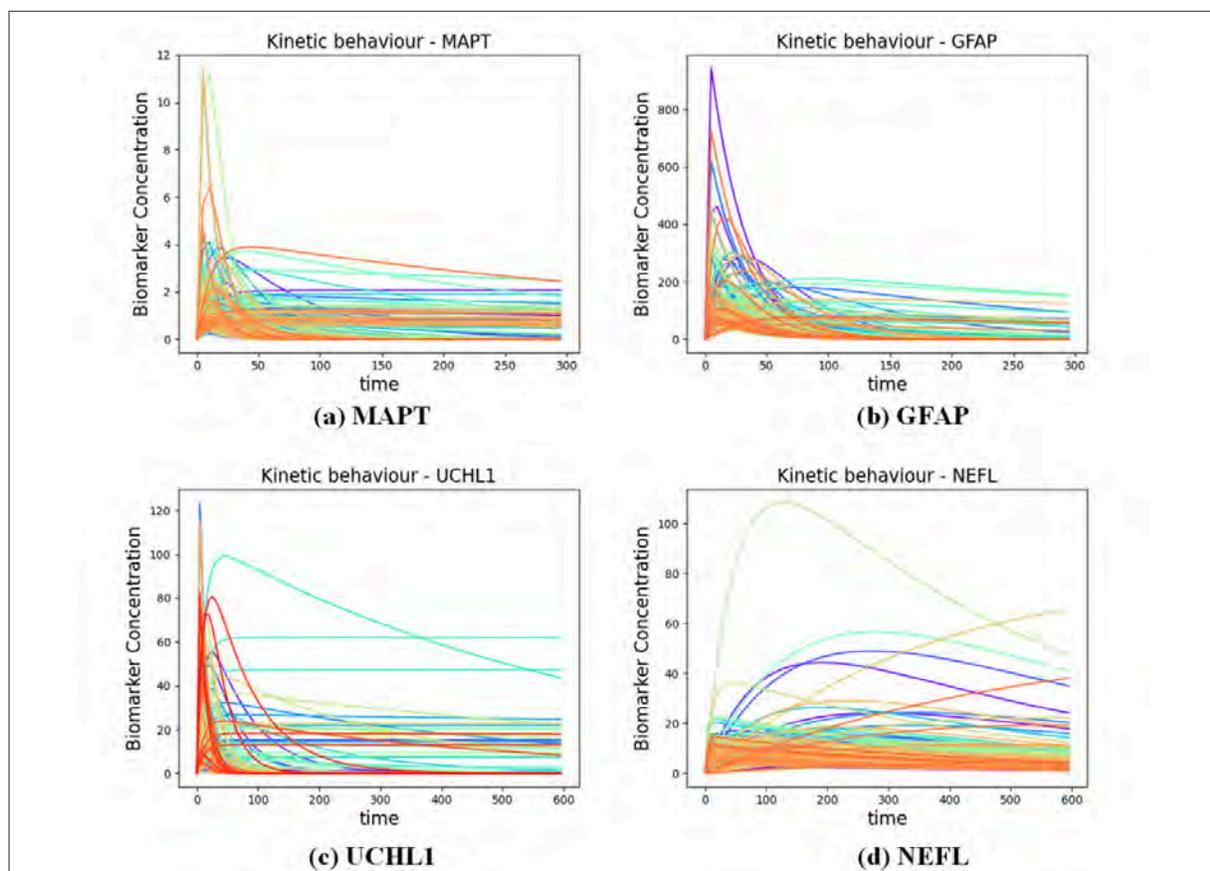
Specifically, a longer half-life was observed for neurofilament light chain (NEFL), and shorter

half-life for microtubule-associated protein tau (MAPT) and ubiquitin carboxy-terminal hydrolase L1 (UCHL1). Based on kinetic models, sensitivity analyses are being performed that will determine the effects of timing of the blood samples, subject age, subject renal function, and subject body mass index on blood biomarker levels after TBI.

Appropriate timing for a Service member to return to duty is critical to their care and ability to perform their job optimally, as mTBI affects performance of duties at the highest level, both physically and/or mentally. By informing the return-to-duty medical decision-making using pharmacokinetic modeling, a patient with symptoms of cognitive or multi-modal dysfunction can return to their assigned duties after the appropriate amount of time.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

FIGURE 8-47: Kinetic behavior of (A) MAPT, (B) glial fibrillary acidic protein (GFAP), (C) UCHL1, and (D) NEFL biomarkers, for all patients with concussion in the dataset. Each curve is associated with one subject.



An Explainable and Statistically Validated Ensemble Clustering Model for Identification of TBI Subgroups

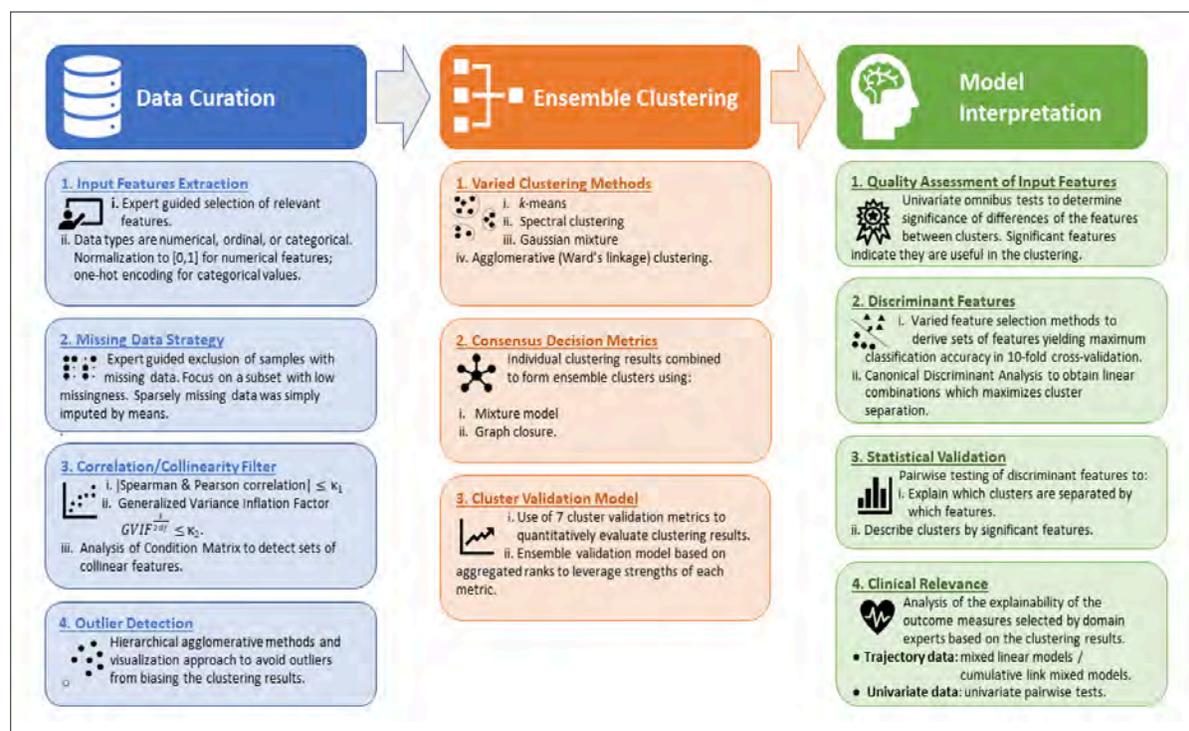
Patients who suffer from TBI, including Service members, are a heterogeneous population that exhibit diverse pathologies, prognoses, and recovery trajectories. This research investigates a model that identifies phenotype features that delineate patients into more homogeneous subgroups and characterize them in terms of injury severity and recovery. This model has the potential to reveal insights that will aid clinicians in improved assessment of TBI sub-phenotypes, optimizing the individualized risk-reward tradeoff of returning to duty.

In research published in IEEE Access (Yeboah et al., 2020), an ensemble cluster analysis framework was developed that integrates

several stages of statistical methodologies to enhance the quality and interpretability of the results (Figure 8-48). Applying this methodology to a TBI dataset obtained from the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System yielded six patient subgroups, with respect to mechanism of injury, severity of presentation, anatomy, psychometric, and functional outcome. This tool extends beyond applicability in TBI patient subgroups, as it can be used for analysis of other clinical datasets, as well as other diverse data science applications in biomedicine.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

FIGURE 8-48: Explainable and statistically validated ensemble clustering model. Image originally featured in Yeboah et al. (2020) and is licensed under [CC BY-NC-ND 4.0](https://creativecommons.org/licenses/by-nc-nd/4.0/).



Clinical Audiometric Patterns of Hearing Loss Following Blast-Related Injury in U.S. Military Personnel

In a study performed by NHRC and published in the International Journal of Audiology (Joseph, Shaw, et al., 2020), researchers used the Blast-Related Auditory Injury Database to examine the post-injury audiograms of 1,186 male Navy and Marine Corps Service members. The Service members' post-injury audiograms were compared with their pre-injury normal hearing thresholds and audiograms, to reveal patterns of hearing loss that resulted from blast-related injury (BRI).

Fifteen percent of the Service members analyzed met criteria for post-injury hearing loss, with most having mild to moderate loss. Those with hearing loss were categorized into pure-tone average (PTA) or single-frequency hearing loss subgroups. Three distinct audiometric patterns emerged: flat, sloping, and rising. PTA hearing loss was most associated with a flat audiometric pattern. The BRI group more commonly had PTA hearing loss (50 percent versus 33 percent, $p < 0.036$) compared to the non-blast-related injury (NBRI) group. Low- and high-frequency PTAs were significantly higher in those with BRI compared to NBRI. Single-frequency hearing loss was mostly unilateral and high frequency.

Post-injury audiometric patterns of hearing loss among military personnel were shown to vary in this study. BRI produced hearing loss across test frequencies and had more clinically actionable post-injury audiograms than NBRI. Read about another study that used the Blast-Related Auditory Injury Database on [page 192](#).

This effort was managed by CDMRP with support and programmatic oversight by CRM/RP/JPC-8.

Objective and Subjective Auditory Effects of TBI and Blast Exposure in Service Members and Veterans

Difficulty comprehending speech in noisy environments can occur after blast exposure or TBI in Service members and Veterans. These deficits may not be captured by standard auditory clinical tests. Additionally, the contribution of cognitive, auditory, or other post-blast symptomological factors to communication challenges is not clear. In a study published in Frontiers in Neurology (Kuchinsky et al., 2020), researchers from DVBIC, now called TBICoE, evaluated the significance of these factors in Service members and Veterans, using subjective and objective tools in the auditory, cognitive, and neurological symptom domains.

Service members and Veterans ($n = 212$; 37.69 ± 10.25 years) underwent auditory and neuropsychological testing at WRNMMC as part of the Congressionally mandated 15-Year Longitudinal TBI Study (FY07 NDAA, Section 721). TBI history (7.33 ± 8.15 years post-injury) included 40 percent with a history of an uncomplicated mTBI, 29 percent with "greater than" an uncomplicated mTBI (complicated mTBI [$n = 16$], moderate TBI [$n = 14$], severe TBI [$n = 15$], penetrating TBI [$n = 16$]), and 31 percent with no history of TBI (orthopedic injury controls [$n = 41$], non-injured controls [$n = 25$]). Participants were characterized as having been exposed to blast if they self-reported "yes" (40 percent) to a question from the Ohio State University Traumatic Brain Injury Identification Method, asking, "Have you ever been nearby when an explosion or blast occurred, that resulted in you feeling confused, disoriented, or having a loss of memory for a few seconds or minutes (or longer)? Think about any combat-related incidents."

Audiological screening included otoscopy, tympanometry, and pure tone air conduction thresholds. To assess communication challenges (i.e., speech-in-noise), the following tests were used: Modified Rhyme test, Standard and Time Compressed/Reverberant Quick Speech-in-Noise

Tests, Listening in Spatialized Noise, and High/Low Context Sentences. Subjective auditory complaints were assessed using the Tinnitus and Hearing Survey. Additional measures were used to assess PTSD, depression, and cognitive domains.

Results from the least absolute shrinkage and selection operator (LASSO) analysis model demonstrates that the factors impacting objective speech recognition included history of TBI and executive function. Self-reported hearing difficulties were associated with blast exposure and PTSD symptoms. Tinnitus complaints were predicted by more severe forms of TBI, PTSD symptoms, and reduced processing speed. Together, this research shows that a history of TBI or blast exposure leads to communication challenges and emphasizes that audiological testing should extend beyond pure-tone audiogram when evaluating the chronic effects of blast or TBI exposure.

This research was supported by DVBIC (now called TBICoE).

Role of Blast-Induced Mild TBI on Sleep Dysregulation and Glymphatic Processes

In conjunction with chronic sleep loss, TBI is a common challenge for the Navy and Marine Corps mission and can negatively impact readiness. The characterization of glymphatic functions and chronic sleep loss in an mTBI model, and its role in the development of neurocognitive deficits, could provide critical information to increase mission readiness.

This project by researchers at NMRC utilized a rat blast-induced mTBI model (single 10.88 psi [75 kPa] blast) to characterize the effects of blast exposure and sleep disturbances on glymphatic function. Research was conducted by inducing sleep pattern alterations (deprivation or induction) after blast exposure. Behavioral tasks were used to evaluate changes in motor and cognitive function after blast with, and without, sleep alterations. Biochemical assays were used to evaluate

alterations in the clearance of amyloid beta (A β) 40 and aquaporin 4, as a surrogate measure of glymphatic function.

An increase in A β 40, a potentially neurotoxic protein, was observed in the hippocampus after sleep deprivation of blast-exposed animals. The behavioral studies showed cognitive deficits in all sleep-deprived groups (blast and sham), and in blast-alone-animals compared to uninjured, normal sleep animals. The data demonstrate that sleep deprivation is more detrimental than sleep induction to cognitive function, and that sleep deprivation following mTBI may affect protein clearance.

Characterization of sleep dysregulation after mTBI could inform clinical decision support tools or guidelines for management of blast-exposed military personnel; and treatment of insomnia after blast may deter accumulation of harmful proteins in the brain.

This research was supported by ONR.

Circadian Rhythm Research Leads to Possible TBI Detection

TBI can cause dysregulation of the circadian rhythms and has been known to impact sleep quality. Mild TBI is also tied to chronic pain, which itself is subject to circadian rhythmicity. Thus, the study of how to regulate circadian rhythms, sleep, and the related neurobehavioral and neurological processes has the potential to help detect and mitigate the impacts of TBI. DEVCOM ARL-funded researchers at Rensselaer Polytechnic Institute's Engineering Research Center on Lighting Enabled Systems and Applications used optimal control methods to study the regulation of circadian rhythms and the sleep process. The objective of the optimization was to entrain the circadian rhythm as quickly as possible, or to maximize neurobehavioral performance during a prescribed performance interval.

To optimize the circadian rhythms and related processes, the researchers developed biometric signals for estimating the state of the circadian rhythms and related processes. These signals are measurements of indirect markers that can be used to estimate relevant states and include biometric data from processes that are driven by the circadian rhythms, such as actigraphy, heart rate, and body temperature. The researchers demonstrated in a pilot study that circadian phase shift estimates, obtained from processed actigraphy signals, are within one hour from those obtained using a clinical standard method that involves salivary sample collection and off-site sample processing.

Utilizing the actigraphy data, the researchers developed and tested an algorithm for sleep/wake detection based on minute-by-minute actigraphy data. The inferred sleep data is then used to compute the subjects' sleep quality features. In collaboration with researchers at Thomas Jefferson University, the team developed a method for detecting mTBI from irregularities in the subjects' sleep quality. Figure 8-49 summarizes the performance of the mTBI detection algorithm in a pilot study that involved 20 subjects—ten healthy, and ten with mTBI.

This research is supported by DEVCOM ARL.

Investigating Sex-Based Differences in Preclinical Mild TBI Models

Mild TBI impacts individuals heterogeneously based on many factors, including the sex of the patient. In FY20, CNRM made critical discoveries regarding sex-based differences after mTBI.

The first such investigation was completed to determine the effects of shock wave exposure in the Advanced Blast Simulator. In C57BL-6J mice, Evans blue dye, which binds to immunoglobulins, was infused either four or 24 hours after blast exposure. At four hours after blast, there was an accumulation of Evans blue in the cerebral cortex, indicating that blast exposure caused damage to the blood-brain barrier (BBB), but when the dye was infused 24 hours after blast, there was no evidence of such accumulation, implying that BBB permeability had resolved within the 24-hour time window. These animals underwent a series of behavioral tests, and there were no differences in performance on the elevated plus maze (anxiety test), forced swim test (depression test), or the sucrose preference test (hedonic test). However, animals that sustained blast exposure spent less time immobile, suggesting an “agitated” depression response.

Additional research was performed to determine the presence and/or extent of chronic sex-based behavioral and pathological changes following

FIGURE 8-49: The mTBI classifier performance for various values of N (the number of subjects used in the training set) and the number of days of data used for each subject. The number within and outside of the brackets indicate the performance of two different feature sets that are used in the classifier. A false positive is defined as a healthy subject that is falsely classified into the mTBI group.

2N	M days	Sensitivity	Specificity	False positive rate	False negative rate
16	3	59%(52%)	89%(84%)	6%(8%)	21%(24%)
16	7	57%(78%)	92%(88%)	4%(6%)	22%(11%)
16	10	68%(82%)	92%(90%)	4%(5%)	16%(9%)
18	3	56%(56%)	92%(83%)	4%(9%)	22%(22%)
18	7	71%(74%)	94%(90%)	3%(6%)	15%(13%)
18	10	77%(87%)	94%(95%)	3%(2%)	12%(7%)

repetitive concussive injury. This work, published in *Frontiers in Neurology* (Tucker, Velosky, et al., 2019), assessed motor, cognitive, and neuropsychiatric functioning in male and female mice after repeated, focal blunt head injury (three events at 24-hour intervals). All injured mice, relative to their control counterparts, exhibited motor deficits and cognitive deficits on the rotarod and active place avoidance tests, respectively, as well as greater agitation on the tail suspension test. Injured male mice were significantly more hyperactive in the open field test than injured female mice. One-year post-injury, all injured mice developed pathological evidence of microbleeds in the cortex as well as increased cortical atrophy in the corpus callosum and optic tracts, as measured via glial fibrillary acidic protein (GFAP) staining. Observation of chronic behavioral and pathological changes in a repetitive concussion model may be the basis for future preclinical links between TBI and neurodegeneration.

In research published in *PLoS One*, that focused on behavior in the acute/sub-acute phase after TBI, Tucker, Winston, et al. (2019) exposed male and female mice to repeated, focal blunt head injury (three events at 24-hour intervals) and assessed fear conditioning, hyperactivity, and depressive-like symptoms. After behavioral analysis, a pathological assessment of injury via immunohistochemistry was performed. Relative to control mice, injured mice were more hyperactive and showed less freezing behavior during fear conditioning; however, injured female mice did not exhibit the amygdala-dependent reductions in cue-induced freezing compared to their male counterparts. Pathological analysis revealed that injured mice developed increased astrogliosis in the optic tracts and corpus callosum and that counts of inhibitory parvalbumin-positive (PV+) interneurons did not change in the cortex and amygdala, but injured male mice had fewer PV+ cells in the hippocampus. The subtle sex-based behavioral changes found by the researchers are hypothesized to be due to excitation-inhibition imbalances among the cortex, hippocampus, and amygdala.

A particularly relevant review recently published in *Frontiers of Neurology* (McCabe & Tucker, 2020), by CNRM-sponsored researchers, provides an overview of clinical and preclinical approaches to sex as a biological variable in blast-related TBI.

These efforts were supported by CNRM.

Developing a Combat-Relevant Translational Model of Heterotopic Ossification

Heterotopic ossification (HO) is a pathological process characterized by ectopic bone growth in the musculature and/or periarticular regions following tissue injury, traumatic limb amputation, and brain or spinal cord injury. HO has been reported in approximately 65 percent of wounded Warfighters with limb loss during Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF); a much higher frequency than previous military conflicts. Symptomatic HO is problematic for Service members since it delays rehabilitation regimens, causes pain, limits range of motion, and requires modifications to prosthetic limbs. To date, there are no clear experimental findings indicating a mechanism for quelling, or preventing, metabolically active HO from manifesting. As noted by Forsberg et al. (2014), “one of the challenges preventing advances in this field has been the lack of robust animal models for HO.”

To offset this problem, researchers at USU, Utah State University, and the University of Utah developed a first-of-its-kind ovine model using the following combat-relevant factors associated with HO: 1) traumatic blast, 2) tourniquet usage, 3) bioburden, 4) negative pressure wound therapy, and 5) displaced bone (Williams et al., 2019). Figure 8-50 is an example of the clinically relevant ectopic bone that the team was able to produce with repeatability and reproducibility.

In the next phase of their work, the team will implement pragmatic and cost-effective solutions to turn the signal “off” to minimize HO formation and recurrence. This effort positively impacts military

readiness, ensures that injured personnel can return to active duty, and could be a significant cost savings for the DOD.

This effort was managed by CDMRP with support and programmatic oversight by CRMRP/JPC-8.

FIGURE 8-50: Heterotopic ossification generated in the ovine model.



Reconstruction and Prosthetics

Large Tissue-Engineered Skeletal Muscle Unit with and without a Tissue Engineered Neural Conduit for the Repair of Volumetric Muscle Loss

Volumetric muscle loss (VML) is the surgical or traumatic loss of a large volume of skeletal muscle that leads to functional impairment, and often peripheral nerve damage and physical deformity. VML accounts for 60–65 percent of military disability patients and significantly affects civilian trauma patients, with an estimated annual health care cost of \$800 billion in the U.S. The current standard of care for VML is the use of autologous tissue from a donor site; however, this technique

is limited, and regenerative strategies for restoring muscle function and improving clinical outcomes are needed.

Researchers at the University of Michigan received an award from the Defense Medical Research and Development Program (DMRDP) to fabricate large engineered skeletal muscle unit (SMU) constructs, which could be used to restore muscle function, recruit native regenerative cells, and integrate with native tissue. SMU constructs were fabricated from isolated muscle progenitor cells, grown in culture, to form 3D cylindrical constructs that were assembled in parallel, forming fused SMUs to achieve the size required to fill the VML defect. The scaled-up fabrication process yielded 3D SMU constructs that were 18 cm in length and 1 cm in diameter (Figure 8-51). To assist in nerve regeneration and reinnervation of the muscle, the team also fabricated engineered neural conduits (ENC) from bone marrow, isolated and cultured to form a tube, and subsequently devitalized, forming a construct of extracellular matrix proteins only.

Scaled-up SMU constructs and ENC were characterized *in vitro* and evaluated in a clinically relevant large animal VML injury model (Novakova et al., 2020). Sheep underwent a 30 percent VML injury of the peroneus tertius (PT) followed by repair with SMU only, or SMU + ENC, and were compared to no treatment animals after a three-month recovery period. The VML-only group exhibited a significant decrease in muscle mass between the contralateral and surgical sides ($p < 0.001$, $n = 15$), indicating a lack of mass recovery. Conversely, there was no significant difference in muscle mass observed between the contralateral and repaired PT of the VML + SMU and the VML + SMU + ENC groups. Assessments of muscle force recovery revealed that in the VML-only group, the maximum force production of the surgical PT was significantly lower than the contralateral PT ($p < 0.001$, $n = 11$). In contrast, there was no distinguishable difference in force production between the repaired PT and the contralateral side of the VML + SMU group

FIGURE 8-51: The SMU. Modularly fused SMUs are approximately 1 cm wide and 18 cm long prior to implantation.



(n = 9) or the VML + SMU + ENC group (n = 11). They also demonstrated that the ENC was able to effectively bridge the gap between the re-routed nerve and the surgical site. When the re-routed nerve was stimulated, a muscle contraction was elicited in 75 percent of the animals repaired with the SMU + ENC, compared to just 25 percent in the SMU-only group.

These results demonstrate the ability of clinically-relevant-sized SMUs to restore muscle mass and force production to a level indistinguishable from uninjured contralateral muscle, in a sheep model, after only three months. The team will be working to assess additional functional measurements.

This effort was managed by CDMRP with support and programmatic oversight by CRM/RP/JPC-8.

Bridging and Babysitting Tissue-Engineered Nerve Grafts Promote Axon Regeneration and Maintain Distal Targets to Treat Peripheral Nerve Injury

Extremity injuries account for up to 79 percent of trauma cases from theater and often result in the loss of entire segments of major nerves and large areas of muscle. There are no regenerative therapies to address such injuries, and the

standard of care is limited to surgical efforts that offer little prospect for restoring meaningful function. Researchers at the University of Pennsylvania, along with collaborators at Rutgers University, the Corporal Michael J. Crescenz VA Medical Center, and industry partner Axonova Medical, are supported by an FY15 award from DMRDP to pioneer a suite of tissue-engineered medical products designed to facilitate nerve regeneration and muscle reinnervation following complex neuromuscular injuries. The University of Pennsylvania researchers pioneered the first dual peripheral nerve repair strategy that provides tissue-engineered living “bridges” across missing nerve segments, while maintaining the full regenerative pathway and receptiveness of target muscle—referred to as “babysitting.” This effort, published in the *Journal of Tissue Engineering and Regenerative Medicine* (Katiyar et al., 2019), resulted in the development of the first axon-based tissue-engineered nerve grafts (TENG) as “living scaffolds” across major peripheral nerve injuries (Figure 8-52-Top). When used to bridge segmental nerve defects, TENGs were found to achieve levels of functional recovery equivalent to the gold-standard sensory nerve autograft in preclinical rat models (Katiyar et al., 2020; Maggiore et al., 2020). In addition, using established porcine

models of major nerve injury (Burrell et al., 2020), the investigators showed that TENGs promote and accelerate ultra-long-distance nerve regeneration and facilitate functional recovery. Furthermore, the team has shown that TENGs can provide pathway and target protection by “babysitting” pro-regenerative host cells and neuromuscular junctions in cases of ultra-long-distance axon regeneration. Here, TENGs extend axons into otherwise axotomized distal nerve sheath, to maintain the pro-regenerative capacity of host Schwann cells and preserve the health of host

motor neurons in the spinal cord (Figure 8-52- Bottom; Maggiore et al., 2020). Current efforts are directed at implementing clinical-grade tissue manufacturing to enable pivotal safety and efficacy trials to satisfy regulatory criteria with the FDA. Once available in the clinic, these next-generation tissue-engineered medical products will greatly improve the quality of life for Warfighters and Veterans as well as civilian patients.

This effort was managed by CDMRP with support and programmatic oversight by CRMRP/JPC-8.

FIGURE 8-52: (Top) Axon-based TENGs serve as “living scaffolds” across major peripheral nerve injuries in a rat model. (Bottom) TENGs extend axons into otherwise axotomized distal nerve sheath to maintain the pro-regenerative capacity of host Schwann cells in a rat model.

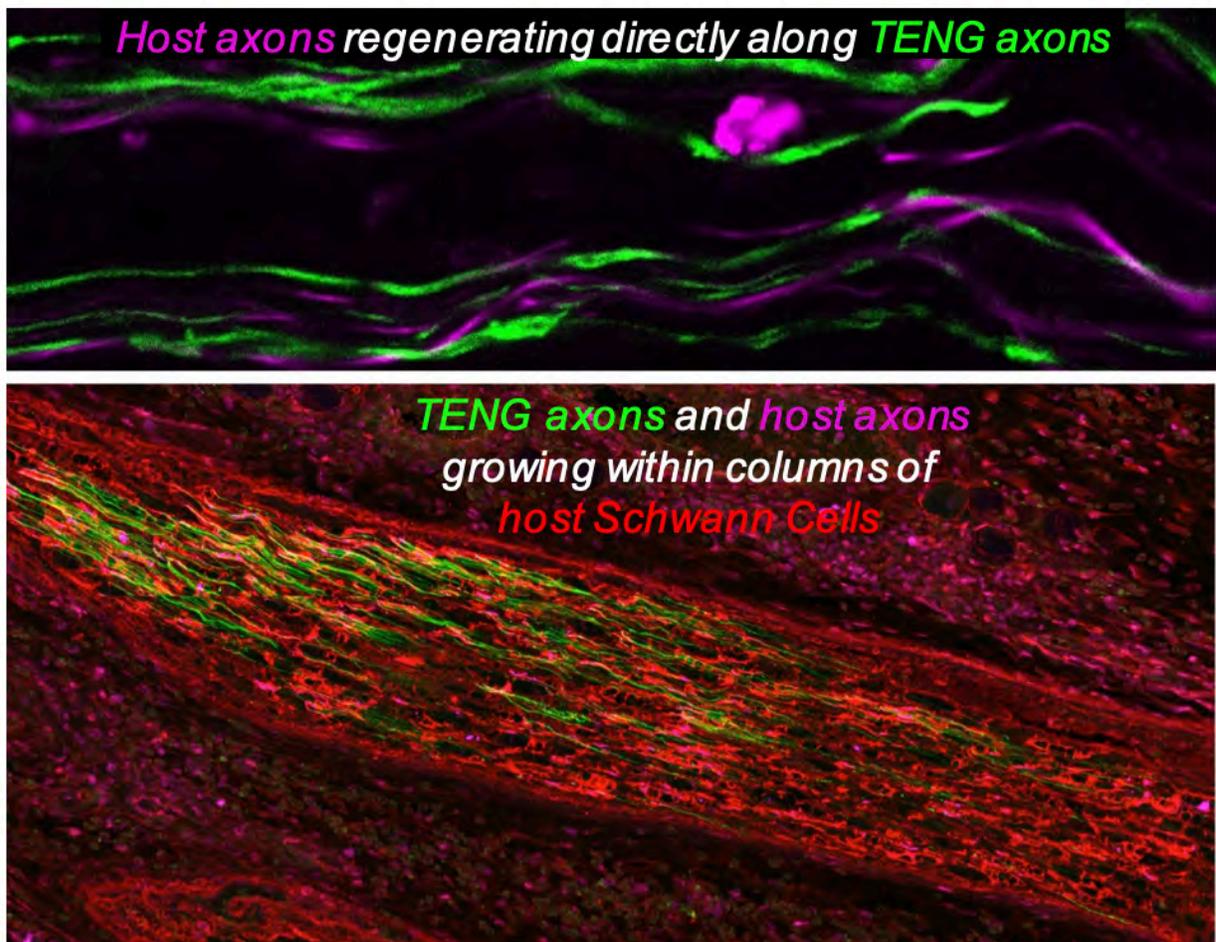




Photo credit: Seaman Luke Cunningham/ U.S. Navy

Engineered Microparticles for Promoting Composite Allograft Transplant Tolerance

Researchers at the University of Pittsburgh, in collaboration with Wake Forest University, received an FY14 Reconstructive Transplant Research (RTR) Program award to evaluate the utility of engineered microparticles (MP) to promote vascularized composite allotransplantation (VCA) acceptance. VCA, the transplantation of multiple tissue types, such as a face or hand, has become a viable option to restore function and appearance in some amputees or severely disfigured individuals. Like solid organ transplantation, VCA recipients must adhere to lifelong immunosuppression. In order to promote transplant tolerance without reliance on harsh immunosuppressive drugs, the team has engineered MPs releasing C-C motif chemokine 22 (CCL22). CCL22 serves to recruit regulatory T cells (Treg), which suppress the effects of other T cells and can promote immune tolerance with prolonged graft survival in the absence of immunosuppression.

The team demonstrated that two doses of CCL22 releasing MPs, termed “Recruitment-MPs,” can lead to long-term survival of greater than 200 days in a rodent hindlimb transplantation model (Fisher et al., 2020). Recruitment-MPs were administered, via injection, into the transplanted hindlimb

immediately after surgery, and animals received the immunosuppressive drug tacrolimus for 21 days, at which point it was discontinued and the second dose of Recruitment-MPs administered. Control animals, only receiving 21 days of tacrolimus, without Recruitment-MPs, rejected the hindlimb within 2–3 weeks after tacrolimus was discontinued. Treatment with Recruitment-MPs reduced markers of inflammation and increased the percentage of Tregs in draining lymph nodes of long-term surviving animals.

The team also engineered a second set of MPs to enrich Tregs at the allograft site (Fisher et al., 2019). Tregs make up only ~2–3 percent of circulating lymphocytes, and this rare population may not be sufficient to resolve an episode of rejection in the setting of VCA transplantation. Engineered Treg-inducing (TRI)-MPs were designed as a biodegradable, controlled-release system for the delivery of transforming growth factor beta 1 (TGF- β 1) and interleukin (IL)-2 to induce Tregs from CD4+ T cells, together with the immunosuppressive drug rapamycin. In a rodent hindlimb transplantation model, recipients received standard immunosuppression for 21 days, and rejection was observed within 2–3 weeks after immunosuppression was discontinued. Recipients receiving two doses of TRI-MPs, injected into the transplanted hindlimb immediately after transplantation and at day 21, survived greater than 300 days with no additional treatment.

Together, these results demonstrate that synthetic MPs are capable of recruiting and enriching Tregs to promote long-term immunosuppression-free survival in a rodent model. Next, the team will be exploring these MPs in a clinically relevant large-animal VCA model.

This effort was supported by the RTR Program with program interest by CRM/RP/JPC-8.

Can a Novel Beam-Walking Test Improve Fall Risk Assessment in Service Members, Veterans, and Civilians Who Use Lower Limb Prostheses?

Existing clinical balance tests are too easy. They do not pose a sufficient challenge to expose subtle, but critically important, differences in balance that underlie fall risk in Service member, Veteran, and civilian lower limb prosthesis users. Consequently, these tests are unable to discriminate between lower limb prosthesis users with, and without, a history of falls, or predict who is at risk for a fall. As a result, there are no effective or accepted screening tests for diagnosing fall risk in lower limb prosthesis users. To address this gap and improve the assessment of fall risk in lower limb prosthesis users, researchers assessed the validity and reliability of a novel Narrowing Beam-Walking Test (NBWT) that provides progressively increasing challenge to balance control.

Over the course of three years, University of Illinois at Chicago researchers have established the criterion validity, reproducibility (test-retest and inter-rater reliability), and predictive validity of the NBWT. This was accomplished by administering the NBWT and four contemporary performance-based balance tests to 60 lower limb prosthesis users. These individuals were followed prospectively for six months to report fall events. Results have been published in a series of papers (Sawers & Hafner, 2019; Sawers & Hafner, 2020; Sawers et al., 2020), with the final product being a valid and reliable test to predict fall risk in lower limb prosthesis users.

The performance-based balance test discriminates fallers and non-fallers with greater accuracy than existing tests. It is now being used in several clinical, industry, and academic centers. The results from this work will help clinicians select balance tests suitable for lower limb prosthesis users, making clinical decisions more objective and evidence-based.

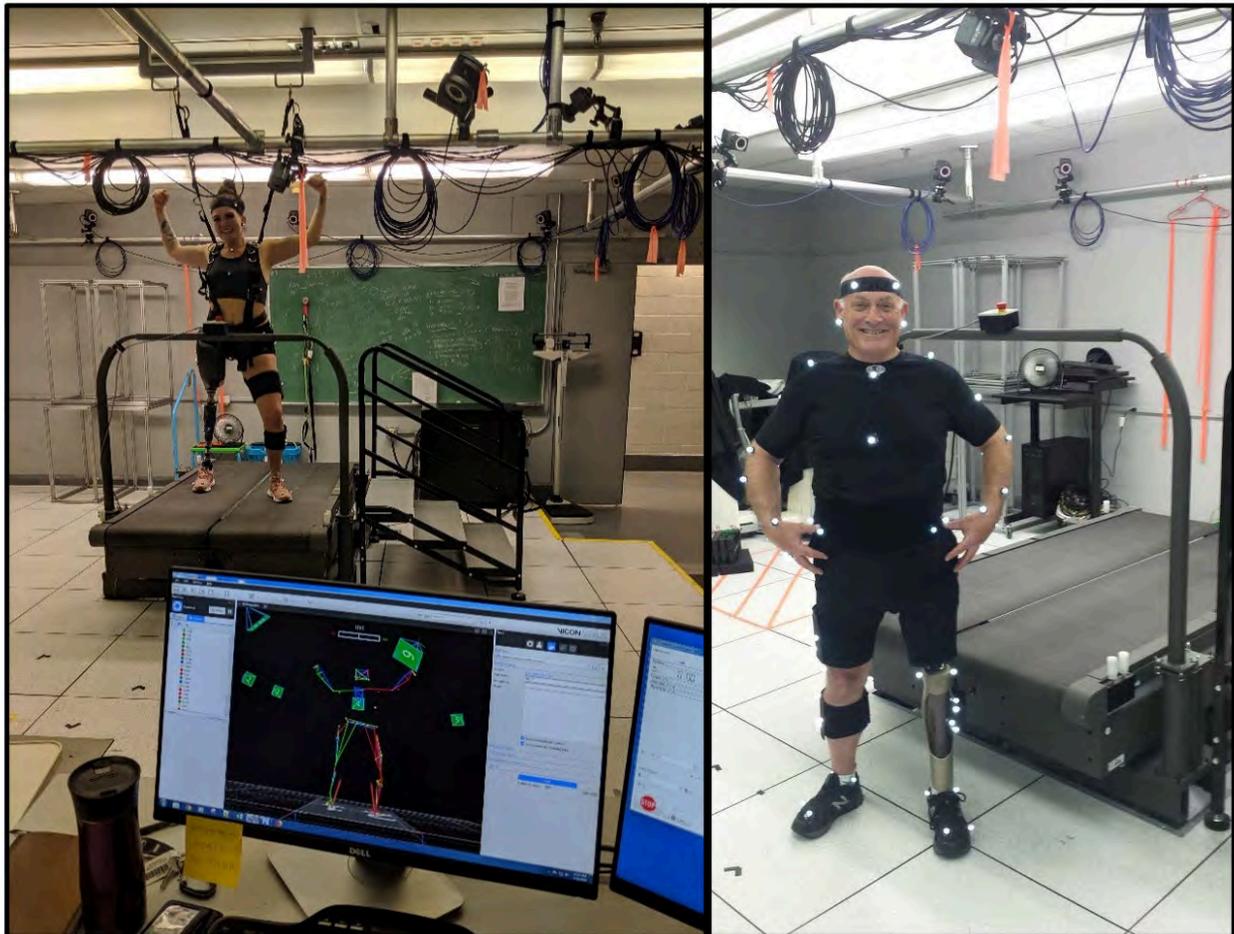
This effort was supported by the Orthotics and Prosthetics Outcomes Research Program with program interest by CRM/RP/JPC-8.

Motorized Hip Orthoses to Improve the Gait Ability of Transfemoral Amputees

A research endeavor at the University of Utah is expected to have an impact on the prosthetics and orthotics field by demonstrating a novel assistive device that works in synergy with existing prosthetic solutions, rather than aiming to replace them. Specifically, the goal is to improve amputees' mobility by providing bilateral hip assistance with a lightweight motorized orthosis. Preliminary results suggest that the motorized hip orthosis developed as part of this work can reduce the clinical impact of transfemoral amputation by improving gait efficiency and stability, thus enhancing mobility; while over the longer-term, reducing secondary health effects such as psychological disorders, back pain, and osteoarthritis that result from uneven gait and compensatory movements. Importantly, the motorized hip orthosis can be used with any commercially available lower limb passive prosthesis; users and clinicians can continue to select the best prosthesis for the individual needs of the user. In addition, control strategies are being developed to improve the gait of transfemoral amputee subjects using either a passive prosthesis or a microprocessor-controlled passive device; thus ensuring that the orthosis provides appropriate assistance for the type of prosthesis being used.

As part of this project, the research team recently published a dataset in Scientific Data (Hood et al., 2020) containing raw and processed biomechanics data from 18 above-knee amputee participants, classified as limited community ambulators (K2, n = 9) and full community ambulators (K3, n = 9), walking at four different speeds. Figure 8-53 depicts patients with the full-body modified plug-in-gait marker-set. Such a comprehensive and open dataset was not previously available to the research field, and can provide the biomechanics community with a new means to understand gait

FIGURE 8-53: (Left) Female participant standing on the treadmill; the computer screen shows the full-body modified plug-in-gait model applied to the markers she is wearing. (Right) Male patient standing in front of the instrumented treadmill wearing the full-body modified plug-in-gait marker set.



compensations with currently available prostheses. Beyond the biomechanics field, this dataset can have an impact on the engineering community, as this new knowledge can be used to refine the design and control of available prostheses. The overall expectation is that providing data collected in this project to the community will help make significant strides in providing the best assistive devices to Service members as they return to normal daily function.

This effort was supported by PRORP with program interest by CRM RP/JPC-8.

Improved Prosthetic Control Strategies Enhance Sloped Walking for People with Transfemoral Amputation

Powered prosthetic legs are a promising new technology that may help people with lower limb loss improve function. A major challenge to overcome for these devices is to achieve clinical implementation. A critical step in reaching this goal is the successful recognition of different terrains that a prosthesis is navigating, and then appropriate coordination of the power delivered at each prosthetic joint. A research team led by scientists at the Georgia Institute of Technology, in collaboration with EACE at the Center for the Intrepid at Brooke Army Medical Center, was able to validate an impedance control strategy for a powered knee and ankle prosthesis to perform

common locomotion tasks, such as level walking, and ascending and descending slopes.

The investigators improved on a previous powered prosthetic system (Figure 8-54). The device has a powered flexion/extension at the knee joint, a powered dorsiflexion/plantarflexion, and passive inversion/eversion at the ankle joint. The device is approximately 7.5 kg, including the battery, which is similar to the missing biological limb mass.

The investigators implemented a hierarchical control paradigm, featuring a high-, a mid-, and a low-level controller. The controller uses machine learning and sensor fusion techniques to estimate user intent, environmental features, and user state in real-time, which allows the user to dynamically adapt to real-world environments. The controller then ensures that the desired torque is appropriately provided to the user.

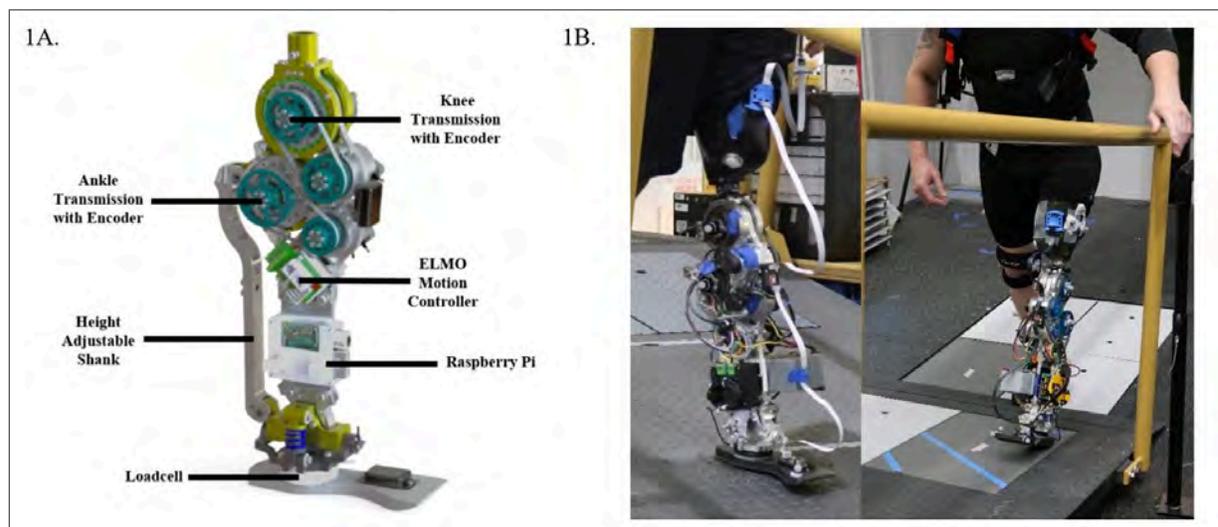
This innovative prosthetic system controller was used on three people with transfemoral amputation who walked on a treadmill. It was also used on four people with transfemoral amputation during a ramp ambulation circuit to test whether the controller could correctly identify the terrain and appropriately control the device.

The advanced powered knee and ankle prosthesis generated reliable gait across all terrains, and was able to correctly recognize each part of the gait cycle 100 percent of the time, across 6,348 transitions using the minimal tuning of impedance parameters. Further steps in developing systems that can predict intent without prior knowledge of the user have yielded good results with a 96 percent accuracy of classifying steps across five different ambulation modes (e.g., level walking, ramps, and stairs). Furthermore, walking speed can be estimated with a resolution of 0.068 ± 0.009 m/s while generalizing to new subjects. This study was published in *Military Medicine* (Bhakta et al., 2020).

These results are good indicators for adopting these technologies in the clinical setting and making these controllers more adaptable to the user. The development of actively controlled powered prosthetic joints may reduce post-amputation compensatory strategies, and assist Service members in ambulating over different conditions in a safe, seamless, and natural manner.

This effort was managed by CDMRP with support and programmatic oversight by CRM/RP/JPC-8.

FIGURE 8-54: (Left) Features of the device include powered knee and ankle joints. (Right) The system enabled multiple users to walk on a ramp—descent and ascent. Images originally featured in Bhakta et al. (2020).



Long-Term Care

Outpatient Medication Prescription Patterns Among Service Members Who Sustained Major Limb Amputation in the Iraq and Afghanistan Conflicts: A Population-Based Analysis

Combat trauma, particularly blast-related polytrauma, may have immediate and lasting secondary impacts on multiple physiological and psychological systems. NHRC, with support from EACE, completed a retrospective study of existing health data gathered during the first 12 months post-injury for patients who sustained combat-related amputations. Their goals were to 1) describe the full range of outpatient medications prescribed; 2) track longitudinal changes in prescription activity by medication type; and 3) identify patient characteristics, including injury-specific measures and diagnoses of pain, psychological, and other disorders associated with medication prescriptions.

The Expeditionary Medical Encounter Database provided casualty records with injury-specific data (e.g., blast injury, injury severity, limb amputation) to identify 1,704 Service members who sustained major limb amputations following combat injury in Iraq or Afghanistan from 2001–2017. Of these, 1,657 (97 percent) had outpatient prescription records during the first-year post-injury in the DOD Pharmacy Data Transaction Service (PDS), which records outpatient medication prescriptions including all new, repeated, and refill prescriptions. The Military Health System was queried for diagnostic codes of psychological and other disorders. Medications were classified according to the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification system. Clinicians identified 13 mutually exclusive and exhaustive medication categories, consisting of existing or condensed AHFS classes: opioids, immunologic/anti-infective, gastrointestinal/genitourinary (GI/GU), central nervous system (CNS), non-opioid analgesics, psychotherapeutic, autonomic nervous system, blood formation/

thrombosis, cardiovascular, electrolyte/caloric, hormone/metabolic, respiratory, and miscellaneous (i.e., all other medications). Prescription measures included percentage of patients, and mean prescriptions for each of the 13 categories, during the first 12 months and within each of the first four quarters (90-day intervals) post-injury.

During the first 12 months post-injury, the 1,657 patients with outpatient prescription records had a total of 107,507, with an average of 65 (standard deviation = 43.4). Patients had prescriptions in an average of 8 of the 13 medication categories. Opioids had the highest total prescriptions (29 percent of prescriptions), percentage of patients with at least one prescription (99 percent), and mean prescriptions (19). The next five highest categories were the CNS, GI/GU, psychotherapeutic, immune/anti-infective, and non-opioid analgesic medications. These five categories, along with opioids, accounted for 85 percent of all prescriptions and generally had the highest prescription activity during each of the first four quarters post-injury. Prescription activity generally declined across the first-year post-injury. Nonetheless, 73 percent of patients had at least one fourth-quarter prescription (i.e., 10–12 months post-injury) including opioids (51 percent), CNS (43 percent), psychotherapeutic (32 percent), or non-opioid analgesics (30 percent).

Regression analyses evaluated associations between independent variables (e.g., Injury Severity Score, blast injury, level of amputation, diagnoses for infection, chronic pain, PTSD) and prescription outcomes measures (i.e., number of medication prescriptions, presence or absence of medication prescription). After adjusting for covariates, analyses demonstrated that chronic pain, PTSD, injury in OEF (versus OIF), infection, and number of limb amputations were significantly associated with higher numbers of total prescriptions, and higher numbers of prescriptions within various individual medication categories (e.g., opioid and non-opioid analgesics, psychotherapeutic and other CNS medications, gastrointestinal). Other significant

factors in the regression analyses were Injury Severity Score and a diagnosis of phantom limb syndrome.

These results can be used to inform rehabilitation planning and clinical guidelines for a wide range of prescription medications.

This work was supported by EACE.

Combination Therapies for the Mitigation of Musculoskeletal Pathologic Damage in a Novel Model of Severe Injury and Disuse

Severe injury results in physiologic and musculoskeletal changes to the patient that are immediate and long-lasting. In response to injury, metabolic and physiologic responses determine length of hospitalization and activity limitations. Reduced mobility from bedrest and injury severity affect muscle and bone health, and are detrimental to rehabilitative success. Therefore, means to counteract adverse effects on muscle and bone after injury and disuse are needed. Pharmacologic (e.g., insulin, oxandrolone), non-pharmacologic (e.g., exercise), and nutritional interventions have been used independently with limited success. The combination of pharmacological interventions and exercise had not been systematically investigated prior to this study for polytrauma injuries.

At the conclusion of the study, detailed in recent publications in the *Journal of Burn Care & Research* (Song et al., 2017; Clark et al., 2019; Clark et al., 2020), the authors demonstrated that muscle homeostasis is disrupted in burn-injured adults. The authors also provided evidence in a rodent burn model with hindlimb loading—representing both burn and musculoskeletal injuries—that skeletal muscle microRNAs and gene expression profiles are altered by exercise. They also provide evidence in a published article in *Physiological Reports* (Song et al., 2019), showing that insulin and exercise improved muscle function in this rat model. Taken together, the data presented by this study team provide evidence that

combination therapy involving pharmacologic and non-pharmacologic interventions has a synergistic impact on recovery for polytrauma patients.

This effort was supported by PRORP with program interest by CRM/RP/JPC-8.

Blue-Light Exposure Increases Sleep Quality and Recovery Following Mild TBI

Patients with mTBI often experience disrupted sleep and abnormal circadian rhythms. Poor sleep quality after mTBI is associated with poor cognitive recovery and neuropsychiatric complications. To improve sleep quality and cognitive deficits, researchers tested blue-wavelength light exposure in a randomized, double-blind trial published in *Neurobiology of Disease* (Killgore et al., 2020). Participants included 36 adults with an mTBI in the previous 18 months. For six weeks, each participant was exposed to a blue-light LED light box for 30 minutes each morning, or to amber light for control. Sleep/wake activity was monitored by wrist actigraphy and sleep diaries. Outcome measures included neurocognitive and neuroimaging changes. The team found that compared to amber-light control, blue-light exposure reduced daytime sleepiness, improved cognitive performance, and was associated with changes in brain structure and functional connectivity. These data suggest that blue-light exposure is a potential treatment for sleep and cognitive symptoms experienced after mTBI, and may encourage brain repair after injury.

This effort was managed by CDMRP with support from PH/TBIRP with programmatic oversight by CCCRP/JPC-6.

Determining the Mechanism of Gait and Gaze Deficits After Mild TBI to Aid in Treatment of Multi-Sensory Impairment

Service members, Veterans, and civilians with head trauma from blunt or blast mechanisms, or those with inner ear disorders, often have deficits in the auditory, visual, and vestibular sensorimotor

domains. This collection of symptoms is known as multi-sensory impairment (MSI), and affects approximately 300–500 per 100,000 in the population. The research team at NHRC developed the Sensorimotor Assessment and Rehabilitation Apparatus (SARA) device to assess vestibular deficiencies and to test rehabilitative improvement in Veterans and civilians with MSI.

Veterans with MSI have a significant ocular misalignment relative to healthy controls. Further, evaluations of vestibulo-ocular reflex (VOR) and dizziness have found that individuals suffering from a TBI develop alternative rapid eye movements (known as saccades) to compensate for an inability to keep the eyes focused on the target of interest. Interestingly, these compensations did not contribute to overall absolute changes in the extent of the VOR. These compensatory eye movements were recruited at similar latencies, without correlation to VOR gain or direction of head rotation. This research was published in *Journal of Vestibular Research: Equilibrium & Orientation* (Le Cao et al., 2020). Devices only measuring VOR changes, such as video head impulse testing, may not be sufficiently sensitive to detect gaze deficiencies after TBI, which contribute to MSI.

Given that VOR gain changes may not accurately predict the underlying physiological status of an individual post-TBI, the investigators ran a trial, published in *Frontiers in Neurology* (Millar et al., 2020), to determine whether five weeks of vestibular rehabilitation would improve gaze and gait stability in participants with mTBI. Gait is closely linked to vestibular function and may also be predictive of underlying cognitive, motor, and mental wellness in individuals with TBI. Using gaze and gait stability exercises improves both subjective and behavioral performance despite no changes in VOR gain in most participants. Of note, 79 percent of participants showed improved dynamic visual acuity after vestibular rehabilitation, and it appears that residual otolith (inner ear) function appears correlated with such change.

Overall, the investigators have determined that subtle compensatory eye movements may be more reflective of and conducive to detecting and rehabilitating vestibular issues after TBI. This finding suggests that SARA may serve as an excellent proxy for more elaborate laboratory equipment impractical for a deployed environment. This can more reliably detect and treat individuals with mTBI to improve return-to-duty decision-making and quality of life for Service members and Veterans with MSI.

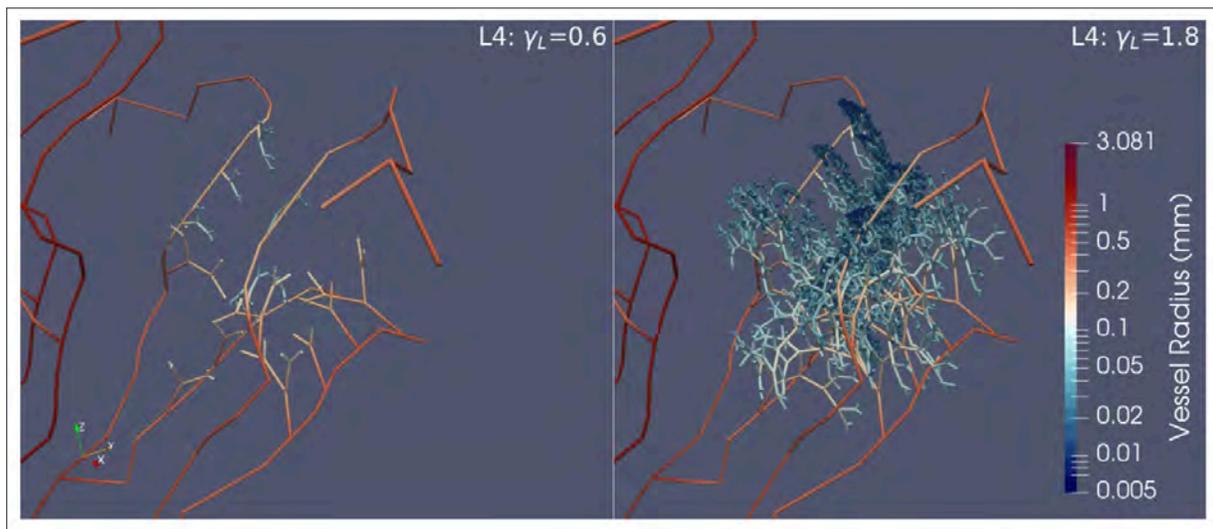
This effort was managed by CDMRP with support from PH/TBIRP with programmatic oversight by CRM/RP/JPC-8.

Models of Angiogenesis Provide Clues to Rehabilitation Following TBI

DEVCOM ARL-funded researchers at Applied Research Associates (ARA) developed a multi-fidelity model of the cerebral microvasculature restructuring that occurs after TBI. Unlike previous models, these models of TBI events and subsequent recovery connected the changes of cerebral vasculature, cell signaling, and altered flow as a codependent system. They also considered micro and macro timescales, modeling short- and long-term protein release/diffusion, and the resulting changes to cerebral blood flow after the initial trauma. Additionally, coupling this model to actual patient MR scans makes this model adaptable to a specific patient profile. The 3D nature of the vessel structure allowed evaluation of vessel recovery and densities as a function of the location of the TBI and the impact on long-term outcomes.

Leveraging the 3D nature of the brain vasculature, ARA was able to place the TBI in the major brain regions: frontal, lateral, superior, and posterior. For each location, they used the model to investigate the volumetric return flow generated by the angiogenesis process over the course of 14 days (Figure 8-55). The model highlights the macro- and micro-scale events that occur within

FIGURE 8-55: Microvasculature restructuring at the end of a two-week simulation. (Left) A buffered protein response to the brain injury and (Right) an induced higher magnitude for protein release. The vessel structure at the end of the two-week window is not only influenced by the location of the brain injury, but also the protein response of the injured tissue.



the two weeks following the injury. ARA showed a strong correspondence between TBI location, protein dispersion, and vessel structuring. ARA also showed that the dynamics of the proteins may be manipulated to determine vessel restructuring, possibly aiding in rehabilitation. Further development of this model will allow for injury-specific analysis to determine possible interventions for best outcomes. The model leveraged MR images provided by the University of North Carolina-Chapel Hill, and resulted in open source software and an article currently under review.

This work was sponsored by DEVCOM ARL.

PTSD Drug Treatment Program

PTSD is a debilitating condition that develops following exposure to a traumatic event or events, including blast injuries. Based on empirical evidence, PTSD impacts mortality, morbidity, self-reported medical symptoms, quality of life/physical functioning, health-compromising behaviors, comorbid substance abuse, and employment. Military service-related PTSD is of particular concern among U.S. combat Veterans due to its estimated lifetime prevalence of 6–31 percent.

This is a two- to four-fold increase in prevalence over that of the U.S. general population. A 2008 RAND report estimated the two-year cost of treating the 1.6 million military personnel who have deployed since 2001 at \$4.0–6.2 billion. Despite the high prevalence and costs of PTSD, only two drugs are FDA-approved for treating PTSD. Post-approval evaluations of these two drugs demonstrate less than 50 percent efficacy in treating military service-related PTSD, and often produce problematic side effects. The primary objective for the PTSD Drug Treatment (PTSD-DT) Program is to, as quickly and efficiently as possible, develop and acquire a safe, affordable, operationally effective, and suitable drug to treat military service-related PTSD. Development of a drug to treat PTSD could improve outcomes after a traumatic event, return individuals to work sooner, and reduce the burden of cost for health care.

By the end of FY20, a total of 65 participants, from one VA site and Tripler Army Medical Center, were enrolled in the PTSD-DT program's enabling study that is validating two recently updated tools used to diagnose and assess the severity of PTSD symptoms. The enabling study results will inform how these tools can be used for the PTSD-DT



Photo credit: U.S. Army

program's Phase 2 drug prototype testing inclusion criteria and outcome measures. During FY20, design continued for the innovative Phase 2 testing approach to simultaneously, and sequentially, evaluate more than one drug prototype in more than one PTSD subtype, with partners established via the Medical Technology Enterprise Consortium (MTEC) prototype Other Transaction Agreement (pOTA).

This program is managed by the USAMMDA WBH PMO.

Imaging Clearance of Alzheimer's Disease Markers in Blast-Exposed Soldiers in Training

Amyloid beta ($A\beta$) deposition in TBI suggests a link between trauma and development of dementia, as amyloid is one of the critical pathological features in Alzheimer's disease. The glymphatic system is

critical to $A\beta$ clearance in the brain. The objective of the current line of research is to develop a unique, multi-modal, functional, and structural imaging platform to address the unmet challenge of in vivo characterization of the glymphatic system, and $A\beta$ deposition, in acute TBI, in order to determine whether there are early markers of risk for neuropsychological and cognitive decline after blast exposure.

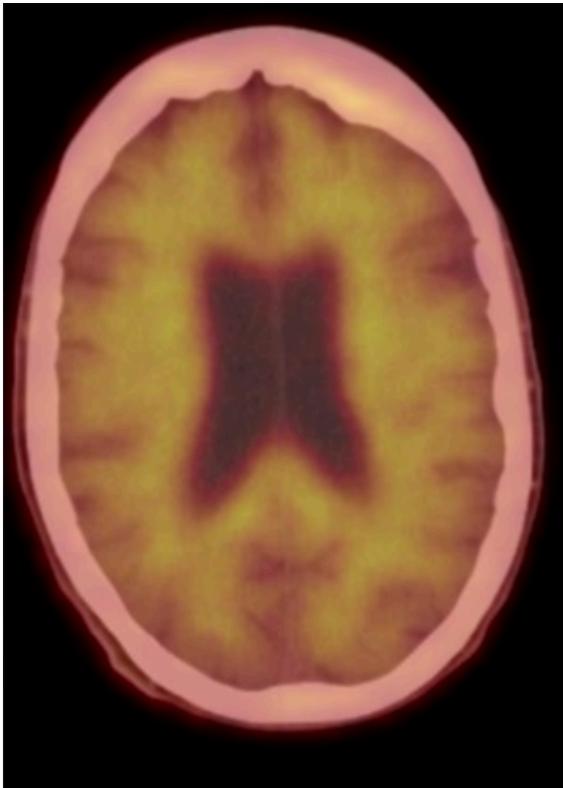
In research being performed by investigators at the University of Missouri, fifteen instructors in breacher training, exposed to regular blasts as part of training Soldiers to breach a building, will be imaged before initiating training and again after the training. Another fifteen individuals working/living at Fort Leonard Wood will be imaged before and after participation in non-blast-exposed activities as a comparison control group. Brain glymphatic activity will be evaluated in vivo with MR diffusion

tensor imaging, and A β deposition by means of amyloid PET. Imaging metrics will be correlated with blast exposure and neuropsychological testing.

As of late FY20, the first four imaging sessions were completed with four breacher instructors. No baseline A β deposits were observed at baseline PET in breacher instructors prior to the breacher course (Figure 8-56), and MRI showed no morphological abnormality. The post-blast study visit is scheduled for December 18, 2020. Control subjects residing in the military base or in Pulaski County are being recruited in FY21.

This research was sponsored by the Leonard Wood Institute in cooperation with ARL.

FIGURE 8-56: Axial fused amyloid PET/CT image at the level of the lateral ventricles in one of the breacher instructors shows normal tracer uptake in the deep brain white matter and no abnormal A β accumulation in the cortex.



Generation of Stem Cell Spheroids as a Therapy to Restore Hearing

Damage to inner ear cells can result in permanent hearing loss. Replacing damaged inner ear cells with stem cells is a potential therapy to restore hearing; however, a roadblock to this therapy is that the inner ear environment is not supportive of transplanted cells, and it is not known how to best perform transplants to form healthy, functional cells. Studies are currently underway in mice to improve the survival and transdifferentiation of implanted human stem cells. In research published in *Acta Biomaterialia* (Chang et al., 2020), researchers created an artificial, 3D stem cell niche, consisting of otic neuronal progenitor (ONP) spheroids, with nanofibrillar cellulose hydrogel and trophic support. Results revealed that transplanted human embryonic stem cell-derived ONP spheroids survived, differentiated into otic neuronal lineages, and extended neurites. Further studies have optimized the protocol to generate spheroids that show characteristics of neuronal progenitors, and a transplantation protocol, using a micropipette aided by microinjection, was developed for minimal damage to spheroids (Heuer et al., 2020). Advancements from this project increase the potential for stem cell therapy as a hearing restoration therapy.

This effort was supported by the Hearing Restoration Research Program (HRRP) with program interest by CRMRP/JPC-8.

Reprogramming the Inner Ear to Regenerate Hair Cells in the Adult Mammalian Cochlea

Service members may experience inner ear damage due to noise or blast exposure, potentially leading to permanent hearing loss. There are no known treatments to restore hearing. However, it has been shown that damage to the inner ear can lead to permanent hearing loss due to the inability to regenerate cells in the adult mammalian cochlea. To reprogram inner ear cells, an international collaboration of researchers activated the Myc and Notch1 signaling pathways in adult mouse cells, enabling proliferation and transdifferentiation of hair-like cells, in vitro and in vivo (Shu et al., 2019). The hair-like cells are still being characterized, but they have shown signs of producing functional transduction channels, and there is evidence that they make connections with surrounding auditory neurons to make synapses. Future research will focus on optimizing the reprogramming of hair cells and further characterization of transdifferentiated cells. This is a critical step in regeneration of cell types required to recover from hearing loss due to inner ear damage.

This effort was supported by HRRP with program interest by CRMRP/JPC-8.

Consortium Studies

CARE Consortium Finds Elongated Recovery Time Post-Concussion and Identifies Potential Biomarkers for Diagnosis and Prognosis

The NCAA-DOD Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium aims to better understand the development of injury and trajectory of recovery from concussion. In their study focused on acute concussion, the CARE Consortium consented over 37,000 student athletes and Service academy cadets and midshipmen at 30 sites. The Consortium had two study arms, the first being a clinical study focused on examining the natural history of



Photo credit: Staff Sgt. Christopher Boitz/U.S. Air Force

acute concussion with a multi-site, longitudinal investigation of concussive and repetitive head impacts. The second arm builds upon the first, with a clinical study allowing for more advanced research projects, such as testing impact sensor technologies, studying potential biomarkers, and evaluating concussion with advanced neuroimaging. Several key findings regarding return-to-activity have recently come out of the study.

Following concussion, the mean return-to-activity time is approximately two weeks. Data from the CARE study suggest that the return-to-play time for individuals with a history of concussions is significantly longer (Mihalik et al., 2020). While resolution of symptoms and successful return to physical activity are used as markers of full recovery, the CARE study data indicate that differences in neuroimaging and proteomic biomarkers can persist

beyond clinical “recovery” (Wu, Harezlak, et al., 2020; McCrea et al., 2020).

Importantly, this study has also found biomarkers that may be useful in diagnosis and determination of prognosis. CARE data suggest that advanced MRI of brain structure and function distinguishes concussed athletes from contact and non-contact controls without concussion. Importantly, these differences correlate with clinical symptom severity and predict time to recovery and return-to-activity after injury (Wu, Harezlak, et al., 2020; Wang et al., 2019; Meier et al., 2019). The research team also found that acute concussion is associated with increased levels of select biomarkers (glial fibrillary acidic protein [GFAP] and ubiquitin carboxy-terminal hydrolase L1 [UCH-L1]), with some evidence of a dose-response relationship in which greater biomarker elevations are observed in more severe grades of concussion (McCrea et al., 2020). In addition, their analyses suggest that measures of total tau and GFAP may be able to distinguish individuals who need more time to return to play (Pattinson et al., 2020).

These findings from the CARE Consortium have important implications for determining recovery and return-to-activity for the athletes, cadets, and midshipmen involved in the study, and for Service members who have suffered concussion.

This effort was managed by CDMRP with support from PH/TBIRP with programmatic oversight by CCCRP/JPC-6.

Data from the Chronic Effects of Neurotrauma Consortium is Publicly Shared in the Federal Interagency Traumatic Brain Injury Research Informatics System

The Chronic Effects of Neurotrauma Consortium (CENC) is a collaboratively funded effort by the DOD and VA Office of Research and Development. The CENC is centered at Virginia Commonwealth University and involves ten studies and five

integrated research cores across more than 30 participating institutions. The original CENC award has been transitioned to a newly funded effort: The Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC), also known as LIMBIC-CENC. The original goals of the CENC were to understand the association (onset, prevalence, and severity) of the chronic effects of mTBI and comorbidities and to probe for correlations to neurodegenerative disease. The largest CENC study was an observational Longitudinal Cohort Study (LCS), with a large volume of controlled, prospective, longitudinal data from OIF, OEF, and Operation New Dawn Service members and Veterans, to understand the late functional and biological effects of mTBI. This study will help inform understanding of the potential risk factors for long-term comorbidities and associated dementia in individuals with military mTBI, including blast exposure. The LCS, and other clinical studies in CENC, examine chronic TBI and comorbidities associated with mTBI, including sensory deficits (e.g., visual, auditory, vestibular), movement disorders, pain (including headache), and cognitive and neuroendocrine deficits. At the end of the CENC period of performance, enrollment in the LCS included over 1,600 participants, with over 1,500 in the longitudinal follow-up phase, an exceptionally high retention rate. Over 75 percent of the cohort had a history of mTBI exposure. A history of mTBI, especially repetitive mTBI, was found to have an effect on outcomes through mediators such as balance, pain, and Service-connected disability. Blast-related mTBI was also observed to be associated with higher rates of health care utilization. Longitudinal assessment and follow-up of these participants continues under the LIMBIC-CENC effort. In FY20, the clinical assessment data from the CENC LCS was made publicly available to qualified researchers through the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System. Additional data from the CENC studies, including neuroimaging data, will continue to become publicly available.



Photo credit: Sgt. Abrey Liggins/ U.S. Marine Corps

The CENC LCS study represents one of the largest datasets in the FITBIR Informatics System to-date and will enhance secondary data analysis, accelerating TBI research progress to support diagnostics and treatment of Service members and Veterans with chronic TBI.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CCCRP/JPC-6.

Transition and Expansion of the Chronic Effects of Neurotrauma Consortium Effort to the Long-Term Impact of Military-Relevant Brain Injury Consortium

The previously funded Chronic Effects of Neurotrauma Consortium (CENC) effort has successfully transitioned under new funding to the Long-term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) effort. Transition and expansion of the CENC effort to LIMBIC involved leveraging the research infrastructure, multi-site and multi-disciplinary expertise, retrospective clinical datasets, prospective longitudinal research

participants, and sites of the established CENC to continue and expand enrollment of relevant populations of Veterans and Service members; expand datapoints collected; collect data in accordance with established guidelines; and identify and describe key characteristics of populations to guide studies on the nature and degree of mTBI late effects in combat Veterans and Service members.

The overall goal of this funding opportunity is to establish a single consortium, of a large longitudinal study and targeted sub-studies, to assess and analyze the late effects of mTBI in a cohort of Veterans and Service members, translate the resulting knowledge, and develop real-world deliverables that can improve both frontline TBI care and long-term support systems for chronic care following mTBI. The LIMBIC seeks to sharpen the focus on comorbidities by determining the prevalence, correlations, and associations of mTBI with important comorbidities, such as dementia and neurodegenerative disease, pain, psychological health, and neurosensory deficits.

LIMBIC will also assist with the identification of mTBI phenotypes by identifying characteristics (e.g., repetitive injury, frequent blast exposure, deployment-only, baseline neurocognitive deficits, presence of neurologic signs, presence of symptoms), biomarkers, and specific populations (e.g., women) that serve as risk (or protective) factors influencing long-term outcomes, as well as economic impact (health care utilization and policy implications).

This effort was managed by CDMRP with support from PH/TBIRP with programmatic oversight by CCCRP/JPC-6.

Low Back Pain, Mental Health Symptoms, and Quality of Life Among Injured Service Members

The Wounded Warrior Recovery Project (WWRP) at NHRC is longitudinally assessing patient-reported outcomes, including quality of life (QOL), mental health symptoms, and health behaviors to better understand the effects of injuries (e.g., primarily blast-related injuries) on the long-term health and readiness of Service members. The WWRP is conducted with funding support from BUMED, under the Wounded, Ill, and Injured Program, and EACE. WWRP enrollment is ongoing, and each of the more than 52,000 Service members injured in Iraq and Afghanistan will be invited to participate in the study.

WWRP is a 15-year, longitudinal, prospective, population-based surveillance project of injured Service members, with participants completing follow-up assessments every six months. This study is conducted predominantly online (www.wwrecoveryproject.org), with supplemental telephone and paper assessments available for Service members who cannot respond online. WWRP includes longitudinal assessments of PTSD and depression symptoms, health-related QOL, and health behaviors (i.e., sleep, alcohol use, physical

activity, cigarette and tobacco use). Additionally, several cross-sectional assessments have been deployed, allowing the research team to examine social support, chronic pain, and functioning and satisfaction ratings for orthotic and prosthetic users. Measures are chosen with the aim of examining the complex relationship between physical and mental health and its impact on QOL. This research allows for further understanding of the long-term outcomes and needs for injured Service members, many of whom were injured due to blasts.

To date, 6,294 injured Service members have provided informed consent and enrolled in the study, and over 37,095 assessments have been completed. Approximately 79 percent of respondents were injured in a blast event. WWRP findings from the past year continue to demonstrate that PTSD and depression are prevalent issues facing injured Service members, and many participants display problematic health behaviors. In the past year, WWRP research has examined the relationships between various health domains with added focus on low back pain and comorbid conditions. Findings suggest that physical, mental, and behavioral deficits frequently co-occur and may adversely impact QOL, and that individuals with low back pain, particularly recurrent low back pain, may be at heightened risk of adverse mental health outcomes.

Understanding the relationships between physical, mental, and behavioral health will allow for the optimization of interdisciplinary clinical care across multiple domains, including mental health, rehabilitation, pain, and chronic illness.

This study was managed by the BUMED Wounded, Ill, and Injured Program.



Photo credit: Col. John Hall/U.S. Army

Conclusion

It is an honor for BIRCO to share so many accomplishments from across the blast injury research and development community in FY20. The breadth of research topics and outcomes should inspire confidence among Service members, their families, and the general public that major advances are being made to protect each Service member from potential blast injuries, and support the injured throughout their treatment and recovery processes. Collaboration across the community—both domestically and internationally—continues to enhance the knowledge base on the spectrum of blast injuries and leads to evidence-based clinical guidelines, programs, and products for blast injury prevention, mitigation, and treatment. BIRCO will continue to support the mission of the EA in coordinating medical research that forms the foundation for the programs and products that target blast injuries.

09



Photo credit: Alejandro Pena/U.S. Air Force

CHAPTER 9: **WAY FORWARD**

This report covers key accomplishments from the DOD blast injury research and development community and the DOD Blast Injury Research Coordinating Office (BIRCO) in FY20. In FY21 and beyond, the blast injury research and development community will continue to pursue strategies for blast injury prevention, mitigation, and treatment. This chapter presents continuing initiatives that will further research and development objectives; foster collaboration and information sharing between research communities; disseminate critical information; and shape future research priorities to fill knowledge gaps across the entire spectrum of blast injury.

BIRCO Initiatives and Engagements

Ongoing and future BIRCO initiatives and engagements aim to direct the research and development community toward closure of blast injury knowledge and capability gaps identified by Congress, by DOD working groups, and through BIRCO initiatives like the International State-of-the-Science Meeting series. These efforts ultimately seek to address the overall knowledge gap of understanding Warfighter blast injuries to improve injury prevention, mitigation, and treatment.

Key BIRCO initiatives in FY21 include continued engagement in the Section 734 Blast Overpressure Study (BOS); leadership of the Military Health System (MHS) Blast Injury Prevention Standards (BIPSR) Recommendation Process; initiating two NATO-affiliated working groups; chairing the DOD Computational Modeling Working Group; and hosting the tenth International State-of-the-Science Meeting.

The goal of the **Section 734 BOS** is to address requirements in Section 734 of the National Defense Authorization Act (NDAA) for FY18, and in subsequent related legislation, by improving DOD's understanding of the impact of blast pressure exposure from weapon systems to the

Service member's brain and auditory health, and informing policy for risk mitigation, unit readiness, and health care decisions. BIRCO is the office of primary responsibility for one of the five lines of inquiry (LOI 2: Weapon Systems). This effort aims to assess and review the safety precautions surrounding the use of heavy weapons in training to account for emerging research on blast exposure and the effects of such exposure on the cognitive performance of Service members. In FY21, the LOI 2 team will finalize the Blast Overpressure Injury Threshold Review, a cross-LOI effort to summarize existing and currently used injury thresholds for low-level blast overpressure exposure to prevent brain and auditory injury. In FY21 and beyond, the LOI 2 team will continue facilitating the integration of the Blast Overpressure Tool into the Range Manager ToolKit. The Blast Overpressure Tool was developed through a Small Business Innovation Research project managed by BIRCO. This new capability could assist installation range management authorities, Service members, unit commanders, and instructors involved in weapon systems training, testing, and combat to make informed risk assessment decisions.

BIRCO will continue to manage the **MHS BIPSR Process** for auditory blast injury and dermal burns. The MHS BIPSR Process is the DOD's first unbiased, stakeholder-driven critical assessment methodology for recommending biomedically valid blast injury prevention standards. These standards support weapon system Health Hazard Assessments, combat platform occupant survivability assessments, and personal protective equipment development and performance testing. In FY21, the auditory blast injury subject matter expert panel will complete their analysis of candidate injury prevention standards and will develop a draft recommendation. In the final steps of the BIPSR Process, BIRCO will host a consensus-building meeting with stakeholders from DOD, other federal government, academia, and industry to share findings and allow for discussion and



Photo credit: Tech. Sgt. Gregory Brook/U.S. Air Force

further investigation of the recommended actions. Final recommendations will be shared with DOD Leadership. Also in FY21, BIRCO plans to convene stakeholders for the BIPSR Process on dermal burns, issue a request for information on relevant injury prediction and simulation standards, and begin to generate intended use cases for a dermal burn injury prevention standard.

Building on previous successes with **NATO Human Factors and Medicine (HFM) Panel Research Technical Groups (RTG)**, BIRCO will chair the HFM-341 RTG, “Validation of Modeling and Simulation Methodologies for Human Lethality, Injury, and Impairment from Blast-Related Threats,” which will commence in FY21. The objective of this RTG is to develop standardized methodologies and criteria to validate computational models and simulation approaches for the entire spectrum of blast-related injuries to mounted and dismounted military personnel. The outcomes will be an approach and criteria to validate component computational models and

simulation techniques. In addition, BIRCO will co-chair the newly formed NATO HFM-Exploratory Team-192 with the U.S. Army Military Operational Medicine Research Program (MOMRP). The primary purpose of this exploratory team, “Blast Exposure Monitoring in Military Training and Operations,” is to understand Service members’ occupational health hazards resulting from repetitive use of weapon systems and explosives during their military careers. The secondary purpose is to recommend further exploration of strategies to prevent injury, mitigate unnecessary exposures, and sustain Service members’ brain health and performance.

Organized by BIRCO, the **DOD Computational Modeling Working Group** aims to shape, focus, and coordinate efforts to enable a capability for the computational modeling and simulation of human lethality, injury, and impairment resulting from the entire spectrum of blast-related threats and environments, from initial point of interaction with the blast hazard to return-to-routine. In

FY21, the working group aims to finalize a strategic plan that provides actionable, impactful guidance and recommendations for developing a DOD Computational Human Body Modeling Framework. This Framework will support model selection for scenario development and execution, guidelines and best practices for inter-model communication, guidelines and best practices for model inputs and outputs, and analyses of results. The working group will also continue engaging with the National Academies to further mutual goals.

In FY21, BIRCO will also host the tenth **International State-of-the-Science Meeting**, “Understanding the Computational Modeling of the Human Body’s Responses to Blast-Related Injury.” This topic ties together several BIRCO initiatives related to computational modeling of blast events and blast injury. The meeting will include plenary sessions with keynote, topic, and scientific presentations; a poster session; and working groups led by expert panel members. Findings and recommendations developed by the expert panel, based on the presentations and working group discussions, will be published and made available on BIRCO’s website.

Engagement with and coordination among DOD’s brain health research community is part of the scope of BIRCO’s role in fulfilling the EA’s responsibilities. In FY21, the **DOD Brain Health Research Coordinator** will work on behalf of the EA to promote, support, and coordinate brain health research and development. For example, they will advise on the development of a path for safe and effective implementation of the Laboratory Assay for Traumatic Brain Injury (LATBI), a product development effort managed by USAMMDA and described on [pages 180](#) and [253](#). As another example, the Brain Health Research Coordinator will serve as a key stakeholder for the FY21 Peer Reviewed Traumatic Brain Injury and Psychological Health Research Program (TBIPHRP). Previously known



as the Psychological Health and Traumatic Brain Injury Research Program, this congressionally directed appropriation has been assigned to CDMRP for management in FY21. The program name has been updated to TBIPHRP to align to the congressional language. In addition, the Brain Health Research Coordinator will continue their involvement in DOD’s Warfighter Brain Health Capabilities-Based Assessment process to propose solutions to requirements and gaps in DOD’s ability to monitor, optimize, restore and support brain health. Through these and other efforts, the Brain Health Research Coordinator will help advance research to yield solutions that improve Service members’ brain health in training, in combat, and at home.



Photo credit: Lance Cpl. Aaron Patterson/U.S. Marine Corps

Finally, BIRCO will initiate the **Blast Bio-effects Working Group** in FY21 with the U.S. Army Aeromedical Research Laboratory (USAARL) and information management experts from the U.S. Army Medical Research and Development Command. The Blast Bio-effects Working Group will develop a long-term plan for sustaining both the Biodynamics Data Resource (USAARL) and DOD Historical Blast Bio-effects Research Data Archive (BIRCO), which contain extensive data on blast injuries, accelerative events, injuries to the whole body, and fatalities. Sustainable databases will allow sharing of valuable knowledge that can impact soldier protection, survivability, and warfighting capabilities; assist in better understanding the effects of blast on humans; and hasten development of appropriate protection and mitigation capabilities.

Ongoing and Future Blast Injury Research and Development Efforts

The prevention, mitigation, and treatment of blast injuries cannot be addressed without the cooperative efforts of organizations across DOD, other federal agencies, academia, industry, and international partners. The following efforts were submitted by the blast injury research and development community as examples of initiatives that will continue to address the challenges of blast injury prevention, acute treatment, and reset in FY21 and beyond.

Facilitating a More Efficient Study Recruitment Process

Study recruitment is a consistent rate-limiting factor across TBI and post-traumatic stress research. To address this challenge, the Center for Neuroscience and Regenerative Medicine (CNRM) at the Uniformed Services University of Health Sciences (USU) created the TBI Research Opportunities and Outreach for Participation in Studies (TROOPS) referral program. TROOPS is a web-based referral program that can expedite and enhance the participant recruitment and referral process. Prospective study participants

self-enroll via a web-based platform that is accessible from any computer, tablet, or smartphone. Referral program staff pre-screen enrollees for eligibility in participating studies and provide enrollee contact information to study teams. This process eases the burden of recruitment on study teams by providing a registry of willing study participants with a wide variety of relevant medical histories and military backgrounds. Check out TROOPS by visiting <https://troops.cnrm.nih.gov/>. For more information about how to use TROOPS, please contact CNRMstudies@usuhs.edu.

Injury Prevention

Research and development efforts in this category aim to prevent blast injury by establishing safety thresholds for human exposure to blast, supporting the design of protection systems, and strengthening guidelines for the safe use of weapon systems. The following three examples represent DOD's many new and continuing injury prevention research projects.

Establishing Cellular Injury Thresholds with a 3D Model

A research team from the University of Wisconsin–Madison will build on their work studying mechanisms of TBI using their in vitro model comprising primary neural cells embedded in a 3D type-I collagen hydrogel ([page 124](#)). The cells can be subjected to varying strain rates. In addition to determining injury thresholds for blunt impact, the researchers plan to investigate and detail cellular injury thresholds for repetitive head impact and inertial, acceleration-based loadings. This work is part of the Physics-Based Neutralization of Threats to Human Tissues and Organs program, sponsored by the Office of Naval Research.



Photo credit: P02 Jonathan David Chandler/U.S. Navy

Scaling Injury Risk Curves to Evaluate Personal Protective Equipment

Assessing the effectiveness of personal protective equipment (PPE) against blast overpressure for high-risk personnel, such as explosive ordnance disposal (EOD) specialists and technicians, requires the development of injury criteria as meaningful metrics to evaluate protection capability. At present, there are no data-driven guidelines or test methodologies to study the effectiveness of the EOD bomb suits and other PPE against blast overpressure. This includes the capacity of legacy and next-generation PPE to mitigate the risk of blast-induced vital organ injury that could undermine Warfighter lethality. The Walter Reed Army Institute of Research (WRAIR) is leading a collaborative, multi-center effort (including Aberdeen Test Center, Virginia Tech, Program Executive Office Soldier–Soldier Survivability,

DEVCOM Soldier Center, DEVCOM Army Research Laboratory, and USU) that will utilize different animal species, in conjunction with surrogate models, to define blast-induced injuries and scaling factors to translate blast-related brain and lung injury to humans. As part of this comprehensive undertaking, the project will define and quantitate the scaled biomechanical underpinnings of blast injury in experimental animal models to establish a foundation for assessments of PPE efficacy. The fundamental similarities in the respective material properties of brain and lung across species suggest that scaling can be calibrated by the measured biomechanical responses in these tissues to blast overpressure of varied magnitudes as a first approximation. The results can then be extended to humans to define injury thresholds and injury criteria. Injury risk curves with and without PPE, with appropriate scaling metrics, can help identify PPE guidelines and evaluate their effectiveness. In addition, methodologies will be developed to standardize future PPE test and evaluation for blast exposure to inform the PPE acquisition process. This project is sponsored by MOMRP/Joint Program Committee (JPC)-5.

INvestigating training assoCiated blast PAthology (INVICTA)

The INVICTA study, led by CNRM in collaboration with WRAIR, is a five-year effort to address concerns about acute, cumulative, and long-term impacts on the brain from repeated subconcussive blast exposure from high explosives and heavy weapons training. INVICTA is a prospective observational study featuring detailed baseline assessment of U.S. Navy SEALs and Range Safety Officers, with serial assessments through three months for SEALs and two years for Range Safety Officers. Assessments include a wide range of blood biomarkers, cognitive testing, and a series of novel measures of sensory, motor and physiologic performance. A better understanding



Photo credit: Senior Airman Dymekre Allen/U.S. Air Force

of repeated subconcussive blast exposure and its acute, sub-acute, and chronic impacts on brain health will inform guidelines to promote enhanced safety in training. This study, sponsored by the Defense Health Agency, is part of the Section 734 BOS effort.

CHaracterization of Acute or Short-term-acquired Military Population Auditory Shifts (CHASMPAS)

Researchers at Walter Reed National Military Medical Center and collaborators from the DOD Hearing Center of Excellence (HCE), the U.S. Army Public Health Center, and MIT Lincoln Laboratory established the “CHaracterization of Acute or Short-term-acquired Military Population Auditory Shifts (CHASMPAS)” study. The primary aim of the CHASMPAS study is to characterize hearing performance in military populations before and after exposure to high-noise and blast operations

from weapon systems identified as highest-risk by the Section 734 BOS Working Group. Those weapon systems are the M777 Howitzer Cannon, M2A1 .50-caliber machine gun, GAU-21 aerial mini-gun, and Carl Gustaf recoilless rifle. The team is also evaluating effects from Bunker Defeat Munitions and grenades. Secondary aims include characterization of the acoustic environment, evaluation of dose-response relationships between exposure and hearing function, and identification of risk factors for auditory injury from noise and blast exposures.

For the CHASMPAS study, researchers conduct hearing assessments for Service members before and after noise and blast exposure, and perform noise and blast measurements during exposure. Boothless audiometry technology is used to evaluate hearing sensitivity and performance in the field environment. A prototype, body-worn,

noise dosimeter, capable of simultaneously measuring both continuous noise levels and blast overpressure waveforms, captures noise and blast exposure data. Weapon system exposures are quantified by the type, number, and strength of munitions. Demographic data are collected from participants, as well as retrospective and longitudinal medical and occupational data.

In FY20, 66 participants enrolled in CHASMPAS, and researchers secured study support from six units at four military installations. Results from this study will be used to inform acoustic injury and blast exposure standards, design improved monitoring methods to target small or early changes in hearing function, develop auditory-risk matrices for noise and blast exposures, and make recommendations for hearing protection devices and tactical communication strategies. This study is supported by MOMRP/JPC-5 and the Defense Health Agency.

Acute Treatment

Studies in this category seek to develop new diagnostic tools, clinical guidelines, therapies, and medical interventions to treat the spectrum of blast-related injuries, with the goal of improving survivability and mitigating long-term disability of Service members with blast-related injuries.

Correlating Neuropathological and Neuroradiological Methods to Improve TBI Diagnosis

A limitation of many current TBI clinical trials, especially those involving mild TBI (mTBI), is inclusion criteria that are based on subjective rather than objective assessments. Neuroimaging methods sensitive to TBI-related damage could improve diagnoses and prove useful for refining inclusion criteria in clinical trials of candidate therapeutics.

The Neuropathological-Neuroradiological Integration Core at CNRM is developing and

testing novel magnetic resonance imaging (MRI) approaches that could potentially identify TBI-related structural abnormalities in vivo. Currently, these abnormalities can only be identified ex vivo using laborious neuropathological methods. The first step in establishing bidirectional correlations between these fields is to develop and test various MRI stains and contrasts using controlled and well-characterized injured tissue specimens. The team is evaluating whether various novel MRI contrasts can help distinguish differences among fixed brain tissue specimens and detect sequelae of damage or injury. They are also assessing the robustness and reproducibility of these MRI methods to ensure their suitability for more routine use.

The second step in this collaborative initiative is to robustly and reliably fuse MRI data with images of the same tissue specimens that are later histologically sectioned and stained. The third step, which is aspirational, is to discover one or more potential quantitative MRI biomarkers that can effectively detect and confirm the sequelae of TBI found by neuropathological methods. If the team achieves this milestone, a future goal is to use objective MRI methods based on solid neuropathological validation to advance TBI diagnosis, clinical trial inclusion, and treatment guidance. This work is sponsored by CNRM and has produced the following publications: Benjamini & Basser (2019), Benjamini & Basser (2020), Pas et al. (2020), and Williamson et al. (2019).

Using Neuroimaging to Study Brain Structure and Function after Blast-Related Mild TBI

CNRM and the National Intrepid Center of Excellence are collaborating to explore the impact of blast exposure on brain structure and cognitive function using multiple MRI modalities. They seek to characterize the neurocognitive deficits present in active-duty Service members with blast-related mTBI; determine whether there are correlations

with the presence and regional distribution of novel tau and amyloid positron emission tomography (PET) tracers [18F]PI-2620 and Florbetaben F18; and correlate these with PET and MRI. This study is supported by CNRM.

Identifying Biomarkers of Inflammation from Occupational Blast Exposure

A collaboration among researchers at the University of Virginia, CNRM, and the Naval Medical Research Center seeks to use a novel ligand to examine central inflammation in military personnel exposed to blast throughout their careers. The research team will compare these results with non-blast-exposed controls. They hope to link the military blast exposures, and any resulting symptoms derived from these exposures, to blood-based biomarkers. This collaborative study began during the summer of 2020 and is supported by CNRM.

Developing a Field-Deployable Blood-Based TBI Diagnostic Device

The U.S. Army Medical Materiel Development Activity (USAMMDA) manages the Laboratory Assay for Traumatic Brain Injury (LATBI) product development effort. The current goal of this effort is to transition a U.S. Food and Drug Administration (FDA)-approved blood-based assay to rule out the need for a computed tomography (CT) scan in the acute phase of a suspected TBI from a benchtop version to a handheld version. The bridging validation study for the handheld device—the i-STAT (Abbott)—was completed and a regulatory packet was submitted to FDA in June 2020, with anticipated approval in early FY21. In parallel, Abbott also began enrollment in a clinical trial for the whole blood point of care LATBI biomarker test with rapid turn-around time in July 2020, with anticipated trial completion in FY22. A blood-based biomarker laboratory test for TBI will greatly enhance the ability of the DOD to objectively assess Service members who are suspected to have a TBI and has the potential to reduce unnecessary evacuations solely for CT scans. Read more about this effort sponsored by USAMMDA on [page 180](#).



Photo credit: Maj. Will Cox/U.S. National Guard

Evaluating Generic Drugs for TBI Treatment

There are currently no FDA-approved drugs for the treatment of TBI. To address this need, USAMMDA has partnered with the University of California, San Francisco and the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Network since 2018 to test multiple TBI drug candidates in Phase 2 clinical trials. Focused investment in Phase 2 trials will improve the quality and quantity of TBI drugs in the pipeline of development, fully characterize drug candidates prior to entering Phase 3 trials, and thereby de-risk further investment on continued development toward FDA approval. Several generic drugs are currently under evaluation for compatibility as multiple arms in a platform adaptive trial design. Testing generic drugs represents the lowest risk and fastest regulatory pathway for TBI drug development. Read more about this effort sponsored by USAMMDA on [page 197](#).

Reset

This research category describes a concept that extends beyond rehabilitation to include all activities necessary to return injured Service members to duty or to productive civilian life. Reset includes research to advance strategies for reducing recovery time, improving rehabilitation programs, maximizing opportunities for return-to-duty and reintegration into the civilian workforce, and improving the quality of life for Service members who have experienced blast-related injuries.

Assessing the Long-Term Effects of Combat-Related Injuries on Quality of Life

The Wounded Warrior Recovery Project (WWRP) at the Naval Health Research Center (NHRC) is longitudinally assessing patient-reported outcomes, including quality of life, mental health symptoms, and health behaviors, to better understand the effects of injuries (primarily blast-related) on the long-term health and readiness of Service members. To date, 6,294 injured Service members have enrolled in the study, and over 37,095 assessments have been completed. Findings suggest that adverse physical, mental, and behavioral health outcomes frequently co-occur and may negatively impact quality of life. WWRP enrollment is ongoing, and each of the more than 52,000 Service members injured in Iraq and Afghanistan will be invited to participate in the study. Understanding the relationships between physical, mental, and behavioral health will help optimize interdisciplinary clinical care across multiple domains, including mental health, rehabilitation, pain, and chronic illness. Read more about this work sponsored by the DOD-VA Extremity Trauma and Amputation Center of Excellence (EACE) on [page 242](#).

Defining and Characterizing a Cohort of U.S. Service Members with Limb Salvage

Advancements in military medicine have dramatically improved the survivability of severe combat-related injuries relative to prior conflicts. Subsequently, the number of Service members presenting with severe extremity injuries skyrocketed and emphasized the need for a greater understanding of the acute and long-term outcomes associated with the care of such injuries. While significant investments and research efforts have been made to understand the sequelae of injuries resulting in limb loss and optimizing the subsequent care of those Service members, the cohort of Service members that entered the limb salvage clinical care pathway has been comparatively less studied, owing in large part to the difficulty in defining this broadly ranging cohort in epidemiological terms. Therefore, the EACE team at USU, in partnership with NHRC, conducted a series of investigations to identify a cohort of Service members who have undergone limb salvage. The research team took a data-driven approach that used International Classification of Diseases-9th Revision diagnosis and procedure codes to define limb salvage. Subsequently, this definition has been used to describe both the demographics and concurrent injuries of this population, as well as identify common complications, secondary health effects, and clinic utilization patterns associated with their acute and long-term care within the Military Health System. The limb salvage definition can be used to enable future high-throughput retrospective analyses, allowing capture of trauma-related limb salvage cases to better study the demographics, clinic utilization, complications, and long-term clinical outcomes of this population. This effort is supported by EACE.



Photo credit: Senior Airman Xavier Navarro/U.S. Air Force

Improving Sensory Function and Pain Management after mTBI

Lingering symptoms of mTBI can include sensory function challenges and pain. Researchers from CNRM are conducting a randomized, double-blind, two-arm, controlled clinical trial to evaluate a non-invasive, closed-loop, acoustic stimulation neurotechnology as a novel treatment for these symptoms of mTBI, measured by the Neurobehavioral Symptom Inventory. The approach involves experimental software algorithms performing real-time analysis of brain signals and delivering changing patterns of acoustic stimulation (audible tones of variable pitch and timing) to the user through standard earbud headphones. The study has nearly completed enrollment, and while the researchers remain blinded until study completion, statistically and clinically significant improvements are evident after the treatment. This study is supported by the Congressionally Directed Medical Research Programs (CDMRP).

Noise Outcomes in Servicemembers Epidemiology (NOISE) Study

Researchers from the National Center for Rehabilitative Auditory Research, Oregon Health and Science University, and HCE are collaborating on a longitudinal epidemiological study that evaluates lifetime noise exposures, chemical and blast exposures, TBI, physical and psychiatric comorbidities, and other exposures and outcomes that can affect auditory function. Their baseline findings from the first 690 participants are described on [page 211](#).

Additional analyses are currently underway using NOISE study data to evaluate associations between blast exposures, post-traumatic stress disorder (PTSD), and hearing loss; estimate the annual rate of hearing threshold change during military service as a consequence of military occupational noise exposure; and examine relationships, if any, between Veterans' functional health status and tinnitus and hearing

capability. The NOISE study data is also being used to validate the Lifetime Exposure to Noise and Solvents Questionnaire; estimate associations between TBI and tinnitus; and evaluate the Tinnitus and Hearing Survey to determine its utility as an instrument to evaluate outcomes of intervention for tinnitus. Many additional analyses are planned to take full advantage of the unique opportunities offered by this rich dataset. This effort was supported by the DOD's Peer-Reviewed Medical Research Program and Joint Warfighter Medical Research Program, as well as a VA Rehabilitation Research and Development Research Career Scientist Award.

Advancing Treatment of Post-Traumatic Headache

Researchers from CNRM are conducting clinical trials of drug treatment and cognitive behavioral therapy approaches to treat post-traumatic headache, which is commonly experienced after mild TBI. The first is a randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and efficacy of erenumab (Aimovig®), a monoclonal antibody that is highly specific for the canonical calcitonin gene-related peptide receptor. This study will be conducted at up to five military treatment facilities over five years. The second study assesses the efficacy, safety, tolerability, feasibility, and user acceptability of cognitive behavioral therapy delivered by a self-guided mobile application. A smartphone-based digital therapeutic could enable access to treatment for thousands of Service members and Veterans who cannot receive treatment in person. CNRM is also testing a smartphone-based cognitive behavioral therapy intervention to treat depression in Service members and Veterans with a history of concussion. These studies are sponsored by CNRM.

Evaluating New Approaches to Treat PTSD

Investigators at CNRM are conducting two clinical trials of new ways to treat PTSD in those who have sustained an mTBI. The first trial assesses the efficacy of Motion assisted, Multi-modular Memory Desensitization and Reconsolidation (3MDR). This approach combines aspects of virtual reality exposure therapy with eye movement desensitization and pre-processing in the Computer Assisted Rehabilitation Environment, taking place over 10 sessions (three preparatory, six 3MDR treatment, and one conclusion). The second is a randomized controlled trial that compares a reconsolidation of traumatic memories (RTM) approach with prolonged exposure therapy, the current best-evidenced treatment for PTSD. The RTM approach has the potential to more rapidly achieve a higher response rate than prolonged exposure therapy. These studies are sponsored by CNRM.

Improving Sleep and Sleep-Related Outcomes after mTBI

Traditional in-person cognitive behavioral therapy for insomnia (CBT-I) has proven effective in treating insomnia. Researchers at CNRM are conducting a study to determine whether a new form of CBT-I, internet-guided CBT-I, is also effective for treating insomnia in Service members and Veterans with a history of TBI. Participants undergo the intervention through the Sleep Healthy Using The internet (SHUTi) platform, which is designed to replicate an insomnia intervention they may receive through a local therapist, psychiatrist, or psychologist. However, this study will be conducted in a self-guided format that enables participants to log in to SHUTi, at their convenience, through a personal computer, tablet, or smartphone, with no in-person visits required. The study period will last for 60 days of intervention followed by a three-month follow-up to assess the long-term effect of the intervention on insomnia.



Photo credit: Lance Cpl. Juan Carpanzano/U.S. Marine Corps

In a separate study, investigators from CNRM and the Portland VA Sleep Disorders Clinic are examining the effect of morning bright light therapy (MBLT) on sleep quality in Veterans with TBI, along with the relationships between improved sleep and behavioral and neurological symptoms and impairments. The levels of various circulating proteins will also be compared between the treatment and placebo groups at baseline, four weeks, and eight weeks (four weeks after cessation of intervention). Levels of these biomarkers will be evaluated to determine whether they relate to changes in neurological and behavioral symptoms or deficits, and if they predict who will be responsive to this intervention. These studies are sponsored by CNRM.

Conclusion

The ongoing and future work described in this chapter is only a sampling of the many excellent research and development efforts happening across DOD, other federal agencies, academia, and industry, as well as internationally, to solve difficult blast injury challenges. The blast injury research community is working relentlessly to better understand injuries and improve their prevention, mitigation, and treatment. As the nature of warfare becomes increasingly complex and lethal, and prolonged field care a more prevalent reality, coordination of efforts to address new challenges will be critical. BIRCO will act within and beyond the blast injury research community to promote a fully coordinated DOD blast injury research program as envisioned by Congress and directed by the Secretary of Defense: one that delivers timely and effective blast injury prevention, mitigation, and treatment strategies to our Service members today and in the future.



Photo credit: MC2 Christain Senyk/U.S. Navy

APPENDIX A: ACRONYMS

A		BG+	Bridging the Gap Plus
AAG	Army Analytics Group	BHBT	behind-helmet blunt trauma
ACT	Auditory Consonant Trigrams	BHDP	Behavioral Health Data Platform
AD	Alzheimer's disease	BHRC	DOD Brain Health Research Coordinator
ADRD	Alzheimer's disease related dementias	BHSAI	Biotechnology High Performance Computing Software Applications Institute
AEN	anterior ethmoidal nerve	BIPSR	Blast Injury Prevention Standards Recommendation
AHFS	American Hospital Formulary Service	BIRCO	DOD Blast Injury Research Coordinating Office
AIS	Abbreviated Injury Scale	BLAST	Blast Load Assessment Sense and Test
ANOR	allowable number of rounds	BLI	bioluminescence imaging
AO	accelerometer-only	BMD	bone mineral density
APHC	U.S. Army Public Health Center	BOOM	Blast Ordnance and Occupational Exposure Measure
ARA	Applied Research Associates	BOP	blast overpressure
ARDS	acute respiratory distress syndrome	BOS	Blast Overpressure Studies
ARL	U.S. Army Research Laboratory	BRI	blast-related injury
ASA(ALT)	Assistant Secretary of the Army for Acquisition, Logistics, and Technology	BSA	bovine serum albumin
ASBREM	Armed Services Biomedical Research, Evaluation, and Management	BSI-18	Brief Symptom Inventory-18
ASD(HA)	Assistant Secretary of Defense for Health Affairs	BUMED	U.S. Navy Bureau of Medicine
AST	aspartate aminotransferase	C	
ATBM	Advanced Total Body Model	C1q	complement component 1q
ATC	U.S. Army Aberdeen Test Center	C4	Composition 4
ATLAS	Adaptable Testing and Load Assessment System	CAP	Consortium to Alleviate Post-traumatic Stress Disorder
Au	gold	CAPER	Comprehensive Ambulatory/Professional Encounter Record
AUC	area under the curve	CARE	Concussion Assessment, Research, and Education
AuNC	gold nanocluster	CAS	central auditory system
AWARD	Automatic Waveform Anomaly Real-Time Detector	CHASMPAS	CHaracterization of Acute or Short-term-acquired Military Population Auditory Shifts
A β	amyloid beta	CAVEMAN	Computational Anthropomorphic Virtual Experiment Man
B		CAVRN	Collaborative Auditory Vestibular Network
B ₄ C	boron carbide	CB2	cannabinoid type-2
B ₆ O	boron suboxide	CBT-I	Cognitive Behavioral Therapy for Insomnia
BCAA	branched chain amino acids		
BABT	behind-armor blunt trauma		
BBB	blood-brain barrier		
BESS	Balance Error Scoring System		
BETS	Blast Exposure Threshold Survey		

CCCRP	Combat Casualty Care Research Program
CCEP	Comprehensive Clinical Evaluation Program
CCI	controlled cortical impact
CCL22	C-C motif chemokine 22
CDMRP	Congressionally Directed Medical Research Programs
CDP	Center for Deployment Psychology
CDR	Clinical Data Repository
CENC	Chronic Effects of Neurotrauma Consortium
CENTCOM	U.S. Central Command
CHI	closed-head injury
CHIMERA	Closed Head Impact Model of Engineered Rotational Acceleration
CI	confidence interval
CMWG	DOD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-Related Threats
CNRM	Center for Neuroscience and Regenerative Medicine
CNS	central nervous system
CoE	Center of Excellence
COI	Community of Interest
COIR	Current Operations Incident Report
COSC	Combat and Operational Stress Control
COTS	commercially available off-the-shelf
COVID-19	coronavirus disease 2019
CPMRP	Chronic Pain Management Research Program
CR	cromolyn
c-REBOA	Complete Resuscitative Endovascular Balloon Occlusion of the Aorta
CRM RP	Clinical and Rehabilitative Medicine Research Program

CRRP	Combat Readiness–Medical Research Program
CRSR	Center for Rehabilitation Sciences Research
CSTS	Center for the Study of Traumatic Stress
CT	computed tomography
CYP2D6	cytochrome P450 2D6

D

DAPI	4',6-diamidino-2-phenylindole
DARPA	Defense Advanced Research Projects Agency
DCoE	Defense Centers of Excellence
DCS	Dynamic Compression Sector
DEERS	Defense Enrollment Eligibility Reporting System
DEVCOM	U.S. Army Combat Capabilities Development Command
DFN	dynamic filter network
DHA	Defense Health Agency
DHA J-9	DHA Research and Development Directorate
DHCC	Deployment Health Clinical Center
DHEA	dehydroepiandrosterone
DMN	default mode network
DMRDP	Defense Medical Research and Development Program
DNA	deoxyribonucleic acid
DOD	Department of Defense
DODD	DOD Directive
DOTMLPF-P	Doctrine, Organization, Training, Materiel, Leadership and Education, Personnel, Facilities, and Policy
DPOAE	distortion product otoacoustic emissions
DRDO	Defence Research and Development Organization
DRIVE	Dynamic Respiratory Impedance Volume Evaluation
DTI	diffusion tensor imaging

DTTI	DOD Defense Trade and Technology Initiative
DVBIC	Defense and Veterans Brain Injury Center

E

EA	Executive Agent
EACE	DOD–VA Extremity Trauma & Amputation Center of Excellence
EF	Experimental Facility
ELISA	enzyme-linked immunosorbent assay
EMED	Expeditionary Medical Encounter Database
ENC	engineered neural conduits
EOD	Explosive Ordnance Disposal
ERG	electroretinography
ERP	Epilepsy Research Program
ES&G	Evidence Synthesis and Research Gap Analysis
ESiT	Environmental Sensors in Training
EVAC	Endovascular Variable Aortic Control
EW	egg white
exomiR	exosomal microRNA

F

FA	fractional anisotropy
fALFF	fractional amplitude of low-frequency fluctuations
FAST	Fast Algorithm for Signal Transformation
FDA	U.S. Food and Drug Administration
FE	finite element
FITBIR	Federal Interagency Traumatic Brain Injury Research
Fitc	fluorescein isothiocyanate
FOV	field of view
FST	Forward Surgical Team
FY	fiscal year

G

GABA	gamma-aminobutyric acid
GCS	Glasgow Coma Scale
GDH	glutamate dehydrogenase
GFAP	glial fibrillary acidic protein
GI/GU	gastrointestinal/genitourinary
GMF	glia maturation factor
GMF-KO	GMF-knockout
GSH	glutathione
GSSG	glutathione disulfide

H

H&E	hematoxylin and eosin
HA	hyaluronan
HAV	Human Acellular Vessels
HC	hair cell
HCE	Hearing Center of Excellence
HCO	Health Care Operations
HExCAT	Homeland Explosives Consequence Assessment Tool
HFM	Human Factors and Medicine
HHA	Health Hazard Assessment
HIDRA	high voltage, in situ, diagnostic radiographic apparatus
HO	heterotopic ossification
HO-1	heme oxygenase 1
HPD	hearing protection device
HRRP	Hearing Restoration Research Program
HSDW	Health Services Data Warehouse

I

Iba-1	ionized calcium binding adaptor molecule 1
iBIPSR	interactive BIPSR
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IED	improvised explosive device
IEEE	Institute of Electrical and Electronics Engineers
IFBIC	International Forum on Blast Injury Countermeasures
IH	impact height
IH100	impact height of 100 cm

IH120	impact height of 120 cm
IHC	immunohistochemistry
IHC	inner hair cell
IL	interleukin
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing
IMR	inertial microcavitation rheometry
INMAS	Institute of Nuclear Medicine and Allied Sciences
INVICTA	INvestigating training assoCiated blasT pAthology
ION	infraorbital nerve
IOTV	Improved Outer Tactical Vest
IPT	Integrated Product Team
IRC	injury risk curve
ISS	Injury Severity Score
IV	intravenous

J

JAM-A	junctional adhesion molecule-A
JIDO	Joint Improvised Threat Defeat Organization
JIFCO	Joint Intermediate Force Capabilities Office
JINCS	JTAPIC Information Management and Collaboration System
JMJD3	Jumonji domain-containing protein D3
JPC	Joint Program Committee
JTAPIC	Joint Trauma Analysis and Prevention of Injury in Combat
JTCG-ME	Joint Technical Coordinating Group for Munitions Effectiveness
JWMRP	Joint Warfighter Medical Research Program

K

KD	King-Devick
KIA	killed in action
kPa	kilopascal

L

LASSO	least absolute shrinkage and selection operator
LATBI	Laboratory Assay for Traumatic Brain Injury
LBCM	lipid bilayer cell membrane
LCN2	lipocalin-2
LCS	Longitudinal Cohort Study
LED	light emitting diode
LIC	laser induced cavitation
LIMBIC	Long-Term Impact of Military-Relevant Brain Injury Consortium
LITES	Linking Investigations in Trauma and Emergency Services
LOI	Line of Inquiry

M

MAPT	microtubule-associated protein tau
MAUT	multi-attribute utility theory
MBLT	morning bright light therapy
MBRP	Military Burn Research Program
MD	molecular dynamics
MD	mean diffusivity
METRC	Major Extremity Trauma and Rehabilitation Consortium
MFC	multi-component flow code
MHS	Military Health System
micro-CT	micro-computed tomography
MIL-STD	Military Standard
miRNA	microRNA
MOD	Indian Ministry of Defence
MOMRP	Military Operational Medicine Research Program
MP	microparticles
MPI	months post-injury
MR	magnetic resonance
MRI	magnetic resonance imaging
MRMC	U.S. Army Medical Research and Materiel Command
MSI	multi-sensory impairment
MSISRP	Medical Simulation and Information Sciences Research Program
MT	microtubule

mTBI	mild traumatic brain injury
MTEC	Medical Technology Enterprise Consortium
MWD	Military Working Dog
N	
NAA	N-acetylaspartic acid
NAA	N-acetylaspartate
NAC	N-acetylcysteine
NACA	N-acetylcysteine amide
NADPH	nicotinamide adenine dinucleotide phosphate
NATO	North Atlantic Treaty Organization
NBRI	non-blast-related injury
NBWT	Narrowing Beam-Walking Test
NCAA	National Collegiate Athletic Association
ncRNA	non-coding RNA
Nd:YAG	neodymium-doped yttrium aluminum garnet
NDA	National Defense Authorization Act
NEFL	neurofilament light chain
NETP	Neurotoxin Exposure Treatment Parkinson's (Research Program)
NFL	neurofilament light
NF-L	neurofilament light
NFκB-RE-Luc	nuclear factor kappa B reporter luciferase
NHRC	Naval Health Research Center
NIC	needle-induced cavitation
NICoE	National Intrepid Center of Excellence
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NIRS	near-infrared spectroscopy
NJIT	New Jersey Institute of Technology
NLR	nucleotide-binding domain leucine-rich repeat containing
NLRP3	NLR family pyrin domain containing 3

NMRC	Naval Medical Research Center
NOISE	Noise Outcomes in Servicemembers Epidemiology
NOS1	nitric oxide synthase 1
NOX	NADPH oxidase
NRL	U.S. Naval Research Laboratory
NSI	Neurobehavioral Symptom Inventory
NSWC-IHD	Naval Surface Warfare Center-Indian Head Division

O

OA	osteoarthritis
OD	oculus dexter
OEF	Operation Enduring Freedom
OHC	outer hair cell
OIF	Operation Iraqi Freedom
ONP	otic neuronal progenitor
ONR	Office of Naval Research
OPORP	Orthotics and Prosthetics Outcomes Research Program
OPR	Office of Primary Responsibility
OR	odds ratio
ORS	Oral Rehydration Salt solution
OS	oculus sinister

P

PA	polyacrylamide
Pa-s	pascal-seconds
PANTHER	Physics-Based Neutralization of Threats to Human Tissues and Organs
PAS	peripheral auditory system
PASAT	Paced Auditory Serial Addition Test
PBI	Practice-Based Implementation
PBS	phosphate buffered saline
PCLC	Post-traumatic Stress Disorder-Checklist
PCS	post-concussive syndrome
P-CVD	polycrystalline chemical vapor deposition
pd	Petri dish
PDGFR-β	pericyte marker platelet-derived growth factor receptor-beta

PDTS	Pharmacy Data Transaction Service
PET	positron emission tomography
PGI-BBD	Post-Graduate Institute Battery of Brain Dysfunction
PH/TBIRP	Psychological Health/Traumatic Brain Injury Research Program
PHCoE	Psychological Health Center of Excellence
piTBHx	pre-injury traumatic brain injury history
PLGA	poly(lactic-co-glycolic acid)
PMO	Project Management Office (USAMMDA)
PMO	Program Management Office (JTAPIC)
PNN	perineuronal net
pOTA	prototype Other Transaction Agreement
PPE	personal protective equipment
PRARP	Peer Reviewed Alzheimer's Research Program
PRMRP	Peer Reviewed Medical Research Program
PRORP	Peer Reviewed Orthopaedic Research Program
PSGL-1	P-selectin glycoprotein ligand-1
psi	pounds per square inch
PT	peroneus tertius
PTA	pure-tone average
pTau	phosphorylated tau
PTE	post-traumatic epilepsy
PTSD	post-traumatic stress disorder
PTSD-DT	Post-traumatic Stress Disorder Drug Treatment
PV+	parvalbumin-positive

Q

QOL	quality of life
qPCR	quantitative polymerase chain reaction

R

RBE	repetitive blast exposure
RD	radial diffusivity
RDT&E	Research, Development, Test, and Evaluation
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
RFI	Request for Information
rfMRI	resting-state functional magnetic resonance imaging
RMTK	Range Manager ToolKit
RNA	ribonucleic acid
RP1	Roma Plastilina No. 1
rpart	recursive partitioning
RPSQ	Rivermead Post-concussion Symptoms Questionnaire
RRS	Resonance Raman Spectroscopy
RTC	U.S. Army Redstone Test Center
RTG	Research Task Group
RTM	Reconsolidation of Traumatic Memories
RTP	return-to-play
RTR	Reconstructive Transplant Research (Program)
RWC	Real Warriors Campaign

S

S&T	science and technology
S1BF	somatosensory barrel-field cortex
SA	soft armor
SAC	Standardized Assessment of Concussion
SAMHSA	Substance Abuse and Mental Health Services Administration
SARA	Sensorimotor Assessment and Rehabilitation Apparatus
SBIR	Small Business Innovation Research
SCBF	spinal cord blood flow
SCI	spinal cord injury
SCIRP	Spinal Cord Injury Research Program
SCO ₂	spinal cord oxygenation
ScvO ₂	venous hemoglobin oxygen saturation

SDMT	Symbol Digit Modality Test
SECARMY	Secretary of the Army
SECDEF	Secretary of Defense
SFDI	spatial frequency domain imaging
SFG	Special Forces Group
SHUTi	Sleep Healthy Using The internet
SiC	silicon carbide
SIDR	Standard Inpatient Data Record
SiMLR	similarity-driven multi-view linear reconstruction
SLIC	seeded laser induced cavitation
SME	subject matter expert
SMU	skeletal muscle unit
SNHL	sensorineural hearing loss
SOHA	Service member Occupational Health Assessment
SOS	Smart Oxygenation System
SoS	State-of-the-Science (Meeting Series)
SSBM	stiff structural biological material
StO ₂	tissue hemoglobin oxygen saturation
STRONG STAR	South Texas Research Organizational Network Guiding Studies on Trauma and Resilience
STTR	Small Business Technology Transfer
SWI	susceptibility-weighted imaging
T	
T	tesla
T&E	test and evaluation
T2	National Center for Telehealth and Technology
TBI	traumatic brain injury
TBICoE	Traumatic Brain Injury Center of Excellence (formerly DVBiC)
TBI-DT	Traumatic Brain Injury Drug Treatment

TBI-QOL	Traumatic Brain Injury-Quality of Life
TBSA	total body surface area
TDP-43	transactive response DNA binding protein-43
TED Initiative	Traumatic Brain Injury Endpoints Development Initiative
TED-I	TRICARE Encounter Data–Institutional
TED-NI	TRICARE Encounter Data–Non-Institutional
TENG	tissue engineered nerve grafts
TGF-β1	transforming growth factor beta 1
TLR4	toll-like receptor 4
TM	tympanic membrane
TMA	TRICARE Management Activity
TMDS	Theater Medical Data Store
TNF-α	tumor necrosis factor alpha
TNT	2,4,6-trinitrotoluene
TONI	Test of Nonverbal Intelligence
TRACK-TBI	Transforming Research and Clinical Knowledge in Traumatic Brain Injury
TRADOC	U.S. Army Training and Doctrine Command
Trails	Trailmaking Test
Treg	regulatory T cell
TRI	regulatory T cell-inducing
Trit-c	tetramethylrhodamin-isothiocyanate
TROOPS	TBI Research Opportunities and Outreach for Participation in Studies
TSWG	Technical Support Working Group
TTCP	The Technical Cooperation Program
TTP	tactics, techniques, and procedures

U

U.S.	United States
UCHL1	ubiquitin carboxy-terminal hydrolase L1
UCH-L1	ubiquitin carboxy-terminal hydrolase L1
UIC	ultrasound induced cavitation
USAMMDA	U.S. Army Medical Materiel Development Activity
USAMRDC	U.S. Army Medical Research and Development Command
USAMRMC	U.S. Army Medical Research and Materiel Command
USD	U.S. dollars
USD(A&S)	Under Secretary of Defense for Acquisition and Sustainment
USD(AT&L)	Under Secretary of Defense for Acquisition, Technology, and Logistics
USD(R&E)	Under Secretary of Defense for Research and Engineering
USSOCOM	U.S. Special Operations Command
USU	Uniformed Services University of the Health Sciences
UT	University of Utah

V

VA	U.S. Department of Veterans Affairs
VAID	Visual Anatomical Injury Descriptor
VCA	vascularized composite allotransplantation
VEGF	vascular endothelial growth factor
VML	volumetric muscle loss
VOR	vestibulo-ocular reflex
VRP	Vision Research Program
VSRT	Verbal Selective Reminding Test

W

WBH	Warfighter Brain Health
WIA	wounded in action
WIAMan	Warrior Injury Assessment Manikin
woSA	without soft armor
WPI	weeks post-injury
WRAIR	Walter Reed Army Institute of Research
WRNMMC	Walter Reed National Military Medical Center
WT	wildtype
WWBG	wireless wearable blast gauge
WWRP	Wounded Warrior Recovery Project

Z

ZO-1	zonula occludens-1
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OTHER

3D	Three Dimensional
3MDR	Motion-assisted, Multi-modular Memory Desensitization and Reconsolidation



Photo credit: Spc. Alex Kirk Amen/U.S. Army



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APPENDIX B: REFERENCES

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APPENDIX C:
DODD 6025.21E



Department of Defense

DIRECTIVE

NUMBER 6025.21E

July 5, 2006

Incorporating Change 1, October 15, 2018

USD(R&E)

SUBJECT: Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries

- References: (a) Section 256 of Public Law 109-163, "National Defense Authorization Act for Fiscal Year 2006"¹
- (b) DoD Directive 5101.1, "DoD Executive Agent," September 3, 2002
 - (c) DoD Directive 5134.3, "Director of Defense Research and Engineering (DDR&E)," November 3, 2003
 - (d) DoD Directive 5025.1, "DoD Directives System," March 2005
 - (e) through (g), see Enclosure 1

1. PURPOSE

This Directive:

1.1. Implements Reference (a) by establishing policy and assigning responsibilities governing coordination and management of medical research efforts and DoD programs related to prevention, mitigation, and treatment of blast injuries.

1.2. Designates the Secretary of the Army, in compliance with Reference (a) and consistent with Reference (b), as the DoD Executive Agent (DoD EA) for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries according to Reference (b).

1.3. Establishes the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. The ASBREM Committee serves to facilitate coordination and prevent unnecessary duplication of effort within DoD biomedical research and development and associated enabling research areas, to include serving as the forum for implementation of subsections (d) and (g) of Reference (a).

¹ Federal legislative information is available through the Library of Congress THOMAS site, <http://thomas.loc.gov>.

2. APPLICABILITY

This Directive applies to:

2.1. The Office of the Secretary of Defense, the Military Departments, the Chairman of the Joint Chiefs of Staff, the Combatant Commands, the Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities, and all other organizational entities in the Department of Defense (hereafter collectively referred to as the “DoD Components”).

2.2. Medical and associated enabling research supported by any DoD Component for prevention, mitigation, and treatment of blast injuries.

3. DEFINITIONS

As used in this Directive, the following terms are defined as follows:

3.1. Blast Injury. Injury that occurs as the result of the detonation of high explosives, including vehicle-borne and person-borne explosive devices, rocket-propelled grenades, and improvised explosive devices. The blast injury taxonomy is provided at Enclosure 2.

3.2. Research. Any systematic investigation, including research, development, testing, and evaluation (RDT&E), designed to develop or contribute to general knowledge.

4. POLICY

It is DoD policy that:

4.1. DoD research related to blast injury prevention, mitigation, and treatment will be coordinated and managed by a DoD EA to meet the requirements, objectives, and standards of the DoD Military Health System as identified by the Under Secretary of Defense for Personnel and Readiness (USD(P&R)) and the unique combat casualty care requirements of the DoD Components.

4.2. Relevant research shall take maximum advantage of the scientific and technical capabilities of industry, academia, DoD Components, and other Federal Agencies.

4.3. The ASBREM Committee will be the venue for joint and cross-Service coordination specified by Reference (a).

4.4. DoD Components will gather and share medical information related to the efficacy of personal protective equipment and of vehicular equipment designed to protect against blast injury.

5. RESPONSIBILITIES AND FUNCTIONS

5.1. The Director of Defense Research and Engineering (DDR&E), under the Under Secretary of Defense for Acquisition, Technology and Logistics, according to DoD Directive 5134.3 (Reference (c)), shall:

5.1.1. Plan, program, and execute the functions and reports mandated for the DDR&E by Reference (a).

5.1.2. Have the authority to publish DoD Issuances consistent with Reference (d) for implementation of this Directive.

5.1.3. Establish, as needed, procedures to ensure that new technology developed under this Directive is effectively transitioned and integrated into systems and subsystems and transferred to and firmly under the control of the DoD Components.

5.1.4. Chair the ASBREM Committee to coordinate DoD biomedical research (see Enclosure 3 for additional detail), and employ that entity to facilitate the DoD EA's coordination and oversight of blast-injury research as specified in Reference (a).

5.1.5. Serve as the final approving authority for DoD blast-injury research programs.

5.1.6. Oversee the functions of the DoD EA and conduct/report on related periodic assessments (per Reference (a)).

5.2. The Assistant Secretary of Defense for Health Affairs (ASD(HA)), under the USD(P&R), shall:

5.2.1. Assist the DDR&E, the DoD EA, and the Director, Joint Improvised Explosive Devices Defeat Organization (JIEDDO), with identification of related operational and research needs, assessment of relevant research efforts, and coordination of planning to resolve capability gaps through focused research efforts.

5.2.2. Be the approving authority for Military Health System prevention and treatment standards developed and proposed by the DoD EA.

5.2.3. Appoint appropriate representatives to related coordinating boards or committees established by the DoD EA.

5.2.4. Ensure that the information systems capabilities of the Military Health System support the DoD EA and the functions specified by this Directive.

5.2.5. Serve as Co-chair of the ASBREM Committee. (See Enclosure 3 for additional detail.)

5.3. The Secretary of the Army is hereby designated as the DoD EA for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, consistent with Reference (a), to coordinate and manage relevant DoD research efforts and programs, and in that role shall:

5.3.1. Give full consideration to the Research and Engineering (R&E) needs of the DoD Components and the Director, JIEDDO, addressing those needs/requirements by:

5.3.1.1. Maintaining a DoD technology base for medical research related to blast injuries and based on the DDR&E-approved program for the DoD Components.

5.3.1.2. Performing programming and budgeting actions for all blast-injury research to maintain the R&E programs based on DDR&E-approved priorities of the DoD Components.

5.3.1.3. Programming and budgeting for blast-injury research based on analysis and prioritization of needs of the DoD Components, consistent with paragraph 5.1 of this Directive.

5.3.1.4. Executing the approved DoD blast-injury research program consistent with DoD guidance and availability of annual congressional appropriations.

5.3.2. Provide medical recommendations with regard to blast-injury prevention, mitigation, and treatment standards to be approved by the ASD(HA).

5.3.3. Coordinate DoD blast-injury-research issues with the staffs of the DDR&E, the ASD(HA), and the Director, JIEDDO.

5.3.4. Support the development, maintenance, and usage of a joint database for collection, analysis, and sharing of information gathered or developed by the DoD Components related to the efficacy of theater personal protective equipment (including body armor, helmets, and eyewear) and vehicular equipment designed to protect against blast injury.

5.3.5. Appoint a medical general or flag officer representative to the ASBREM Committee.

5.3.6. Ensure that information is shared as broadly as possible except where limited by law, policy, or security classification and that data assets produced as a result of the assigned responsibilities are visible, accessible, and understandable to the rest of the Department as appropriate and in accordance with Reference (e).

5.4. The Secretaries of the Navy and the Air Force shall:

5.4.1. Forward their respective approved blast-injury medical R&E requirements to the DoD EA for consideration and integration.

5.4.2. Appoint medical general or flag officer representatives to the ASBREM Committee and appoint representatives to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

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5.4.3. Coordinate with other DoD Components on the assignment of Joint Technical Staff Officers to Army medical research entities, research and acquisition organizations, or installations for coordination of research programming and execution needs pertaining to their Component.

5.4.4. Provide an appropriate system for identification, verification, prioritization, and headquarters-level approval of their respective blast-injury R&E requirements before submission to the DoD EA.

5.5. The President of the Uniformed Services University of the Health Sciences (USUHS), under the ASD(HA) and USD(P&R), shall:

5.5.1. Ensure that education relating to blast-injury prevention, mitigation, and treatment is included in the USUHS medical and continuing education curriculum and programs.

5.5.2. Appoint a representative to any coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.6. The Chairman of the Joint Chiefs of Staff shall:

5.6.1. Coordinate input to the DoD EA and ensure integration of the requirements processes of the Joint Capabilities Integration and Development System² with the processes employed under this Directive.

5.6.2. Appoint a relevant senior representative to the ASBREM Committee.

5.6.3. Appoint representatives to organizational entities of the ASBREM Committee and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.7. The Commander, U.S. Special Operations Command shall establish procedures and processes for coordination of relevant Defense Major Force Program 11 activities with those planned, programmed, and executed by the DoD EA and shall also:

5.7.1. Forward that command's approved blast-injury R&E requirements for consideration and integration to the DoD EA.

5.7.2. Appoint representatives to organizational entities of the ASBREM Committee, as appropriate, and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

² CJCSI 3170.01E, "Joint Capabilities Integration and Development System," May 11, 2005, is available at http://www.dtic.mil/cjcs_directives/cjcs/instructions.htm.

5.7.3. Coordinate with the command on the assignment of Joint Technical Staff Officers to Army medical research entities, research and acquisition organizations, or installations for coordination of research programming and execution needs.

5.7.4. Provide an appropriate system for identification, verification, and headquarters- level approval of that command's blast-injury R&E requirements before submission to the DoD EA.

5.8. The Director, JIEDDO, consistent with Reference (f), shall:

5.8.1. Support development, maintenance, and usage of a joint database for collection, analysis, and sharing of information gathered or developed by DoD Components related to the efficacy of theater personal protective equipment (e.g., body armor, helmets, and eyewear) and vehicular equipment designed to protect against blast-injury.

5.8.2. Appoint representatives to organizational entities of the ASBREM Committee, as appropriate, and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.8.3. Assist the DoD EA, the DDR&E, and the ASD(HA) with identification of related operational and research needs, assessment of relevant research efforts, and coordination of planning to resolve capability gaps through focused research efforts.

6. AUTHORITY

The DoD EA identified by this Directive is hereby delegated authority to do the following:

6.1. Obtain reports and information, consistent with the policies and criteria of DoD Directive 8910.1 (Reference (g)), as necessary, to carry out assigned responsibilities and functions.

6.2. Communicate directly with the Heads of the DoD Components, as necessary, to carry out assigned functions, including the transmission of requests for advice and assistance. Communications to the Military Departments shall be transmitted through the Secretaries of the Military Departments, their designees, or as otherwise provided in law or directed by the Secretary of Defense in other DoD issuances. Communications to the Commanders of the Combatant Commands shall normally be transmitted through the Chairman of the Joint Chiefs of Staff.

6.3. Communicate with other Federal Agencies, representatives of the Legislative Branch, members of the public, and representatives of foreign governments, as appropriate, in carrying out assigned responsibilities and functions. Communications with representatives of the Legislative Branch shall be coordinated with the Assistant Secretary of Defense for Legislative Affairs and the Under Secretary of Defense (Comptroller)/Chief Financial Officer, as appropriate, and be consistent with the DoD Legislative Program.

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7. SUMMARY OF CHANGE 1. This change reassigns the office of primary responsibility for this directive to the Under Secretary of Defense for Research and Engineering in accordance with the July 13, 2018 Deputy Secretary of Defense Memorandum (Reference (h)).

8. EFFECTIVE DATE

This Directive is effective immediately.



Gordon England

Enclosures – 3

- E1. References, continued
- E2. Taxonomy of Injuries from Explosive Devices
- E3. ASBREM Committee

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E1. ENCLOSURE 1

REFERENCES, continued

- (e) DoD Directive 8320.2, “Data Sharing in a Net-Centric Department of Defense,” December 2, 2004
- (f) DoD Directive 2000.19E, “Joint Improved Explosive Device Defeat Organization (JIEDDO),” February 14, 2006
- (g) DoD Directive 8910.1, “Management and Control of Information Requirements,” June 11, 1993
- (h) Deputy Secretary of Defense Memorandum, “Establishment of the Office of the Under Secretary of Defense for Research and Engineering and the Office of the Under Secretary of Defense for Acquisition and Sustainment,” July 13, 2018

E2. ENCLOSURE 2

TAXONOMY OF INJURIES FROM EXPLOSIVE DEVICES

E2.1.1. Primary. Blast overpressure injury resulting in direct tissue damage from the shock wave coupling into the body.

E2.1.2. Secondary. Injury produced by primary fragments originating from the exploding device (preformed and natural (unformed) casing fragments, and other projectiles deliberately introduced into the device to enhance the fragment threat); and secondary fragments, which are projectiles from the environment (debris, vehicular metal, etc.).

E2.1.3. Tertiary. Displacement of the body or part of body by the blast overpressure causing acceleration/deceleration to the body or its parts, which may subsequently strike hard objects causing typical blunt injury (translational injury), avulsion (separation) of limbs, stripping of soft tissues, skin speckling with explosive product residue and building structural collapse with crush and blunt injuries, and crush syndrome development.

E2.1.4. Quaternary. Other “explosive products” effects – heat (radiant and convective), and toxic, toxidromes from fuel, metals, etc. – causing burn and inhalation injury.

E2.1.5. Quinary. Clinical consequences of “post detonation environmental contaminants” including bacteria (deliberate and commensal, with or without sepsis), radiation (dirty bombs), tissue reactions to fuel, metals, etc.

E3. ENCLOSURE 3

ASBREM COMMITTEE

E3.1. ORGANIZATION AND MANAGEMENT

The ASBREM Committee shall:

E3.1.1. Consist of general and flag officer and Senior Executive representatives of relevant DoD Components.

E3.1.1.1. Standing members include relevant senior officials of the DoD Components. At a minimum, the DDR&E, the ASD(HA), and representatives of the DoD Components' Acquisition Executives.

E3.1.1.2. The standing membership may be expanded by invitation of the Chair when issues require senior-level coordination outside the scope of the principal members. Such invited members will include a medical flag officer from the Joint Staff, a designee of the DoD EA specified by this Directive, the Director, JIEDDO, the Director of the Combating Terrorism Technology Support Office, and others as appropriate.

E3.1.2. Be chaired by the DDR&E or Senior Executive designee and co-chaired by the ASD(HA) or Senior Executive designee.

E3.1.3. Convene at the discretion of the Chair and Co-chair.

E3.1.4. Invite the attendance of observers from DoD boards, committees or offices, or from other Federal Agencies with interests in the deliberations of the ASBREM Committee.

E3.1.5. Establish subcommittees, Joint Technology Coordinating Groups, and other entities, as required, to facilitate and execute committee business.

E3.2. FUNCTIONS

The ASBREM Committee shall:

E3.2.1. Review medical RDT&E program plans and accomplishments for quality, relevance, and responsiveness to military operational needs, the needs of the Military Health System, and the goals of Force Health Protection.

E3.2.2. Review program plans and budgets in support of the various guidance documents relevant to National Security and to the missions and functions of the Department of Defense.

E3.2.3. Provide coordination, recommendations, and support to DoD EA(s) and other DoD officials as requested, directed, or otherwise appropriate.



Photo credit: Senior Airman Jonathan Stefanko/U.S. Air Force



Photo credit: Staff Sgt. Christopher Muncy/U.S. Air Force

APPENDIX D: SUPPLEMENTAL TABLES

The Congressionally Directed Medical Research Programs (CDMRP) is a global funding organization that manages biomedical programs in cancer research, military medical research, and other disease- and injury-specific research areas. The following table lists CDMRP research programs with blast injury-related research activities in FY20. More information on the CDMRP can be found at <https://cdmrp.army.mil>.

CDMRP Research Program	Program Focus
<p>Chronic Pain Management Research Program (CPMRP)</p>	<p>The CPMRP funds research efforts focused on the prevention, and improved management, of chronic pain in Service members, Veterans, and the American public. The CPMRP places specific emphasis on the utilization of non-opioid interventions to combat persistent and recurrent pain.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Chronification of pain (i.e., the transition of acute pain to chronic pain) • Development of novel non-μ-opioid receptor-targeted therapies for the treatment of chronic pain • Implementation Science (for evidence-based, efficacious interventions to manage chronic pain) • Comparative Effectiveness (for evidence-based, efficacious interventions to manage chronic pain)
<p>Combat Readiness Medical Research Program (CRRP)</p>	<p>The CRRP funds research relating to development of military-relevant advanced technology and therapeutic research related to forward-deployable solutions that can promptly address life threatening injuries, medical threats, and treatments for Warfighters in current and future battlefield settings.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Multiple-use scalable wound care solutions • Solutions that address hemorrhage control such as non-compressible torso hemorrhage and blood products • Repair and/or restoration of combat-related genitourinary organ and tissue damage • Solutions for the assessment of mild traumatic brain injury (mTBI) in deployed and far-forward settings, to include portable devices • Enhanced delivery and utilization of telemedicine platforms • Infectious diseases, including sepsis
<p>Defense Medical Research and Development Program (DMRDP)</p>	<p>The DMRDP provides execution management support for the six Defense Health Program core research program areas. Each of these major research program areas is strategically guided by a committee, called a Joint Program Committee (JPC), which consists of DOD and non-DOD medical and military technical experts. The CDMRP provides program and award management support primarily for basic through translational research (Program Elements 6.1 through 6.3) and also works closely with the JPCs to transition products to advanced development.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Develop and field sensors to characterize the potentially injurious environments Soldiers are exposed to during training • Elucidate the complex relationship between vision and TBI, recovery, and impacts on quality of life • Development and preclinical testing of novel chemotypes as therapies for wound infection

CDMRP Research Program	Program Focus
<p>Epilepsy Research Program (ERP)</p>	<p>The ERP funds research to develop an understanding of the magnitude of post-traumatic epilepsy (PTE) within the military and to expand research into the basic mechanisms by which TBI produces epilepsy.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Epidemiological characterization and identification of risk factors for developing PTE following TBI • Identification of markers or mechanisms that address PTE • Development of new models or better characterization of existing models for PTE, including repetitive TBI
<p>Hearing Restoration Research Program (HRRP)</p>	<p>The HRRP funds innovative research that has the potential to maximize operational performance/effectiveness, medical readiness, and quality of life for Service members, Veterans, and others living with significant auditory system injuries.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Accelerate translation of biological regeneration/repair mechanisms into therapies that treat auditory system injury and restore auditory function • Diagnostic tests that help differentiate sensory, neural, synaptic, and central processing disorders, that may inform applicability and outcomes for current or future hearing restoration therapeutics • Develop reliable in vitro human models to facilitate the understanding, derivation, and characterization of human auditory cells, and/or to facilitate the evaluation of hearing restoration therapies • Develop and/or validate techniques/methods beyond the audiogram to diagnose acute auditory system injury in austere or remote environments
<p>Joint Warfighter Medical Research Program (JWMP)</p>	<p>The JWMP funds mature research projects close to yielding tangible benefits to military medicine. The JWMP focuses on six program areas: Medical Simulation and Information Sciences, Military Infectious Diseases, Military Operational Medicine, Combat Casualty Care, Radiation Health Effects, and Clinical and Rehabilitative Medicine.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Simulation technology and medical training • Prophylactics and novel therapeutics to treat multi-drug resistant organisms in combat wound infections, countermeasures that prevent and mitigate Service member injury • Development and validation of effective evidenced-based prevention, screening and assessment strategies, as well as treatment and rehabilitation interventions for concussion/mTBI • Identification and development of medical techniques and materiel (medical devices, drugs, and biologics) for early intervention in life-threatening battle injuries • Neuromusculoskeletal injury (including amputees), sensory systems (including balance, vision, and hearing), acute and chronic pain, and regenerative medicine

CDMRP Research Program	Program Focus
<p>Military Burn Research Program (MBRP)</p>	<p>The MBRP funds projects that support a broad research portfolio in the treatment of burns and the trauma associated with burn injuries sustained during combat or combat-related activities.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Burn care solutions for use by a non-medical first responder in a prolonged field care scenario • Burn care solutions for use by the medical first responder in the pre-hospital setting (not necessarily in a prolonged field care scenario)
<p>Neurotoxin Exposure Treatment Parkinson's (NETP)</p>	<p>The NETP program supports Parkinson's research investigating the underlying biologic mechanisms and therapeutic interventions of neuro-degenerative effects caused by deployment, environmental, and occupational exposures in Service members and Veterans</p> <p>Example focus area relevant to blast injury:</p> <ul style="list-style-type: none"> • Quantifiable gene–environment interactions and the risk for or progression of Parkinson's disease following neurotoxin exposure
<p>Orthotics and Prosthetics Outcomes Research Program (OPORP)</p>	<p>The OPORP funds research that evaluates orthoses and/or prostheses using patient-centric outcomes relevant to Service members, Veterans, and other individuals with limb loss and/or limb impairment. The intent of this research is to generate clinically useful evidence that will enhance and optimize patient outcomes.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Orthoses or Prostheses Form – Optimize patient outcomes through the analysis and characterization of variables related to the form of currently available clinical options • Orthoses or Prostheses Fit – Optimize patient outcomes related to human-device interface through the analysis of variables in currently available clinical options that facilitate fit-related metrics • Orthoses or Prostheses Function – Optimize patient outcomes through the analysis of variables related to currently available device function with respect to activities of daily living and other real-world activities
<p>Peer Reviewed Alzheimer's Research Program (PRARP)</p>	<p>The PRARP funds research that address the long-term consequences of traumatic brain injury as they pertain to Alzheimer's disease (AD) and Alzheimer's disease related dementias (ADRD).</p> <p>Example overarching challenges relevant to blast injury:</p> <ul style="list-style-type: none"> • The paucity of clinical studies to examine the interrelationship between TBI and subsequent AD/ADRD for the military, Veteran, and civilian communities • The need for technologies, tests, surveys, questionnaires, devices, biomarkers, or analyses to detect TBI sequelae for AD/ADRD utilizing new and/or pre-existing datasets • The paucity of epidemiological research to examine the interrelationship between TBI, risk and resiliency factors, and subsequent AD/ADRD for the military, Veteran, and civilian communities

CDMRP Research Program	Program Focus
<p>Peer Reviewed Medical Research Program (PRMRP)</p>	<p>The PRMRP funds research across the entire spectrum of medical research toward improving the health and well-being of Service members, Veterans, and their families.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Post-traumatic headache • DNA vaccine technology for post-exposure prophylaxis • Neuroprosthetics • Post-traumatic osteoarthritis • Tinnitus
<p>Peer Reviewed Orthopaedic Research Program (PRORP)</p>	<p>The PRORP funds research to advance the treatment of and rehabilitation from musculoskeletal injuries sustained in combat. The PRORP seeks to optimize recovery and restoration of function following orthopaedic injuries.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Diagnostic and treatment strategies for compartment syndrome • Development of rapid limb stabilization and novel wound protectants for severely wounded limbs to enable transport • Development and optimization of battlefield-feasible diagnostic capabilities, decision support tools, interventions, and rehabilitation strategies that can facilitate retention on duty • Development of advanced tissue regeneration therapeutics in nerve, muscle, and/or composite tissue for the restoration of traumatically injured extremities • Identification of best practices to address infection at the skin-implant interface for osseointegrated prosthetic limbs
<p>Psychological Health and TBI Research Program (PH/TBIRP)</p>	<p>The PH/TBIRP funds research efforts aimed at improving prevention, detection, and treatment of psychological health disorders and TBI. Research funded by PH/TBIRP spans the translational research spectrum from basic research to clinical trials. CDMRP provides program and award management support for PH/TBIRP funds.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Investigations of blast physics for improved understanding of mechanism and for enhanced design of personal protective equipment • Comparison of behavioral and neural pathologies in blast-induced and mechanically-induced TBI • Evaluation of rehabilitative therapies for TBI injury, including tele-rehabilitation and virtual reality • Evaluation of neuroprotective and/or therapeutic compounds to treat TBI • Development of field-ready diagnostic devices for post-traumatic stress disorder and TBI <p>This program aligns to the “Peer-Reviewed Traumatic Brain Injury and Psychological Health Research Program (TBIPHRP)” in DOD appropriations. In FY21, CDMRP has been assigned to manage this congressionally directed appropriation. The program name has been updated to TBIPHRP to align to the congressional language.</p>

CDMRP Research Program	Program Focus
<p>Reconstructive Transplant Research (RTR) Program</p>	<p>The RTR Program funds innovative research that will foster new directions for, and address neglected issues in, the field of reconstructive transplantation, specifically for vascularized composite allotransplantation-focused research.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Immune system regulation • Improved access to reconstructive transplantation • Reconstructive transplantation rehabilitation • Graft surveillance—clinical monitoring • Psychosocial issues associated with vascularized composite allotransplantation
<p>Spinal Cord Injury Research Program (SCIRP)</p>	<p>The SCIRP funds collaborative research to advance treatment and rehabilitation after SCI.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Preserving and protecting spinal cord tissue at time of injury for improved neurologic outcomes • Rehabilitation and regeneration – maximizing the function of the residual neural circuitry, including harnessing neuroplasticity and recovery to improve function after SCI • Psychosocial issues relevant to people with SCI, their families, and/or their care partners
<p>Vision Research Program (VRP)</p>	<p>The VRP funds innovative research that will significantly advance the understanding, prevention, diagnosis, mitigation, and/or treatment of eye injury or visual dysfunction associated with military-relevant trauma.</p> <p>Example focus areas relevant to blast injury:</p> <ul style="list-style-type: none"> • Eye injury or visual dysfunction as related to a military-relevant traumatic event • Diagnosis, stabilization, and treatment of eye injuries in austere environments and prolonged field care settings • Restoration of visual function after trauma-related vision loss or severe visual impairment



DOD BLAST INJURY RESEARCH COORDINATING OFFICE

**ADVANCING BLAST INJURY RESEARCH
TO PROTECT AND HEAL THOSE WHO SERVE**

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