DEPARTMENT OF DEFENSE
BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

3–5 NOVEMBER 2015

STATE-OF-THE-SCIENCE MEETING REPORT

Summary of Proceedings, Key Findings, and Expert Panel Recommendations

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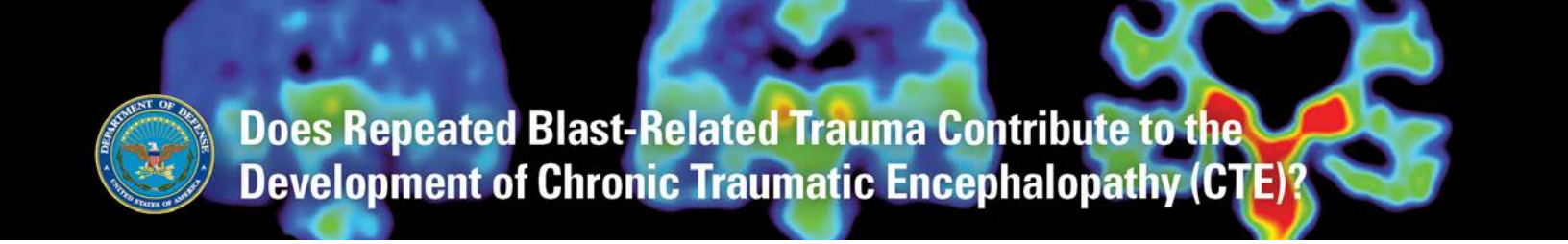

PREFACE

On behalf of the Department of Defense (DoD) Executive Agent for Medical Research for Prevention, Mitigation, and Treatment of Blast Injury, I wish to commend the meeting Planning Committee, meeting presenters, Expert Panel members, and attendees of the 2015 International State-of-the-Science (SoS) Meeting examining the potential relationship between blast-related trauma and Chronic Traumatic Encephalopathy (CTE). These participants critically assessed the state-of-the-science to identify knowledge gaps and to help focus future research efforts.

I also wish to acknowledge and thank the scientific investigators whose research is key to understanding the effects of blast-related traumatic brain injury (TBI). These efforts will advance our knowledge of the underlying biological mechanisms of blast-related TBI and will help improve strategies to prevent, screen, diagnose, and treat Service Members and civilians, alike.

I renew my request to the meeting participants and the communities they represent to continue working together to solve the compelling research questions aimed at identifying the causes of, markers of, and treatments for, CTE. The traditional path of single disciplines working in silos has made slow progress. It is imperative that experts from diverse disciplines invested in blast-related TBI collaborate to address the critical research questions discussed in the SoS Meeting to guide the development of enhanced protection equipment, medical screening and assessment tools, and targeted pharmacological and behavioral interventions.

The report that follows summarizes the proceedings of the 2015 International SoS Meeting and the collaborative work carried out by all attendees, who represent a diverse group of scientists, engineers, medical researchers, health care professionals, protection system development experts and program directors. Meeting participants included representatives from the DoD, other Federal agencies, academia, industry, foreign allies, and the sports community. Topics addressed in this proceedings report include research findings, existing gaps, and recommendations for future research.

Thank you for your contributions, which made this meeting such a great success.

Michael J. Leggieri, Jr.
Director
DoD Blast Injury Research Program Coordinating Office
US Army Medical Research and Materiel Command

EXECUTIVE SUMMARY

Blast-related injury is a potential threat to the health and performance of Service Members. Repeated exposure to blast-related traumatic brain injury (TBI) may induce long-term neurodegeneration and chronic medical needs. Questions about the potential association between head injury and chronic traumatic encephalopathy (CTE) have been raised amidst brain health concerns for military and contact sports populations.

To address these questions, the Department of Defense (DoD) Blast Injury Research Program Coordinating Office (PCO) organized the 2015 International State-of-the-Science (SoS) Meeting on the potential relationship between blast-related trauma and CTE. This meeting brought together subject matter experts from the DoD, other Federal agencies, academia, industry, foreign allies, and the sports community. Topical and research presentations identified requirements, defined the scope of the problem, addressed policy issues, and summarized the state-of-the-science. Concurrent working group sessions gathered attendees to discuss five specific research questions. Following the meeting, a six-member Expert Panel convened to identify major findings and recommendations critical to advancing the state-of-the-science. Findings and recommendations resulting from this meeting will help guide future scientific research and the development of prevention, assessment, and treatment strategies.

Based on the meeting presentations, poster session and concurrent working group discussions, the Expert Panel identified one overarching finding, followed by thirteen findings that included research and knowledge gaps, clinical gaps, and potential research opportunities. The overarching finding is that existing scientific evidence is insufficient to link blast-related TBI with CTE. Seven subsequent Expert Panel findings described research and knowledge gaps, which include a lack of 1) standard definitions of blast and blast exposure, 2) adequate access to blast-exposed clinical tissue with well-annotated medical and exposure information, 3) validated and clinically-relevant animal models, 4) longitudinal and prospective studies with neuropathological components to characterize the risk factors and spatiotemporal development of CTE, 5) data access and data sharing within the scientific community, 6) substantiated risk factors for CTE, other than head trauma, and 7) evidence-based return-to-duty (RTD) guidelines. Three Expert Panel findings identified clinical gaps which include a lack of 1) clear and standardized clinical diagnostic criteria for CTE, 2) fluid and imaging biomarkers for diagnosis and treatment of CTE, and 3) neuroimaging approaches capable of diagnosing CTE or distinguishing CTE from other neurodegenerative disorders. Finally, three Expert Panel findings identified potential research opportunities, including 1) use of extant data to investigate CTE risk factors, 2) continuous monitoring of populations exposed to blast to explore dose-response relationships between blast intensity and injury severity, and 3) sensor technology development and materials science to advance data gathering and prevention strategies.

Based on these findings, the Expert Panel identified recommendations to advance the state-of-the-science on the potential relationship between blast-related trauma and CTE. Among the following six recommendations, the Expert Panel identified the first four as the highest priority for addressing pressing research needs.

- First, **creation of a coordinated brain bank and tissue repository** system, is recommended with a robust plan for donation of clinical specimens that are annotated with medical and blast exposure data; this would enable exploration of the relationship between neuropathology and risk factors or clinical features.
- Second, **development of standardized clinical diagnostic criteria for CTE** is recommended to enable premortem identification of the condition, ideally in concert with neuropathological information.
- Third, **development and validation of clinically-relevant animal models** is recommended to explore potential biological mechanisms linking blast injury and development of CTE.
- Fourth, **development of biomarkers** is recommended to enable premortem diagnosis and study of CTE in living persons.
- Fifth, **strengthening of ongoing longitudinal studies** and **initiation of new prospective studies** to assess candidate risk factors of CTE as well as spatiotemporal development of CTE and other candidate neuropathological changes linked to long-term sequelae resulting from blast exposure.
- Sixth, **implementation of existing prevention and mitigation strategies** in at-risk or exposed populations, given that treatment strategies for CTE are not yet available.

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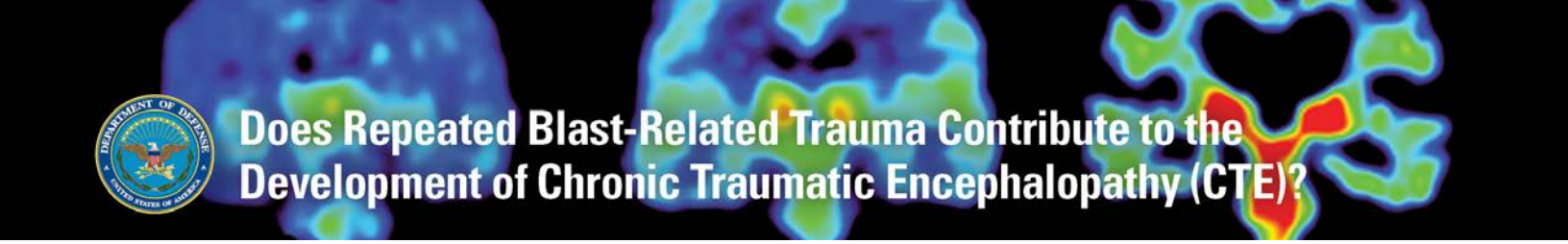

INTRODUCTION

More than 300,000 US Service Members have been diagnosed with a traumatic brain injury (TBI) since 2000. Most of these injuries are noncombat related (e.g., motor vehicle accidents, falls, training, sports), and the vast majority are mild. Blast-related, mild TBI (mTBI) is the most common injury that Service Members encounter in the combat settings of Iraq and Afghanistan, which leads to the following question: What are the long-term impacts of blast exposures, especially if there are multiple exposures that are not associated with acute symptoms? The question of a possible association between head impacts and chronic traumatic encephalopathy (CTE) in the military has a well-publicized parallel to the contact sports community who, together with the Department of Defense (DoD), has made considerable investments in establishing multi-institutional and multidisciplinary collaborative research programs focused on CTE.

Clinical and scientific communities have yet to reach broad consensus on the relationship between brain injury and CTE. The DoD Blast Injury Research Program Coordinating Office (PCO) hosted the International State-of-the-Science Meeting on 3–5 November 2015 in McLean, Virginia, to further explore the potential relationship between blast-related trauma and CTE. This meeting brought together subject matter experts from across the DoD, other Federal agencies, academia, industry, foreign allies, and the sports community to address meeting objectives (see Table 1) assessing the current state-of-the-science with respect to the potential relationship between blast-related trauma and CTE.

The SoS Meeting Planning Committee included clinical, research, and program representatives from the DoD, the National Institutes of Health (NIH), One Mind, the National Football League (NFL), and the National Collegiate Athletic Association (NCAA) (see Appendix C for a full list of Planning Committee members). The role of the Planning Committee was to refine meeting objectives, oversee and provide feedback for the literature review (see Background section), formulate working group questions (see Working Group Summary section), and solicit and rank meeting presentations (see Topic Presentations and Research Presentation sections). The Planning Committee also identified a six-member panel to serve as the Expert Panel, who were charged with chairing the working group sessions and identifying the major meeting findings and

Table 1: SoS Meeting Objectives

- Discuss the evidence linking repeated blast exposure to neurodegeneration
- Assess the pathophysiology, underlying mechanisms of injury, and progression of blast-induced neurodegeneration
- Identify specific features that can contribute to the characterization of CTE as a unique neurodegenerative condition
- Examine relevant animal injury models for blast-induced neurodegeneration
- Discuss strategies for prevention, mitigation, early diagnosis, and treatment of blast-induced neurodegeneration
- Explore the link between blast-induced neurodegeneration and CTE
- Identify the knowledge gaps that will inform future research directions

recommendations needed to advance the state-of-the-science with respect to the potential relationship between blast-related trauma and CTE (see Appendix D for biographies of the Expert Panel members).

One hundred twenty-four participants from the DoD, the Department of Veterans Affairs (VA), the NIH, academia, medical community, industry, and international organizations attended the meeting (see Appendix E for the list of meeting participants). The agenda (see Appendix F) consisted of presentations, a poster session, concurrent working group sessions, and Expert Panel member briefings summarizing the findings from working group sessions. Following the meeting, an Expert Panel session reviewed meeting data and formulated recommendations. Selected presentations from the SoS Meeting are available from the DoD Blast Injury Research Program website at: https://blastinjuryresearch.amedd.army.mil/sos

The present meeting proceedings document summarizes background information from a literature review prepared to inform meeting participants in advance of the meeting (see Background). The meeting proceedings document also covers two types of meeting presentations. First, topic presentations set the stage for the meeting by identifying requirements, defining the scope of the problem, addressing policy issues, and describing the state-of-the-science (see Topic Presentations section). Second, research presentations described current and ongoing scientific investigations including 1) pathological characteristics of blast-induced TBI, 2) risk factors and CTE, 3) blast-induced neurodegenerative mechanisms, 4) neuroimaging and biomarkers, and 5) treatment strategies (see Research Presentations section).

Key to the meeting was an opportunity for the scientific community to engage in rigorous dialogue about the knowledge gaps and requirements for advancing the state-of-the-science with respect to the potential relationship between blast-related trauma and CTE. The consolidated outputs from the five working group sessions are presented in the Working Group Summary. Finally, outputs from the Expert Panel session are summarized in the SoS Expert Panel Findings and Recommendations.

BACKGROUND

Blast injury is defined by the DoD as "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"[1]. Blast injuries are assigned by DoD taxonomy into five categories, from primary to quinary, based on injury type. The blast injury taxonomy includes injuries caused by blast overpressure, blunt force injuries and penetrating injuries (See Appendix G); these injury types, representing, primary, secondary, and tertiary blast injuries, can include TBI.

CTE is described as a progressive neurodegenerative disorder affecting individuals exposed to head injury and resulting in cognitive, behavioral, and/or motor deficits. However, broad consensus on the existence of, and diagnostic criteria for, CTE has not been achieved in the clinical and scientific community (Hazrati et al., 2013; Karantzoulis & Randolph, 2013; McCrory, Meeuwisse, Kutcher, Jordan, & Gardner, 2013; Randolph, 2014; Wortzel, Brenner, & Arciniegas, 2013). Still, multiple academic research groups and government organizations are gathering and analyzing evidence that may provide significant insights into the potential links between exposure to head injury and the development of CTE (Hinds, 2014; McKee et al., 2013; McKee, Stein, Kiernan, & Alvarez, 2015; Omalu et al., 2011; Riley, Robbins, Cantu, & Stern, 2015; Saigal & Berger, 2014). Considering the number of athletes, Service Members, and Veterans who are exposed to single and/or multiple brain injuries and/or subconcussive head impacts, CTE potentially represents a major public health issue.

To inform the 2015 International SoS Meeting, the DoD Blast Injury Research PCO requested a literature review to address specific research questions (see Table 2). During the SoS Meeting, Dr. Matt Aldag, Booz Allen Hamilton, summarized the findings of the literature review across topic areas including neuropathology, exposure to head injury, biomarkers, and treatment and prevention.

[1] DoD Directive 6025.21E, July 5, 2006

Table 2: Literature Review Research Questions and Findings

Research Questions	Findings
What is the current evidence describing the pathophysiological basis of CTE? • What biological processes following head injury are associated with the development of CTE? • What advances in neuroimaging or biomarkers of CTE may lead to the development of diagnostic tools or therapeutic strategies?	• An initial consensus has recently identified a specific neuropathology thought to be required for a diagnosis of CTE. • Ongoing biomarker development, including neuroimaging and biospecimen-based modalities, may enable identification and study of CTE neuropathology in living persons. • Treatment of CTE has not been established; therefore, current mitigation strategies focus on prevention.
What associations are known between the mechanism(s) of head injury (e.g., single or multiple exposures, impact or nonimpact injury) and the development of CTE? • Does the frequency of exposure to head injury correlate with the development of CTE? • Are there any known distinctions between how impact injury, nonimpact injury, and blast-induced injury are associated with the development of CTE?	• Largely because of limitations in clinical data collection, associations between CTE development and 1) frequency of head injury or 2) type of head injury cannot be determined.

Neuropathology

To date, all clinical neuropathological evidence of CTE has been collected from postmortem autopsies of subjects with a history of exposure to head injury (Gardner, Iverson, & McCrory, 2014; Smith, Johnson, & Stewart, 2013). Multiple research groups have described macroscopic (i.e., gross anatomical) and microscopic (i.e., cellular and molecular) abnormalities potentially associated with CTE. Macroscopic-level observations include a reduction in brain weight, the enlargement of ventricles, and abnormalities in specific brain structures. Although these observations vary across studies and research groups, a recent National Institute of Neurological Disorders and Stroke (NINDS) consensus conference determined that perivascular accumulation of tau proteins in neurons, astrocytes, and cell processes in an irregular pattern at the depths of cortical sulci was pathognomonic (i.e., uniquely indicative) of, and required for neuropathological diagnosis of, CTE (McKee et al., 2016). Research groups have proposed classification frameworks based on neuropathology describing CTE as a progressive disease and as a collection of related neuropathologies.

Exposure to Head Injury

Existing clinical literature describing neuropathologically-confirmed CTE does not substantively inform whether the condition is potentially associated with head injury frequency (e.g., single versus multiple exposures) or head injury type (e.g., impact,

nonimpact, blast). Head injury exposure data are inconsistent across case studies, which prevents systematic analysis. Many clinical CTE studies characterize head injury exposure as exposure to sport or occupation and do not include data describing injury frequency, severity, or the time elapsed between injuries.

Biomarkers

Development of objective biomarkers could enable the identification and study of CTE neuropathology in living persons, which would greatly enhance understanding of the underlying biological mechanisms and would potentially inform diagnostic, treatment, and prevention strategies. Investigators are working to develop neuroimaging and biospecimen-based biomarkers targeting the pathophysiological mechanisms associated with CTE and the biological processes following head injury exposure. Neuroimaging modalities include positron emission tomography (PET), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MR spectroscopy), and magnetic resonance imaging (MRI). Biospecimen-based biomarkers, which could be more deployable and cost-effective, compared to resource-intensive neuroimaging modalities, include measurement of proteins found in cerebrospinal fluid (CSF) or blood plasma.

Treatment and Prevention

Treatment of CTE has not been established. Current mitigation strategies focus on prevention of head injury and/or concussion (DeKosky, Blennow, Ikonomovic, & Gandy, 2013; Jordan, 2014), including the use of protective headgear and/or application of return-to-activity guidelines to minimize exacerbation of injury prior to complete recovery. Although consensus on the understanding of CTE is still being established, researchers are already investigating potential treatment approaches. Several animal model studies suggest that the blockade of tau aggregation is a potential strategy. Because of CTE's neuropathological similarities with Alzheimer's disease (AD) and TBI, potential pharmacological and behavioral interventions for these conditions could also be applied to CTE (Antonius et al., 2014; Levin & Bhardwaj, 2014).

Limitations

Limitations in the conclusions that can be drawn about links between exposure to head injury, CTE-associated pathology, and clinical symptoms stem in part from the characteristics of existing evidence and methodological issues. For example, postmortem CTE autopsy cases, which are often referred to researchers by families with concerns about neurobehavioral problems (Antonius et al., 2014), are limited by significant selection (ascertainment) biases (Daneshvar et al., 2011; Karantzoulis & Randolph, 2013; Maroon et al., 2015). Data about the clinical symptoms associated with CTE are also retrospective and often derived from interviews with family members, which make the data subjective and limited by recall biases (McCrory, Zazryn, & Cameron, 2007).

Research Needs

CTE has drawn significant public and media attention given the large at-risk population (e.g., military Service Members, contact sport athletes). Experts have noted concern about the potential clinical and legal consequences of a widespread misunderstanding of CTE (Wortzel et al., 2013). Given these factors, the need for additional research is clear, and investigators have called for specific actions (Iverson, Gardner, McCrory, Zafonte, & Castellani, 2015; Montenigro et al., 2014; Randolph, 2014):

- Initiation of cross-sectional, prospective, longitudinal, and/or epidemiological studies; initial work could compare retired athletes to demographically matched controls without exposure to head injury and assess whether a higher risk for clinical symptoms is supported; additional work could investigate the links between CTE-associated pathology and observed clinical symptoms
- Development of standardized protocols for studying pathology, including establishing control data
- Development of clinical diagnostic criteria and clinical research criteria
- Continued biomarker development, such as determining whether PET imaging can detect differences in tau between groups with and without head injury exposure, with different clinical manifestations, including comorbidities (as well as control subjects)

ESTABLISHING A SHARED UNDERSTANDING OF BLAST INJURY AND CHRONIC NEURODEGENERATION

For the first day-and-a-half of the meeting, speakers from government and academia summarized research community perspectives and research findings, which set the stage for the working group discussion and presentations that followed. These presentations sought to establish a shared understanding of the current scientific knowledge of blast-related trauma and the development of chronic neurodegeneration. Topic presentations discussed Service Member needs, the prevalence of military and civilian TBI, policy considerations, government program efforts, and perspectives from the research community. Following the topic presentations, scientific presentations sharing research data, findings, and future recommendations served to inform the state-of-the-science.

Note: *The opinions and research findings described in this section are those of the presenters and are not necessarily those of representative organizations or Expert Panel members.*

Keynote Presentation

Dr. John F. Glenn, US Army Medical Research and Materiel Command (USAMRMC) delivered the meeting's keynote address. In his address, he discussed the various efforts underway to mitigate threats to brain health in Service Members. Throughout a military career, Service Members may face many types of brain health threats, including blast injury and head trauma; specific threats are determined by adversary, conflict environment, and operational realities. The USAMRMC seeks to mitigate the risks Service Members face by enhancing Warfighter health, fitness, protection, and resilience, as well as improving health care delivery and those systems that support recovery, rehabilitation, and reintegration. For example, today's Service Members are better prepared to deploy and fight in high-altitude regions because of research determining the mitigating factors for pulmonary and cerebral effects of altitude sickness. Responding to Service Member health needs is challenging because of changing threats and the fact that responsible utilization of mitigation strategies requires testing to ensure quality, safety, and effectiveness. The USAMRMC is working to meet these challenges, with both material products and as the knowledge needed to prevent, mitigate, and reduce health risks in a tactical environment.

Blast-induced head injury and associated psychological trauma are signature injuries of today's conflicts. Ensuring brain health to enhance and sustain force readiness across the military lifecycle is a major focus of the USAMRMC (see Figure 1). Modern military medical needs have changed in an era that must also accommodate long-term health consequences and when a majority of Service Members who sustain injury seek a return to duty. Additionally, the military health system must be able to help individuals stand down from duties when needed, recover as rapidly as possible, and return to full function. The potential for progressive neurodegenerative conditions like CTE raises critical questions about identification and intervention in at-risk individuals.

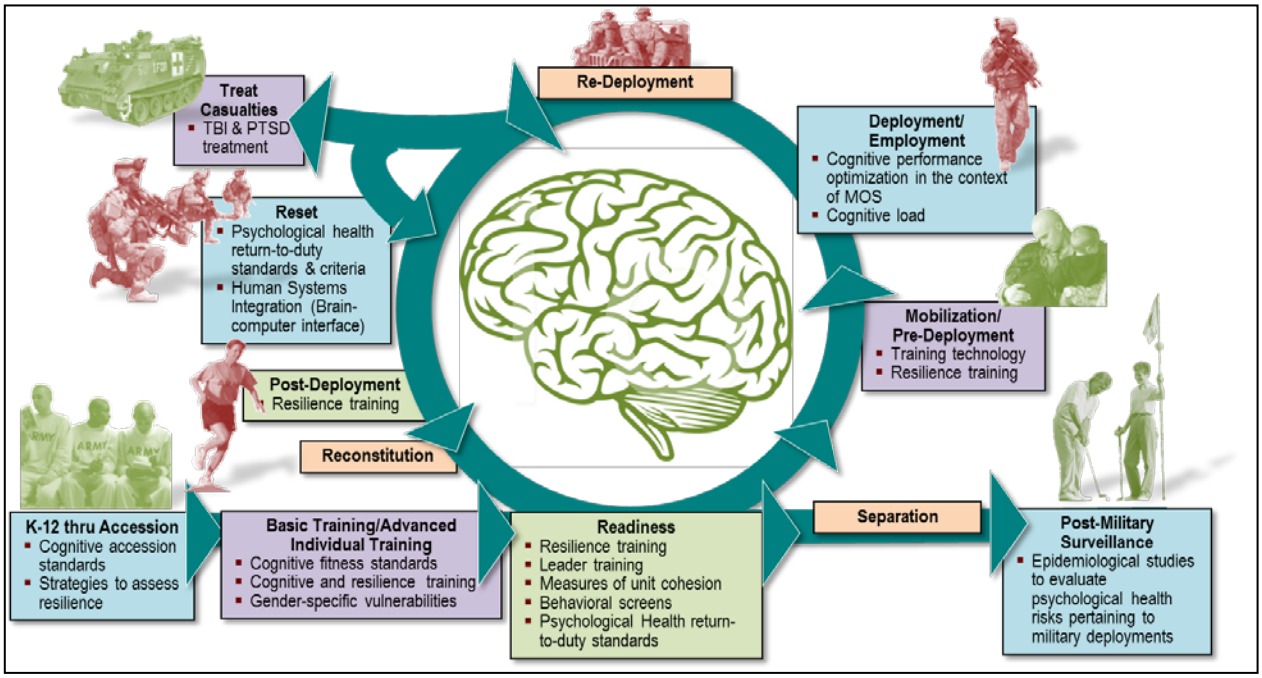

Figure 1: Brain Health Across the Military Lifecycle

Topic Presentations: Setting the Stage

Following the keynote presentation, speakers from government and academia presented information on key topics which set the stage for the meeting by identifying requirements, defining the scope of the problem, addressing policy issues, and describing the state-of-the-science. The topic presentations discussed DoD perspectives, activities of Federal research partners, and perspectives from the academic research and sports communities.

DoD Perspectives

Exposure to blast is a common occupational hazard for Service Members, and blast-induced TBI may be an outcome of that exposure. Scientific and medical research

informs DoD policy efforts seeking to mitigate the effects of blast-related TBI while maintaining operational priorities.

COL Sidney Hinds, Director of Defense and Veterans Brain Injury Center (DVBIC), described the mission and activities of the DVBIC, highlighting collaborative efforts with other DoD organizations to improve research, treatment, and education for TBI. These efforts seek to ensure that Service Members and Veterans get the care and treatment necessary to mitigate the effects of TBI and associated comorbidities. For example, the DVBIC participated in the development of a consensus DoD definition of TBI (see Table 3), which is fundamental to tracking, reporting, and studying the condition in Service Members.

Table 3: DoD Definition of TBI

Traumatically induced structural injury or physiological disruption of brain function as a result of external force, that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event: • Any period of loss of or decrease of consciousness, observed or self-reported • Any loss of memory for events immediately before or after the injury • Any alteration in mental status (confusion, slowed thinking, disorientation)

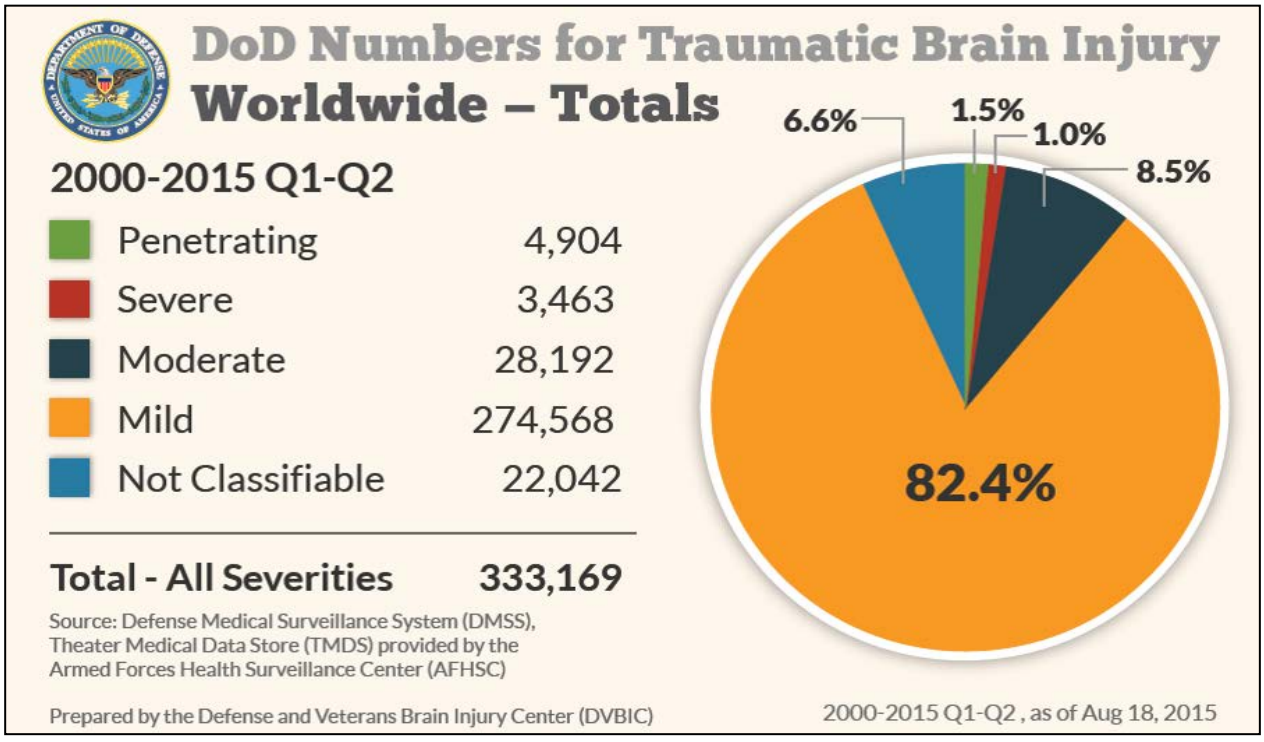

Figure 2. Diagnosed DoD TBI, 2000–2015

The majority (over 82 percent) of DoD TBIs reported in the last 15 years were diagnosed as mild TBI, which is also known as “concussion” (see Figure 2). Over 80 percent of all TBIs are diagnosed in nondeployed environments. Blast-induced TBI is a

common mechanism of injury, for example, vehicle blast was the cause for 39 percent of TBI in Operation Enduring Freedom (OEF) and 51 percent of TBI in Operation Iraqi Freedom (OIF).

To aid in identifying Service Members involved in potentially concussive events, the 2012 Department of Defense Instruction (DoDI) 6490.11, which solidified the 2010 directive type memorandum 09-033, created incidence-based reporting requirements to identify and track Service Members who have been exposed to potentially concussive events. Implementation of DoDI 6490.11 requires that Service Members have 24 hours of downtime and a medical evaluation if they are involved in one of the following events: (1) was inside a vehicle associated with a blast event, (2) was within 50 meters of a blast, (3) experienced a direct blow to head or a loss of consciousness, or (4) was exposed to more than one blast event. The Blast Exposure and Concussion Incident Report identified 16,760 Service Members as having been involved in a potentially concussive event between August 2010 and June 2014; of those Service Members, 2,734 (16.3 percent) were diagnosed with a concussion.

Several DoD programs have been established to understand the long-term effects of TBI (see Table 4). However, more research is needed to establish the existence of links between the long-term effects of single or multiple concussions and CTE. The research investment needed to investigate potential links includes the following: (1) well-designed longitudinal studies, (2) valid clinical indicators, imaging studies, and biomarkers that permit a premorbid determination of those who might be at risk, and (3) high-quality preclinical studies.

Table 4: DoD Efforts to Understand the Long-term Effects of TBI

- The Center for Neuroscience and Regenerative Medicine's Brain Tissue Repository
- Chronic Effects of Neurotrauma Consortium
- DVBIC Executed, Congressionally Mandated 15-year Longitudinal Study
- National Research Action Plan

Pathophysiological consequences of blast exposure can be expected to be dependent on the characteristics of blast wave overpressure. LT Uade DaSilva, Naval Medical Research Center in collaboration with the Walter Reed Army Institute of Research (WRAIR) Blast Research Program, reviewed observations resulting from the study of mortar and artillery operators exposed to repeated blast during training. Currently, less is known about the effect of blast exposure on human physiology than the effect of blast exposure on buildings and structures. Human exposure to blast is a mix of incident and reflective pressures, both of which need to be considered in ongoing and future research efforts.

	Right	Front	Left	Back
Mean	1.63	2.11	1.67	1.07
SEM	0.036	0.040	0.061	0.035

	Right	Front	Left	Back	T.SNR	B.SNR
Mean (psi*ms)	1.5	2.1	2.7	1.3	NR	NR
SEM	0.053	0.057	1.181	0.046	NR	NR

Figure 3: Mortar Blast Exposure Data Gathering

The WRAIR/NMRC collaboration has been studying mean and peak overpressure exposure using helmet-mounted sensors (front, back, left, and right) worn by operators during training with field artillery and mortar weaponry. For both types of weaponry, mean and peak overpressure varied by operator role (i.e., position relative to weapon when carrying out role) and direction from operator. Recently completed analysis of measurement from field artillery (M119) found that peak overpressure was highest for the chief of section role, while mean exposure was generally consistent across roles. Artillery radio telephone operators, who are generally at a greater relative distance from weaponry, were exposed to unexpected levels of mean overpressure, which may have been the result of blast waves rebounding off nearby surfaces and vehicles. Preliminary findings from ongoing measurement and analysis (see Figure 3) of two types of mortar weaponry (81mm and 120mm) indicate that mean overpressure exposure was higher for the larger gun across most roles. Pressure exposure increased at a certain distance from the weapon, potentially an indication of pressure forces rebounding off the ground before reaching the helmet-mounted sensors.

The collaborative also collected the pilot exposure data of shotgun breachers, who are subjected to significant head- and chest-level blast pressures. Reaction time tests five minutes after operational exposure are three times slower compared to pretest values, potentially demonstrating substantial acute effects. Breachers, as well as mortar and artillery crew members, also report symptoms of persistent headache, mood disorders, and sleep disturbances, particularly among more experienced operators and instructors.

Ms. Theresa Lattimore, Readiness Division of the Healthcare Operations Directorate at the Defense Health Agency (DHA), presented on behalf of Ms. Elizabeth Fudge about policy considerations for the prevention and management of the acute and chronic effects of TBI. From within the Readiness Division, Operational Medicine collaborates

with external partners to identify the actions that could be codified to make a beneficial impact across the DoD (see Figure 4). To implement these actions, Operational Medicine supports Health Affairs (HA) for policy-level initiatives (e.g., action memoranda, DoDIs) or DHA for logistical or implementation-level initiatives.

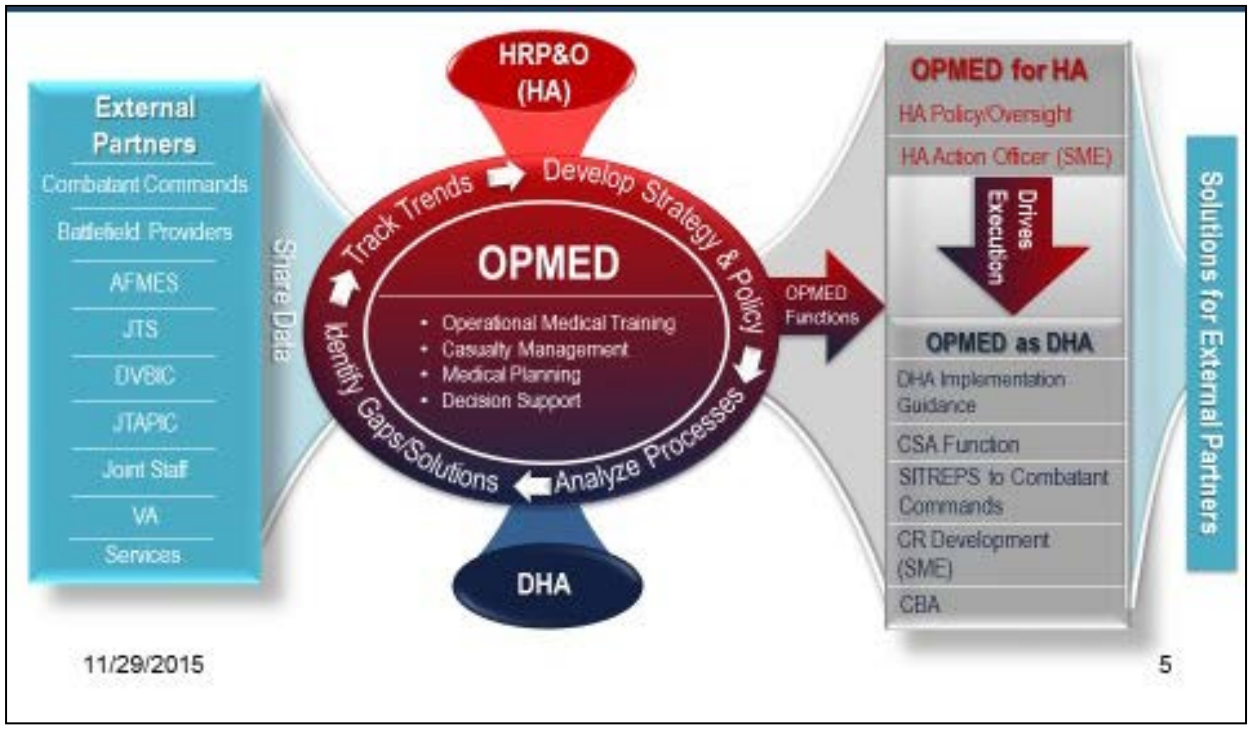

Figure 4. Readiness Division

Current TBI-related policy initiatives include the HA TBI definition and reporting memo, DoDI 6490.11 (requiring line leaders to report potentially concussive events), DoDI 6490.13 (requiring pre- and post-deployment neurocognitive assessments), service-specific policies, and combatant command policies. Aspects of these policy initiatives seek to codify and standardize TBI reporting, in part to enable future Service Member and Veteran electronic health records to track and identify at-risk beneficiaries as clinical understanding of the interaction between TBI exposure and chronic health outcomes advances. Recent demonstrations of significant gaps in point-of-injury documentation and data collection highlight policy challenges that need to be addressed to ensure that future health records are able to identify at-risk individuals in the health system.

Successful policy development requires consideration of political, operational, and scientific/clinical perspectives. A major issue affecting ongoing TBI-related policy development is the current lack of, and need for, a diagnostic test for concussion or TBI. From a medical/clinical perspective, this issue affects both the short- and long-term

health of personnel by enabling the identification, prevention, or mitigation of TBI and related neurodegenerative outcomes like CTE. From an operational perspective, a diagnostic test would determine personnel readiness and would therefore affect combat and/or logistical planning. Policy development and implementation need to strike a balance between maximizing inclusiveness (i.e., screening as many people as possible) for medical/clinical reasons without placing an undue burden on operations. These different perspectives must be considered as policy relevant to TBI diagnosis is developed and implemented.

Future TBI-related policy efforts will focus on an integrated collection of studies designed to examine outcomes in Service Members and their effects on family members. These studies include: (1) The Natural History Study, which focuses on the long-term physical and mental health effects of TBI incurred by members of the Armed Forces during their service in OIF/OEF; (2) The Caregiver Study, which focuses on the effects of injury on family; and (3) the Archival Studies, which will use data collected at Walter Reed Army Medical Center (WRAMC) and Walter Reed National Military Medical Center (WRNMMC) during routine clinical evaluations to examine acute and chronic TBI outcomes in Service Members who served prior to 2008. Policy will also be guided by the output of the Chronic Effects of Neurotrauma Consortium (CENC), the Consortium to Alleviate PSTD, and the DoD Brain Bank, developed in partnership with the Center for Neuroscience and Regenerative Medicine (CNRM).

Federal Government Partners

The DoD works in partnership with federal government organizations to promote brain health research. Veterans are a key population for medical and research efforts focused on chronic brain health. The long-term effects of head injury are a concern for civilian populations as well, especially given widespread participation in contact sports.

Dr. Stuart Hoffman, VA Office of Research and Development, presented on VA TBI research efforts dedicated to improving the future of care for Veterans with brain injury. Survival following injury is much higher in modern, post-2001, conflicts when compared to previous wars. There are more Veterans who have survived blast injuries and TBI than ever before. VA's mission is to understand the nature of brain injuries and ultimately reintegrate Veterans back into their communities. VA funding for TBI research has increased dramatically over the last decade, from less than $2 million in 2006 to more than $39 million in fiscal year 2015. While the relationship between TBI and neurodegeneration is still poorly understood, VA is enhancing ongoing research efforts to address whether Veterans who have accumulated multiple brain injuries are at risk of progressive neurodegenerative disorders such as CTE.

To that end, and in response to Executive Order 13625 (Section 5: PTSD, TBI, Suicide Prevention), VA worked with the DoD, the Department of Health and Human Services (HHS) and the Department of Education to establish the National Research Action Plan

(NRAP), which coordinates federal activities across the continuum—from research to clinical care practice (see Figure 5).

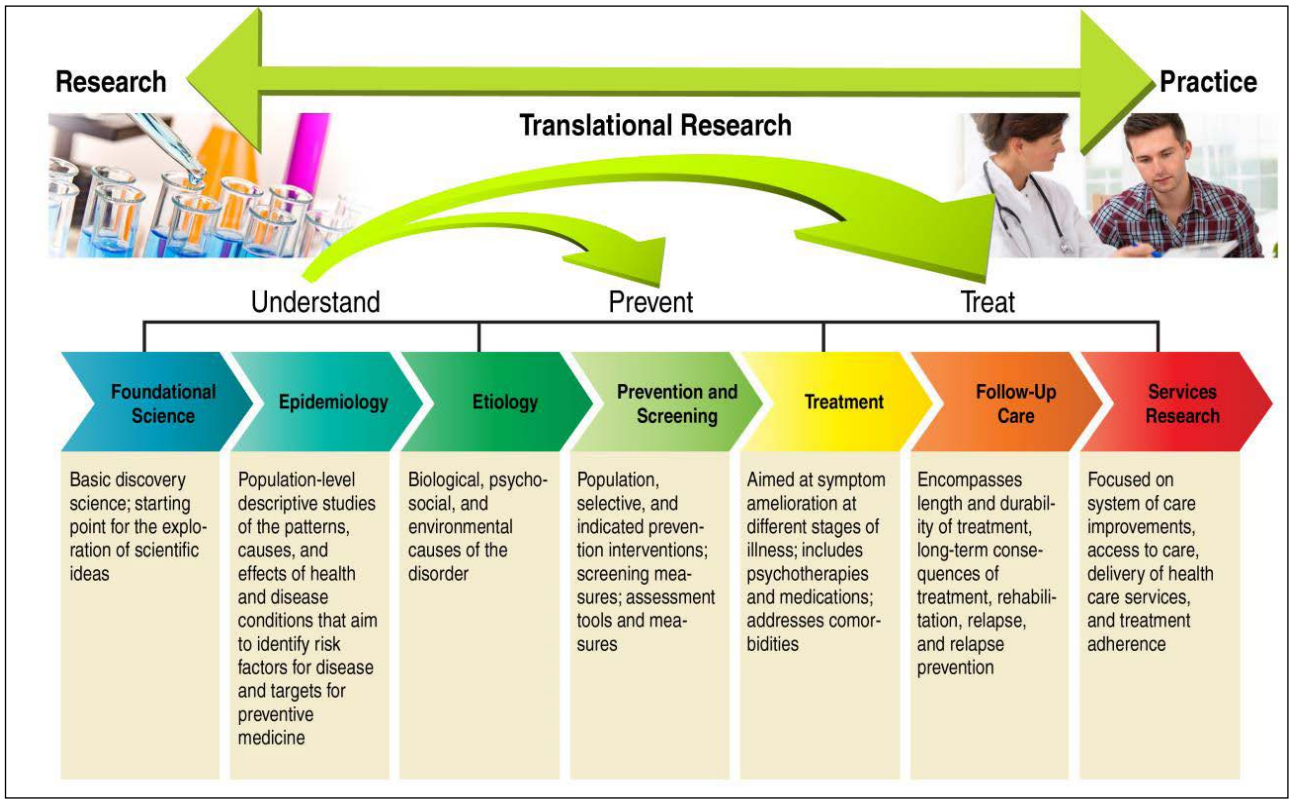

Figure 5: NRAP Continuum Alliance

Stemming from the NRAP, the CENC develops projects across several participating national research sites dedicated to exploring the long-term effects of TBI. The CENC is charged with examining the association between chronic TBI and common comorbidities; determining whether a causal link exists between mTBI and neurodegenerative disease and other comorbidities; identifying diagnostic and predictive indicators of neurodegenerative disease; and developing/advancing methods to treat chronic neurodegenerative disease to improve the health of Veterans.

The most recent VA State of the Art Conference established a number of recommendations for future TBI research, including understanding the effects of gender differences in TBI outcomes; developing standardized animal injury models using common data elements; examining genetic markers for injury responses, recovery, and resilience; distinguishing the effects of injury type and number of insults on the mechanisms of degeneration; and improving the reach, efficacy, and acceptance of telemedicine for rehabilitation and clinical monitoring. These recommendations reflect VA's policy commitment to determining and addressing the long-term effects of repeated exposures of blast and blunt trauma on the brain.

Dr. Patrick Bellgowan, National Institute of Neurological Disorders and Stroke (NINDS), discussed research efforts across the NIH to address knowledge gaps in the pathophysiology of CTE. The NINDS is one of 12 NIH institutes supporting TBI research, which, across intramural and extramural initiatives, addresses basic science and clinical investigations. In 2012, the NFL pledged $30 million to support CTE research at NINDS.

In 2012, the NINDS held the Neuropathology of Chronic Traumatic Encephalopathy Workshop, which brought together basic and clinical scientists to identify key research questions to advance the understanding of CTE. Questions addressed several areas, such as the risk factors for CTE, and identified the most relevant animal models, methodological concerns for conducting postmortem and antemortem studies, and potential diagnostic markers for CTE. In addition to these questions, Dr. Bellgowan noted that while a substantial amount of research has explored CTE in young to middle-aged men, there are few studies in youth, women, and geriatric populations.

Since 2013, the NINDS has been funding postmortem CTE studies to address gaps in understanding, including neuropathological characteristics, incidence, and prevalence. In February 2015, the NINDS supported a consensus workshop with the goal of defining required criteria for neuropathological diagnosis of CTE. Attendees established consensus about the postmortem neuropathological features required for CTE, namely perivascular accumulation of tau protein in deep cortical sulci. Attendees also identified features supporting a neuropathological diagnosis of CTE, as well as that exclude a neuropathological diagnosis of CTE.

The NINDS is preparing to release funding for antemortem research projects focusing on brain imaging and other biomarkers for detection, measurement, and characterization of CTE and its progression over a three- to five-year period in individuals with a possible CTE diagnosis. The goal is to form a better understanding of the neurological mechanisms that could lead to a consensus diagnosis of CTE and that could be used in future clinical trials aimed at preventing or slowing disease progression. NIH-funded CTE studies will collect, and bank, a variety of biomarkers and genetic data. Data from these studies will use the common data elements from the Federal Interagency Traumatic Brain Injury Research (FITBIR) data dictionary, and will be made available for secondary use in FITBIR, thereby maximizing the NINDS's research investment and enabling more rapid solutions using a big data approach.

Other federal programs can advance CTE research. The Metabolomics Workbench, supported by the NIH common fund, gives NIH-funded investigators supplementary funds for data analysis into the unique chemical fingerprints that specific cellular processes leave behind. The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium combines imaging and genetic data from datasets across the

world. Currently, there is no TBI-specific effort within ENIGMA, but the aim is to develop a working group that will enable the concatenation of TBI datasets.

Several CTE research programs have emerged recently across various federal agencies and academic institutions. Ensuring communication between research programs will be increasingly important to enable formation of compatible consensus outcomes.

Academic and Sports Community Perspectives

Multiple academic research groups have been gathering and analyzing evidence to investigate the potential links between brain injury and CTE. Broad consensus on neuropathological, clinical, and functional features of CTE have not been definitively established. Investigators continue to address research questions to determine the risks of head injury and chronic neurodegeneration.

Dr. Steven Broglio, University of Michigan Injury Center, discussed ongoing research of sports-induced concussion on cognitive function and gait in college-aged students. Previous research of concussion incidence and long-term mental health, followed by similar work in modern CTE cases, particularly in professional football, has brought national attention to the potential long-term effects of concussion. Given that 75 percent to 80 percent of military concussions are unrelated to combat (Cameron, Marshall, Sturdivant, & Lincoln, 2012), there may be informative research parallels between NCAA athletes and the military population.

The risk of sports-related concussion extends beyond football, as shown in a recent study of NCAA athletes which found that the five sports with the highest concussion rate were, in order from highest to lowest, men's wrestling, men's ice hockey, women's ice hockey, men's football, and women's soccer (Zuckerman et al., 2015). When comparable men and women's sports are examined, a slightly higher incidence of concussion is observed in women, who also seem to have longer recovery times. Factors driving this higher incidence in women are not clear; some hypothesize that higher susceptibility to injury or higher likelihood of reporting injury play a role.

Research studies of retired professional football players with three or more reported concussions found a higher prevalence of mild cognitive impairment and memory problems when compared to retirees without a history of concussion (Guskiewicz et al., 2005). However, later studies of college-age students with a self-reported history of concussion revealed no difference in cognitive performance compared to those without a history of concussion (Broglio, Ferrara, Piland, Anderson, & Collie, 2006; Broglio, Pontifex, O'Connor, & Hillman, 2009). Differences in these findings may be explained by differences between study populations or that cognitive measures used in the collegiate population were not sensitive enough to detect changes. Subjects with a history of concussion exhibited significantly different electrophysiological response compared to

those without concussion, as measured by event-related potentials (ERPs) during sensory processing behavioral tasks (Broglio et al., 2009); these electrophysiological observations are thought to potentially reflect subtle changes in the brain resulting from concussion.

Subsequent study of functional balance and gait found that former high school athletes with a history of concussion had significantly different balance patterns and gait mechanics (e.g., spending less time on one leg) compared to those without concussion (Martini et al., 2011; Sosnoff, Broglio, Shin, & Ferrara, 2011). That these balance and gait behaviors are also seen in aging led to the proposal of an accelerated decline hypothesis—that, because of exposure to head injury and other potential factors, concussed individuals have a more rapid decline in performance as they age compared to those without concussion (Broglio, Eckner, Paulson, & Kutcher, 2012). However, recent unpublished work indicates that declines across age in cognitive function and gait do not differ between concussed and nonconcussed former high school athletes, raising questions about the accelerated decline hypothesis. Additional studies examining concussion in those presumed to have more extensive exposure, such as college athletes and professional athletes, are needed to further explore the accelerated decline hypothesis.

The NCAA and DoD are collaborating on the Grand Alliance Concussion, Assessment, Research and Education (CARE) Consortium (see Figure 6), a three-year prospective study across 30 colleges and universities to monitor the natural history of concussion in collegiate athletes and cadets at military academies 20 to 40 years postinjury. To date, 14,000 athletes and cadets have been enrolled, and 398 have been diagnosed with concussion. This study will be the most comprehensive study of concussion and head impact ever conducted and may provide critical insight to the risks, treatment, and management of concussion.

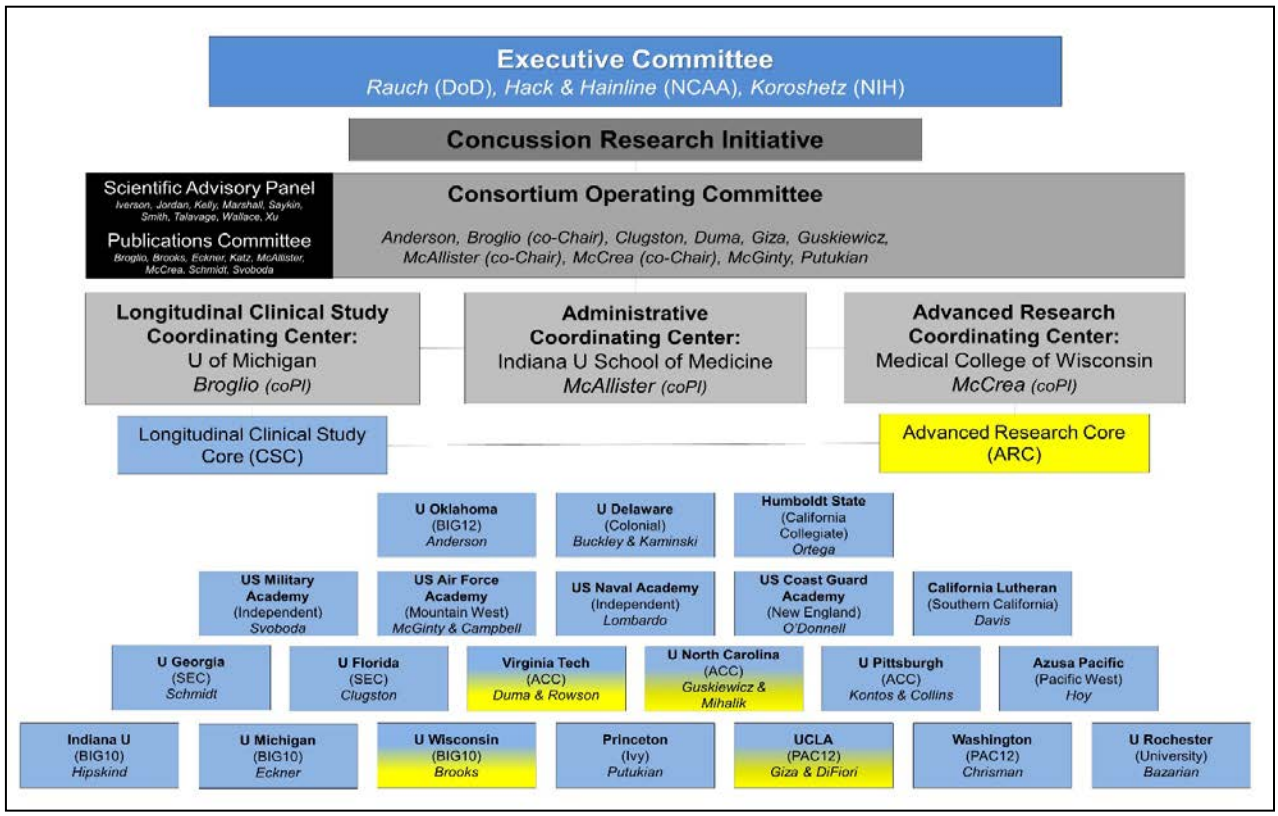

Figure 6: NCAA-DoD Grand Alliance CARE Consortium

Dr. Joseph Maroon, University of Pittsburgh Medical Center, presented his clinical perspectives on concussion in contact sports, blast injuries in the military, and their possible relationship to CTE. Little is known about the possible long-term structural, emotional, and psychological effects of concussion in military and sports. This lack of knowledge has prompted research into understanding the pathological mechanisms of TBI and other clinical factors associated with CTE. Experts have observed that athletes generally recover more quickly from concussion than soldiers; the reasons for the observation are not clear, but some believe the unique aspects of blast injury are responsible for the differences in recovery time.

A recent two-day conference at the University of Pittsburgh concluded that the benefits of often prescribed complete rest (cocooning) following concussion may be limited or detrimental and that early physical activity, in some cases, may be superior to promote neurogenesis, synaptogenesis, and neuroplasticity. In the last decade, leading clinical neuropathologists have been examining the brains of athletes and military Service Members suspected of having CTE-related neurocognitive changes after a history of TBI or blast injury to the brain. While researchers have explored the potential risk factors of CTE, based mainly on case reports, the only consistent risk factor supported by current evidence is a prior exposure to concussion or TBI.

Researchers are investigating multiple biological mechanisms potentially unifying the underlying pathogenesis of concussion, posttraumatic stress disorder (PTSD), and CTE. Concussion is known to be initially caused by an acute neurometabolic mismatch of neuronal glucose, potassium, and calcium released immediately following brain trauma (Giza & Hovda, 2001, 2014). Another proposed immunoexcitotoxic mechanism posits that repeated TBI, without intervening brain healing, may induce brain-derived microglia to continuously release destructive inflammatory cytokines, chemokines, and proteases (Blaylock & Maroon, 2011); additionally, the release of excitotoxic neurotransmitters (glutamate) might lead to the neurodegenerative changes seen in CTE. Multiple frequent concussions may chronically activate microglia, which accelerates the inflammatory and excitotoxic events and interrupts the reparative mechanisms (e.g., growth factor release) that normally occur after a single injury to heal the brain. Studies have also suggested that activation of microglia can occur without exposure to physical brain trauma in mental health disorders such as schizophrenia (Bloomfield et al., 2015) and PTSD (von Känel et al., 2007).

A recent review of existing neuropathologically confirmed CTE cases has revealed methodological limitations (including duplication in the case report literature) and a lack of evidence supporting associations between CTE and age of death, genetic risk factors, suicide, and premorbid dementia (Maroon et al., 2015). The identification of approximately 100 cases of CTE in football players in the last 10 years compared to about 30-40 million youth and adults who have played football during this same period raises questions about the prevalence of CTE. Several recent publications have also raised questions about whether CTE neuropathology observed postmortem is the cause of the clinical symptoms associated with the condition (Castellani, Perry, & Iverson, 2015; Davis, Castellani, & McCrory, 2015; Meehan, Mannix, Zafonte, & Pascual-Leone, 2015; Smith et al., 2013). Addressing these questions is important in light of recent surveys which report a public perception that a concussion is associated with permanent and life-changing effects (Harris Poll, 2015); this perception does not reflect current clinical understanding.

Research Presentations: State-of-the-Science

The presentations described above provided a broader context for the following scientific talks that addressed (1) pathological characteristics of blast-induced TBI, (2) risk factors and CTE, (3) blast-induced neurodegenerative mechanisms, (4) neuroimaging and biomarkers, and (5) treatment strategies.

Pathological Characteristics of Blast-Induced TBI

Researchers use neuropathological evidence to identify and characterize CTE. These neuropathological observations are also a window into the mechanisms that may drive chronic neurodegeneration after TBI.

Dr. William Stewart, Queen Elizabeth University Hospital, presented on behalf of Dr. Douglas Smith from the University of Pennsylvania about lessons learned from studies in animal models regarding the neuropathology of blast-induced TBI. Diffuse axonal injury (DAI) is generally believed to be the primary clinical neuropathological sequelae in impact (nonblast) mTBI or concussion. However, preclinical studies in blast have repeatedly failed to demonstrate DAI acutely in primate (Lu et al., 2012), swine (Bauman et al., 2009) and rodent (Long et al., 2009; Risling et al., 2011) models. Evidence in support of axonal injury is also an inconsistent finding in imaging and pathology studies in humans; potential confounding factors where axonal pathology has been described at autopsy include drug overdose, antemortem anoxia, and concurrent impact TBI (Ryu et al., 2014).

However, while DAI is not a consistent observation in pure blast TBI models, reports across species document evidence of glial (Lu et al., 2012), microglial (Säljö, Bao, Hamberger, Haglid, & Hansson, 2001 [see Figure 7]), and vascular pathologies (Bauman et al., 2009).

Better neuropathological characterization of the blast-induced pathology in human tissue is a high-priority research need to inform and direct development of appropriate animal models. Additionally, ongoing efforts to define common data elements in preclinical research will help drive consensus between groups. Greater collaboration in the field is needed.

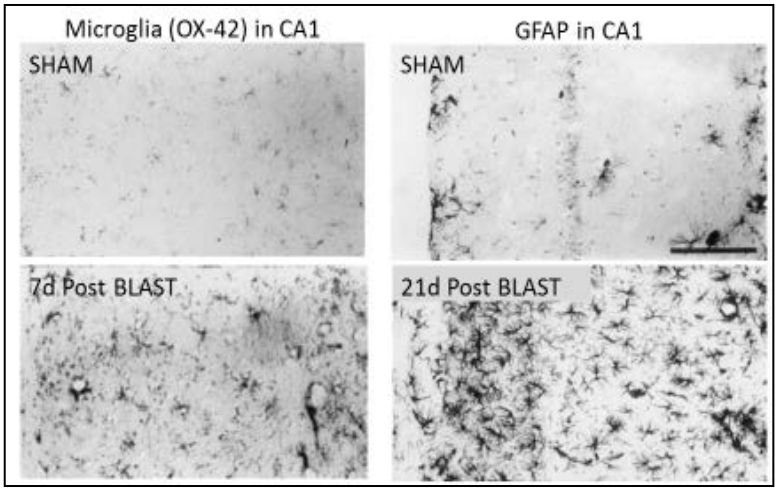

Figure 7: Microglial Activation and Astrocytosis After Blast Injury

Opportunities for clinical neuropathological research are limited. Dr. Daniel Perl, Uniformed Services University of the Health Sciences (USUHS), reviewed neuropathology findings from case studies of acute and chronic blast TBI, including observations of unique pathological lesions in the form of glial scarring. Few

neuropathological studies exist describing acute or chronic effects of blast TBI in humans.

Observations of unusual glial scarring in an index case of chronic blast TBI led to a recent collaboration between the USUHS CNRM and the Joint Pathology Center comparing neuropathology following chronic blast TBI (five cases), acute/subacute blast TBI (three cases), chronic civilian impact (nonblast) TBI (five cases), and civilian controls with no TBI history (three cases). A notable pattern of glial scarring was observed in all chronic blast TBI cases. A parallel pattern was seen in two Service Members who survived four days postblast: reactive astrocytes (which are thought to reflect the initiation of glial scarring) were found in the subpial region and gray-white matter junction. *Ex vivo* high-resolution MRI (7 Tesla) imaging of tissue from a single chronic blast TBI case provided a preliminary indication that the detection of gray-white matter abnormalities associated with glial scarring may be possible in living persons. Glial scarring was observed in structural areas associated with known functions thought to be adversely affected by chronic TBI or CTE. Current theory about how blast waves interact with human physiology predicts that damage will occur at structures consisting of, or proximate to, tissues of different densities, which is a characteristic of structures with glial scarring in this preliminary study. Tau pathology was not observed consistently across chronic blast TBI cases; however, it is possible that tau aggregation would have developed in these patients over time. Observed patterns of axonal pathology also did not differentiate between acute/subacute and chronic blast cases.

These preliminary findings were observed in spite of small sample size, limited data on blast exposure number and nature of injuries, limited postconcussive symptomology data, and limited exposure histories for nonblast (impact) TBI cases. Larger, controlled studies comparing blast and civilian impact TBI and using available clinical and operational data to inform exposure history are recommended. High-resolution imaging of lesions associated with gliosis may also benefit clinical studies of blast-exposed Service Members. Based on these preliminary observations, the development of animal models with human tau or that characterize postblast gliosis would also be beneficial.

Risk Factors and CTE

Dr. Robert Cantu and Mr. Philip Montenigro, Boston University Alzheimer's Disease and CTE Center, reviewed research about neuropathological and clinical features of CTE. Characterized by a unique pattern of tauopathy, CTE is defined as a progressive neurodegenerative disorder in those with a history of brain trauma (frequently with multiple exposures) that results in cognitive, behavioral, mood, and or motor deficits.

In postmortem analysis, CTE is distinguished from Alzheimer's disease (AD) by its characteristic pattern of tauopathy, including perivascular accumulation of neurofibrillary tangles at sulcal depths and superficial cortical layers (McKee et al., 2013). A recent case-series of neuropathologically confirmed CTE identified the presence of amyloid-

beta (Aβ) deposition in 52% of CTE subjects (Stein et al., 2015). The presence of Aβ pathology in these subjects occurred at an earlier age with altered dynamics compared to the normal aging population and those with AD. Additionally, Aβ deposition was associated with a greater severity of CTE tauopathy and dementia symptoms. With support from the NINDS and National Institute of Biomedical Imaging and Bioengineering (NIBIB), consensus neuropathological diagnostic criteria for CTE were recently established (McKee, Alvarez, et al., 2015).

Currently CTE can only be diagnosed by postmortem neuropathological exam. In an effort to identify a common clinical presentation of CTE, Stern et al. (2013) performed a retrospective analysis of clinical histories, medical records, and next-of-kin reports among autopsy-confirmed CTE cases without co-morbidities. In more than 70% of cases, symptoms occurred in three clinical domains: Behavior, Mood, and Cognition. Symptom clusters gave rise to two subtypes: 1) Behavioral/Mood, which had an earlier age of onset and predominant symptoms of explosivity, rage, depression, and mild cognitive symptoms later in life; and 2) Cognitive, which had a later age of onset and predominately memory, executive, and attention issues. Recently, we proposed clinical criteria for the diagnosis of CTE (Montenigro et al., 2014) and for the first time applied these criteria to two case-reports (Montenigro, Bernick, & Cantu, 2015). To date, studies to validate and improve upon the proposed clinical criteria are ongoing; an expert clinical consensus panel has already utilized the proposed criteria to retrospectively clinically diagnose 99 cases while panel members remain blinded to the neuropathological diagnosis (Mez et al., 2015).

Brain injury is the primary known risk factor for CTE. For professional football players, the number of years played and years since retirement both correlate with CTE severity (McKee et al., 2013). Career length may be associated with CTE severity by serving as a proxy for the number of injuries accumulated; years since retirement may be associated with the amount of time neuropathology was allowed to progress. Next-of-kin reported concussion frequency and steroid use are not correlated with severity of CTE pathology. It is not yet known which specific aspect(s) of brain injury (source, frequency, location) influence the risk for or natural progression of CTE. Closed-head impacts in collision sports (e.g., football, boxing) cause sudden acceleration or deceleration of the brain inside the skull that may introduce internal brain injuries without visible fracture or contusion. Closed-head brain injuries may result from forces propagated through two biomechanical pathways.

The first is the “common” pathway to injury, which is homogeneous in nature and occurs where the brain is structurally vulnerable to injury. When strains overwhelm the underlying brain tissue through the common pathway, a previously described *acute* close-head brain injury pattern occurs termed the “gliding contusion” (Löwenhielm, 1975). The *chronic* neuropathological characteristics of CTE share certain similarities to, and may be associated with, the *acute* close-head brain injury pattern of the gliding contusion. See Figure 8 for a side by side comparison. The second aspect of a close-head brain injury is the “focal” or “local” pathway, which is heterogeneous in nature and specific to the type and location of impact. Thus, closed-head brain injuries result from a combination of both common (homogeneous) and local (heterogeneous) pathways to tissue injury.

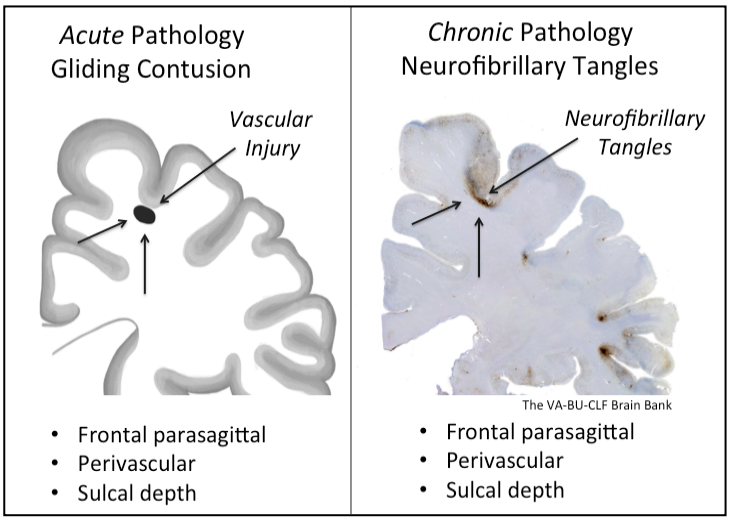

Figure 8: Acute and Chronic Effects of Close-Head Impacts

The common pathway is thought to play the major role in the accumulation of injury that results in long-term impairment and CTE tauopathy as game play results in repetitive closed-head impacts. However, we hypothesized that sport specific differences in impact exposure might alter the pathological and clinical manifestations of CTE through differences in the biomechanical forces introduced through the local pathway of closed-head impacts.

Novel new (secondary) analysis of previously reported cases in McKee *et al* (52)	Pro Football	Pro Boxing
Late stage CTE (III–IV)	25	7
Mean decade age at symptom onset	50–60	50–60
Mean decade age at time of death	70–80	80–90
†Late stage CTE “with motor features”	18.8% (3/16)‡	83% (5/6)‡
Late stage CTE with cerebellar dentate neurofibrillary tangles	57% (12/21)	71% (5/7)
Late stage CTE with severe (++/+++) dentate neurofibrillary tangles	17% (2/12)‡	80% (4/5)‡

†Motor symptoms include parkinsonism, gait changes and dysarthria, unrelated to motor neuron disease.
‡Statistically significant difference in the proportions between groups ($P < 0.05$, Fisher’s exact test).

Figure 9: Comparison of CTE Clinicopathological Features in Boxers vs. Football Players

Football players are generally exposed to repeated linear forces due to frontal, head-to-head contact. Boxers are generally exposed to rotational acceleration resulting from the hook-punch to the chin. Rotational acceleration is thought to have a greater effect on the mid-brain and cerebellum,

which was observed in a recent case comparison of a single professional football player and single professional boxer (Montenigro et al., 2015). Tissue analysis from both individuals met consensus based neuropathological criteria for stage III CTE. Yet the boxer sustained greater neuronal dropout and tau-positive neurons within the dentate of the cerebellum. These neuropathological differences were mirrored in a secondary analysis of the data from (McKee et al., 2013): when professional boxers and football players were compared (See Figure 9), boxers were more likely than football players to have CTE with motor symptoms and neurofibrillary tangles in the cerebellar dentate, a higher proportion of which were severe (Montenigro et al., 2015).

Blast-Induced Neurodegenerative Mechanisms

Dr. Gregory Elder, James J. Peters VA Medical Center, reviewed animal model research of blast-induced behavioral alterations and pathology. Investigators at the Naval Medical Research Center (NMRC) developed an animal model designed to mimic blast-induced mTBI. Exposure to multiple blasts resulted in no major neuropathological abnormalities, but is associated with transiently impaired spatial learning as assessed by the Morris Water Maze test (Ahlers et al., 2012).

Distinguishing the overlapping symptoms of PTSD and postconcussion syndrome has proven problematic to clinicians and has created the need for animal models to study and tease apart the behavioral components of these conditions. Recent experiments have demonstrated the induction of PTSD-related traits following exposure to blast. In behavioral assessments, animals exposed to multiple blasts exhibited increased anxiety, acoustic startle, and cued fear responses when compared to controls. In blast-exposed animals, abnormal behavioral responses persisted for three days following exposure to a predator scent. These behavioral abnormalities were also accompanied by changes in stathmin 1, a microtubule-associated protein highly expressed in the amygdala that plays a role in learning and fear responses. Subsequent DNA methylation profiling in these animals has indicated epigenetic changes potentially underlying long-term, chronic effects (Haghighi et al., 2015).

An increase of beta amyloid (Aβ) plaques has been reported following closed-impact TBI in humans (DeKosky et al., 2007) and in animal models (Loane et al., 2009). However, recent work in blast-exposed rodents indicates a decrease of Aβ in rats at 24 hours and 1 week postblast (De Gasperi et al., 2012). In addition, APP levels increased in blast-exposed animal models, similar to observations following closed-impact TBI. To date, tau pathology or neurofibrillary tangles have not been observed in this blast-exposed animal model.

Blast-induced vascular pathology may be relevant to the study of CTE given that perivascular tau accumulation is one defining characteristic of the disorder. Exposure to multiple blasts is associated with vascular abnormalities, with dysmorphic vessels exhibiting irregular vessel walls, and debris in the lumen (see Figure 10); the neurophil

surrounding such vessels was normal suggesting that blast effects are specific to the vasculature. Acute blast exposure in this animal model was also associated with a degradation of the glycocalyx, a supportive matrix lining the inner walls of blood vessels, and poorer spatial learning performance; both abnormalities could be rescued with prophylactic application of hyaluronidase during blast exposure. Chronic effects of blast exposure include remodeling of the extracellular matrix in rats. In addition to chronic vascular effects, neuroinflammatory-related changes following blast exposure are being considered as a potential mechanism of injury (Elder et al., 2015).

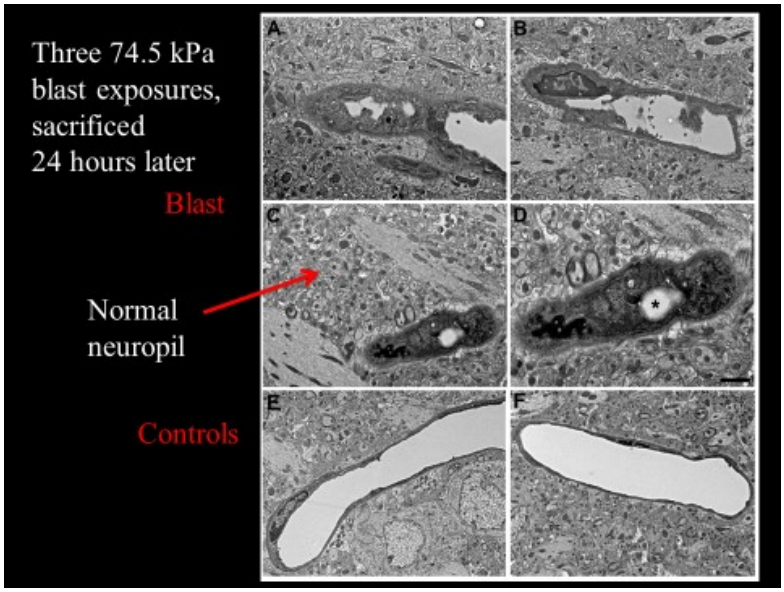

Figure 10: Electron Micrograph Images of Blast-Exposed and Control Vascular Tissue

Dr. Peethambaran Arun, Center for Military Psychiatry and Neuroscience at the Walter Reed Army Research Institute, presented findings from two animal models of brain injury describing effects on phosphorylated tau (pTau) and amyloid precursor protein (APP) levels in the brain.

Rats given a single exposure to blast injury (blast tube, 19 psi) or impact-acceleration injury (weight drop, 500 g from 250 cm above the skull's surface) showed decreased levels of tissue nonspecific alkaline phosphatase (TNAP) and elevated levels of pTau at 6 and 24 hours in the brainstem, hippocampus, and cortex compared to a sham control group. Plasma levels of alkaline phosphatase enzyme activity were also reduced at 6 and 24 hours after exposure to an impact injury, but not blast; this result may be explained by alkaline phosphatase coming into the plasma from internal organs following blast exposure. Levels of alkaline phosphatase in the brain decreased after both blast and impact injuries. At 24 hours, APP levels were elevated in the brainstem, hippocampus, and cortex of both injury groups. These data suggest two processes are set in motion by blast or impact injury: (1) a decrease in TNAP, which may lead to the accumulation of pTau, and eventual development of CTE; and (2) an accumulation of APP, which may trigger an AD-like pathology.

Six hours after rats are repeatedly exposed to blast (two 19 psi blasts within 1 minute), pTau levels are elevated in many brain areas (e.g., brain stem, cortex, cerebellum, mid-brain), and remain significantly elevated in the hippocampus at 24 hours and 14 days. In

rats exposed to two blasts, pTau levels are compared to rats exposed to a single blast. APP levels, while also higher following exposure to two blasts, did not increase at the 6-hour time point, but were elevated at 24 hours and remained so through the 14-day time point.

The lack of a common pattern of elevation for pTau and APP supports the hypothesis that neurobiological mechanism of CTE may be distinct from AD, although the accumulation of APP at later time points suggests that blast can trigger an AD-like pathology. Future neuropathological work will examine the pattern of pTau deposits to determine whether it is located in the superficial layer of cortex, as in CTE, or in the global layer, as is seen in AD.

Dr. Alexander Lin, Brigham and Women's Hospital, reviewed research using MR spectroscopy to identify postconcussion neurochemical alterations that may serve as biomarkers for CTE. MR spectroscopy measures relative concentrations of brain metabolites in living persons and can characterize acute (minutes to days) and chronic (years) neurometabolic changes following injury that may be associated with CTE.

Early application of MR spectroscopy demonstrated a potential role for predicting functional outcomes following severe head injury. Studies in comatose patients with severe head injury resulting from car accidents found that those with a less than 20 percent reduction of N-acetylaspartate (NAA; a chemical found within neural cell bodies that is thought to correlate with number of functioning neurons) had positive recovery outcomes; patients with a larger than 50 percent reduction in NAA remained in a persistent vegetative state (Ross et al., 1998). MR spectroscopy measurements were later shown to be predictive of Glasgow Coma Scores in adults with severe head injury (Shutter, Tong, & Holshouser, 2004).

MR spectroscopy can also characterize metabolic changes following mild brain injury. In a study of subjects with a single concussion, MR spectroscopy showed an acute reduction of NAA compared to controls that recovered over time. In subjects with two concussions, NAA reduction was similar but recovered more slowly (Vagnozzi et al., 2008).

Research in athletes exposed to head trauma aims to identify metabolic changes that may serve as CTE biomarkers. MR spectroscopy of retired football players with CTE-related complaints and a history of multiple concussions indicated elevated levels of choline (a marker of cell damage) and lower levels of glutathione (a marker for neural formation) in the anterior cingulate compare to controls (Lin, Liao, Merugumala, Stern, & Ross, 2014). Elevated levels of choline and myo-insitol (a potential marker of glial cells) were observed in soccer players compared to a control group of noncontact sport athletes (Koerte et al., 2015).

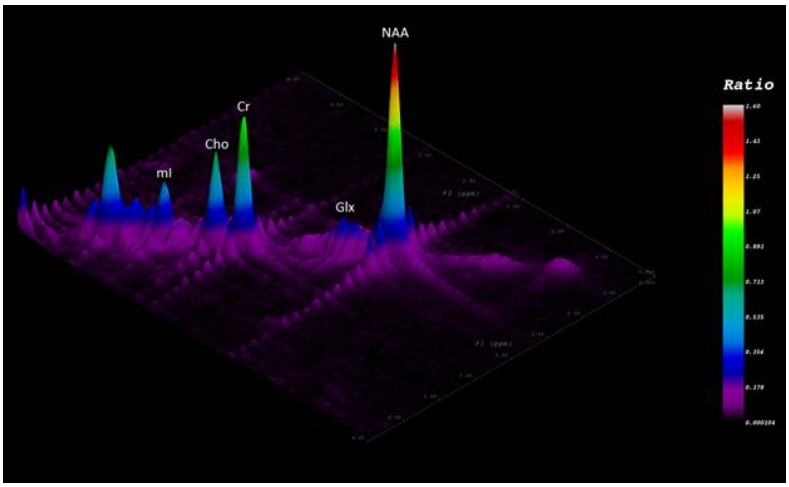

Figure 11: Representative 2D MR Spectrum of a Retired NFL Player

Development of two-dimensional MRS (2D MRS; see Figure 11) has enabled identification and quantification of previously undetectable brain metabolites. Application of 2D MRS in retired football players with CTE-related complaints and a history of multiple concussions indicated elevated levels of glutamate; however, the degree of glutamate did not correlate with the degree of concussion exposure. These and other observations have led researchers to hypothesize about changes in brain metabolite levels during exposure to injury and development of CTE. For example, a better understanding of the timing of glutamate decrease could help identify time points for the potential application of intervention strategies that mitigate its neurotoxic effects. Future research combining MRS with neuroimaging modalities may advance understanding of how neurometabolic changes following brain injury or CTE are localized.

Dr. David Cook, VA Puget Sound Health Care System and University of Washington, reviewed research findings describing alterations in pTau expression, blood–brain–barrier dysfunction, and cerebellar damage in the brain following blast injury. To investigate these phenomena, an animal model of blast injury was developed that uses a shock tube to generate a blast wave similar to TNT in the open field. Rodents exposed to this blast wave exhibited aberrant pTau in the hippocampus for up to 30 days following injury and transient perivascular pTau accumulation was detected before abating within 4 hours following exposure.

In vivo two-photon laser scanning microscopy was used to study blood–brain–barrier integrity in blast-exposed animals. Transient microvascular alterations and microglial responses were observed in focal areas following blast exposure. Delayed blood vessel dysfunction and microglial/macrophage accumulation was observed, indicating that some instances of these phenomena are not directly related to the immediate biomechanics of blast exposure.

Following blast exposure, the cerebellum appears to be particularly susceptible to blood–brain–barrier disruption, especially in ventral areas, and cerebellar Purkinje cells exhibit pTau accumulation and plasma membrane integrity alterations. Additionally, the loss of Purkinje cells was observed following exposure to a single blast; cell loss was

greater following exposure to multiple blasts. Purkinje cell losses are observed in patch-like microdomains. These observations are similar to reports of Purkinje cell loss in postmortem neuropathological examination of former boxers (Corsellis, Bruton, & Freeman-Browne, 1973). In animal models, blast exposure causes alterations in a motor task (rotoraod) and elevated astrogliosis 30 days following injury. Similarly, Veterans exposed to blast exhibit hypometabolism in the cerebellum that correlates with the number of exposures and sensorimotor integration symptoms.

Dr. Charles Rosen, Department of Neurosurgery at West Virginia University, discussed research investigating the role of endoplasmic reticulum (ER) stress responses in blast-induced neurodegeneration. ER stress responses are thought to be associated with neurodegeneration through the induction of pTau pathology (Hoozemans et al., 2009; Ho et al., 2012; Nijholt, van Haastert, Rozemuller, Scheper, & Hoozemans, 2012). ER stress response is mediated in part by two intracellular cascades: (1) the PRKR-like endoplasmic reticulum kinase (PERK) pathway, and (2) the inositol-requiring enzyme 1 (IRE1) pathway (see Figure 12). Stressors to the ER disrupt normal equilibrium between these two pathways and induce relative overactivation of the PERK pathway, which elevates the transcription factor C/EBP homologous protein (CHOP), leading to cell apoptosis though activation of caspase proteins.

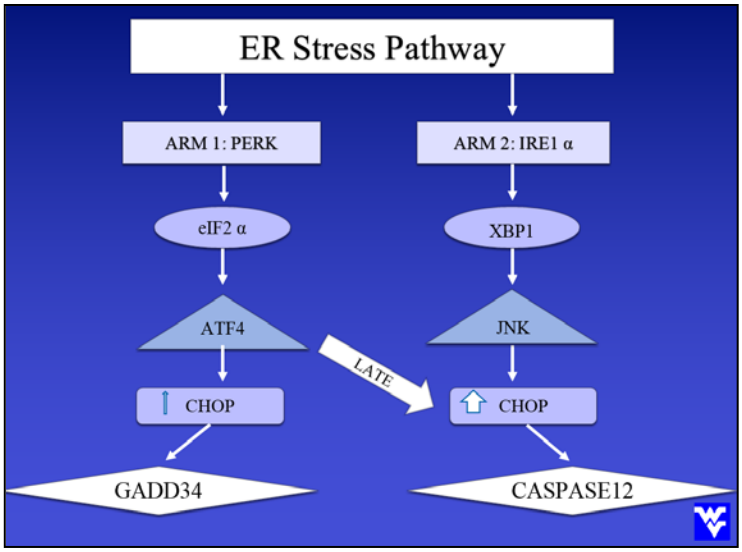

Figure 12: Activation of PERK Pathway Increases Apoptosis

To investigate intracellular signaling pathways associated with ER stress response and blast exposure, a rodent model was developed using a blast tube apparatus. Validation experiments demonstrated induction of a physiologically relevant blast wave, and that animals exposed to the blast wave exhibited astrogliosis, pTau pathology, and activation of the PERK pathway with elevation of CHOP. Exposure to single or repeated blast induced maladaptive behavior (reduced anxiety), as assessed by the Elevated Plus Maze, despite retention of normal motor activity. In addition, these animals exhibited delayed learning and memory deficits 21 days following blast, as assessed in the Morris Water Maze. Administration of Salburinal 30 minutes prior to blast exposure inhibited activation of the PERK cascade and restored normal behavior on the Elevated Plus Maze. These data indicate that blast exposure induces ER stress responses that mediate TBI-relevant behavioral outcomes. Modification of the ER stress response

could prove to be a beneficial strategy for preventing blast-related neurodegeneration and abnormal behavior.

Neuroimaging and Biomarkers

Successful development of objective biomarkers could enable the identification of CTE pathology in living persons, which would greatly enhance research capabilities and would inform potential diagnostic and treatment strategies. Investigators are pursuing neuroimaging modalities and biospecimen analysis as potential biomarkers of CTE.

Dr. Denes Agoston, USUHS, presented findings from preclinical research characterizing the long-term neuropathological and behavioral effects following single and repeated mild, blast-induced TBI. Repeated mild blast TBI (rmbTBI) is considered a primary risk factor for developing neurodegenerative conditions such as CTE. Pathophysiological processes linking single and multiple blast exposures to neurodegeneration are not fully elucidated.

Using a shock tube model in rats, exposure to a single blast resulted in (1) memory impairment that persisted for the entire 71-day experimental period and (2) transient elevation of anxiety behavior that recovered to normal levels by 71 days. Proteomics analysis of brain regions mediating the above mentioned neurobehavioral functions (e.g., dorsal hippocampus, ventral hippocampus, amygdala, prefrontal cortex) from blast-exposed rats revealed region-specific changes in the levels of the select biomarkers (e.g., interferon gamma, IL-6), indicating that different brain regions have different vulnerability to blast exposure. Measurement of serum biomarkers suggested neuroinflammation, vascular damage, and axonal damage in these animals. These results indicate long-lasting functional and molecular changes resulting from a single blast exposure.

Inducing rmbTBI in the shock tube (5 exposures, 24-hour interval) resulted in more pronounced neuropathological and behavioral effects when compared to single blast exposure. Rats exposed to rmbTBI had more pronounced memory deficits (including spatial memory) and increased cell death 21 days postinjury when compared to rats exposed to a single blast. Preliminary experiments, however, indicate that the most damaging between-exposure interval is one hour in the rat model; this timeframe is thought to be equivalent to several days or weeks in humans. Further defining the complex temporal relationship between human and rodent pathologies involved in the neurodegenerative processes is critical to translating preclinical findings to clinically relevant information useful for diagnosis, treatment, and rehabilitation of brain injury.

Dr. Meghan Robinson, VA Boston Healthcare System, presented findings from neuroimaging studies at the Translational Research Center for TBI and Stress Disorders (TRACTS) that examined chronic effects of blast injury. Recent research suggests that acute concussion symptoms are not predictive of long-term changes to

the brain. Additionally, Service Members exposed to blast often under-report concussion, indicating a population suffering from the effects of blast injury that lack assessable concussion symptoms. Given these observations, investigators at TRACTS are seeking to explore variables other than concussion symptoms that could potentially characterize the chronic effects of blast injury. Two recent studies have drawn from a cohort of Veterans and Service Members recruited by TRACTS who have completed neuropsychological testing, clinical assessment, physical assessment, and MRI scans.

One study examined alterations of functional connectivity following blast exposure (Robinson et al., 2015). Subjects exposed to blast at close range (<10 meters) exhibited decreases in functional connectivity as assessed by seed-based resting state connectively analysis of MRI scans (see Figure 13); decreases were not observed for those exposed to longer range (>10 meters) blasts and were independent of blast concussion. Clinical factors such as sleep, pain, or PTSD were controlled for in these comparisons. Differences in functional connectivity were not observed in subjects with concussion history.

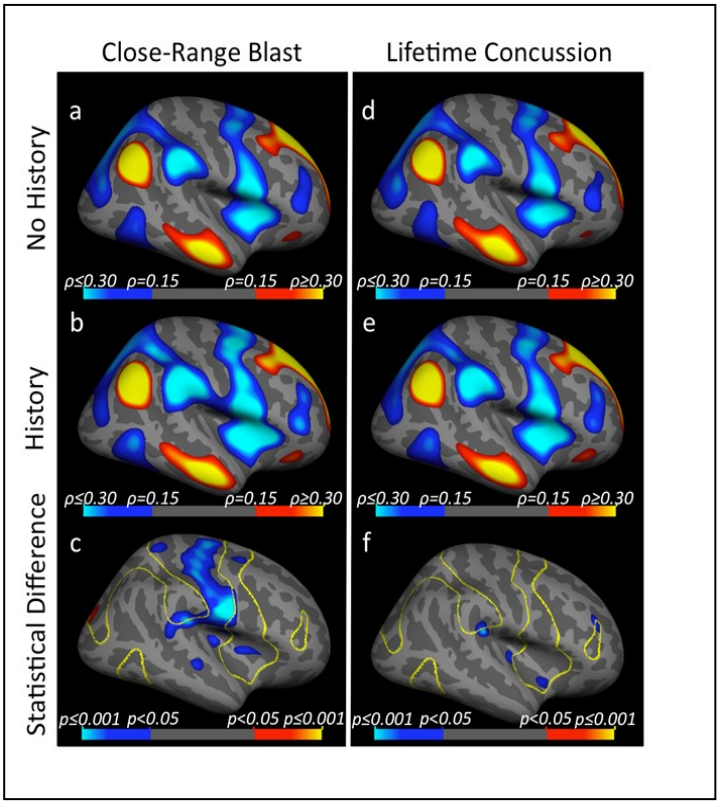

Figure 13: Functional Connectivity Analysis in Close-range Blast Exposure and Concussion (Blunt or Blast)

A second study sought to determine whether blast exposure influenced age-associated degradation of white matter tissue integrity (Trotter, Robinson, Milberg, McGlinchey, & Salat, 2015). DTI indicated more pronounced cross-sectional age associations with white matter integrity among subjects exposed to blast (<100 meters away). Independent clinical factors, such as sleep, pain, or PTSD, could not account for this effect on white matter integrity. These observations suggest the existence of an underlying neurodegenerative process.

Taken together, these studies indicate that blast exposure may be an important consideration, independent of acute concussion symptoms, for potential chronic health effects among Service Members and Veterans. They identify a potential clinical guideline for determining which blasts (i.e., < 10 meters) pose a higher relative risk to health.

Dr. Jessica Gill**,** National Institutes of Nursing Research, reviewed findings resulting from a study of TBI biomarkers in Service Members that could potentially be applied to CTE. Enhanced detection of tau and amyloid beta protein in peripheral blood has been made possible by development of a sensitive analytical technique that amplifies the signal yielded by the traditional enzyme-linked immunosorbent assay (ELISA) by a factor of 300 to 1,000. Analysis of peripheral blood samples was carried out in Service Members at Madigan Army Medical Center who were deployed within the last 16 months (Olivera et al., 2015). Among 70 Service Members who self-reported exposure to TBI during deployment, 58 (82.8 percent) reported exposure to blast.

The presence of tau protein in blood was associated with TBI exposure and chronic injury symptoms. The concentration of total tau protein in peripheral blood plasma was significantly higher in subjects with self-reported TBI exposure compared to nonexposed controls (see Figure 14). Among TBI subjects, plasma concentration of tau was significantly higher in individuals reporting three or more exposures compared to those with fewer than three exposures. Total plasma levels of tau were also correlated with chronic TBI symptoms, as assessed by the Neurobehavioral Symptom Inventory.

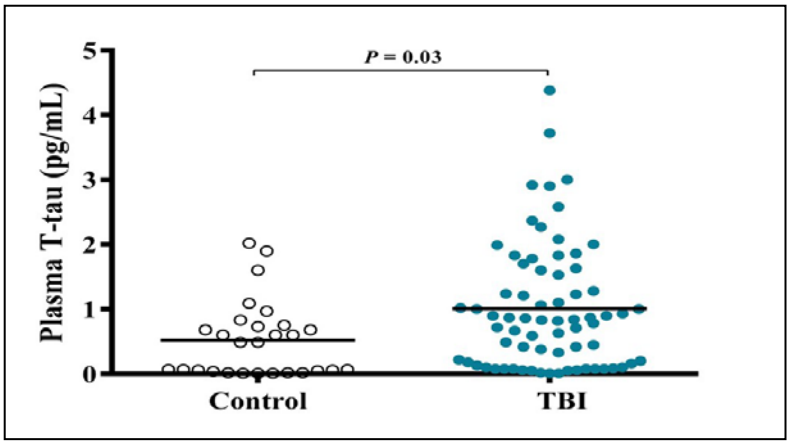

Figure 14: Total Tau Concentration in Control and TBI Subjects

Findings also indicate a potential relationship between plasma amyloid beta and blast injury. Concentration levels of amyloid beta protein were higher in subjects self-reporting that they were exposed to at least one TBI compared to controls; however, this difference was not statistically significant. Among TBI subjects exposed to blast, amyloid beta levels were significantly higher than those of nonexposed controls.

Dr. David Okonkwo, University of Pittsburgh Medical Center, reviewed neuroimaging research characterizing neuropathology in relation to neuropsychological outcomes associated with chronic TBI. Recent pilot work in 17 subjects with chronic TBI and 4 control subjects used High Definition Fiber Tracking (HDFT) to image white matter tracks, PET using Pittsburgh Compound B (PiB) to detect Aβ deposition, and flurodeoxyglucose PET (FDG PET) to detect metabolic activity.

HDFT generates data specific to individual subjects by using novel quantitative metrics to circumvent mathematical limitations of voxel-based analysis; these metrics include

generalized Q-space imaging algorithms followed by deterministic tractography. These quantitative metrics do not pursue group mean statistics and are specific to the individual patient. Quantitative tractography metrics can be applied in two ways: (1) examine anatomical asymmetries in white matter to identify and localize specific tracts that have been subjected to loss or abnormalities within the contralateral side of subject's injury and also within the control subjects and (2) identify and localize abnormalities in white matter arborization, which has been observed in other studies examining subjects exposed to blast injuries.

Ongoing pilot study observations indicate a significant, age-adjusted increase of Aβ deposition in TBI subjects when compared to controls; this signal of increased Aβ was observed in brain regions vulnerable to AD. In gray matter regions of interest to AD, increased Aβ deposition was strongly associated with reduced metabolic activity, which is an expected pattern for those with dementia. In a small cohort of trauma-related dementia patients, increased Aβ deposition was observed in association with decreased metabolic activity, which appears to be similar to AD-related dementia. Additionally, white matter anisotropy in this cohort was associated with reduced metabolic activity and increased Aβ deposition.

The observations can enable testing of the hypothesis that white matter injury induces pathophysiological processes that can culminate in long-term change in humans and animal models exposed to TBI. Future research will assess whether white matter abnormalities are associated with functional outcomes assessed by neuropsychological tests (e.g., verbal recall, serial reaction time, processing speed index, trail making) in subjects with chronic TBI. Additionally, initiation of FDG PET imaging is planned to characterize tau protein accumulation. Neuroimaging outcomes will also be correlated with CSF and serum TBI biomarkers.

Dr. Dara Dickstein, Icahn School of Medicine at Mount Sinai, presented on behalf of Dr. Sam Gandy and described molecular imaging research of TBI and CTE, including review of case studies. Several PET ligands exist that bind with tau or amyloid protein aggregates, which are associated with TBI and CTE neuropathology. Questions remain about the binding specificity of ligands, particularly those that target tau, and interpretation of PET binding signals as accurate reflections of neuropathology or disease states in these conditions.

PET imaging has identified amyloid deposition following TBI. Application of the PiB radioligand indicated the presence of amyloid in acute TBI and is retained 48 hours, 54 days, and 399 days following injury. Preliminary studies in acute TBI suggest that PiB retention is observed in moderate to severe TBI with visible contusions on MRI. However, an ongoing PET study in boxers one month postknockout did not observe amyloid retention with PiB. To date, the presence of amyloid has been associated with

severe TBI, with PiB retention in some subjects with TBI and neuropsychological impairment (Kawai et al., 2013).

Investigators have sought to characterize tau following TBI with PET imaging (Barrio et al., 2015; Chien et al., 2013; Mitsis et al., 2014). These studies indicate the presence of pTau in varying brain distribution patterns bringing to light questions about the binding specificity of tau ligands and the potential contribution of age-related tauopathy. Studies have indicated that age-related tauopathy is predominately localized in the hippocampus and entorhinal cortex as opposed to a case with severe AD with pTau staining extending into the temporal neocortex (Crary et al., 2014). To establish that these ligands can be used to study CTE, it is important to characterize the distribution pattern of pTau for age-related tauopathy and AD.

Recent case reports in two subjects (aged 68 and 70 years) with TBI history and memory-related neurocognitive problems yielded mixed results: One was tau-positive and amyloid-negative, while the other was tau-negative and amyloid positive. These observations have led investigators to ask whether CTE can be distinguished from AD using PET imaging and cognitive assessment. An ongoing study to address this question is seeking to image amyloid (using the [^{18}F]-Florbetapir ligand) and tau (using the [^{18}F]-T807 ligand) in conjunction with neuropsychological assessment in subjects with a history of concussion; controls have been the most difficult study group to recruit.

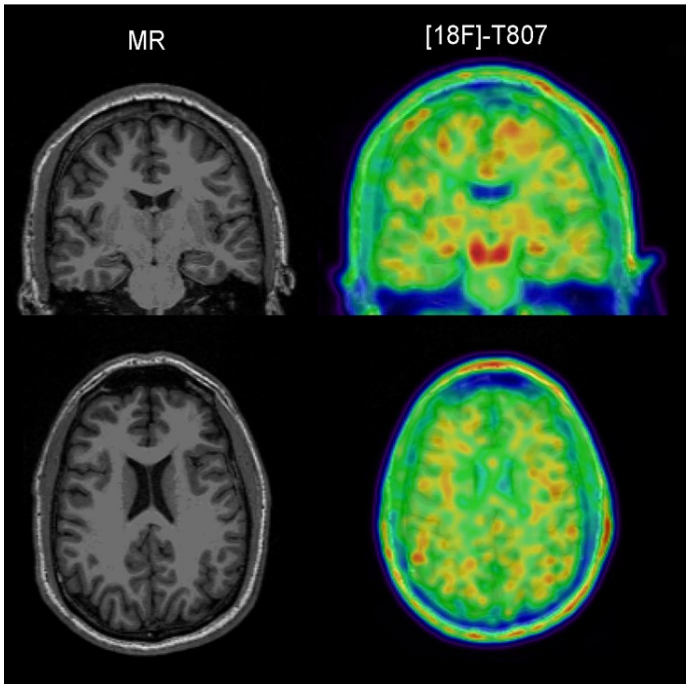

Figure 15: Possible Presence of Diffuse Tau Detected via [18F]-T807 PET

Review of an additional case report indicated neuroimaging findings that appear to reflect behavioral symptoms. The subject was a 39-year-old retired professional football player with multiple concussions and severe functional impairment, including sleep disturbances, headaches, short-term memory loss, as well as impulsive and aggressive behaviors. The subject had kept meticulous neuroimaging, neuropsychological assessment, and concussion history records, enabling longitudinal assessment. Neurocognitive assessments indicated a five-year decline in several functional areas, including executive function, verbal reasoning, motor skills, narrative memory, and word retrieval.

MRI records showed diffuse cortical thinning in several brain areas; this was most pronounced in the left frontal and temporal areas, which correlate with areas of the brain governing neuropsychological functions that declined in this subject. Subcortical volume decrease was greatest in the globus pallidus. [^{18}F]-Florbetapir PET imaging for amyloid deposition was negative in this subject, but binding of [^{18}F]-T807 ligand indicated the presence of tau aggregation (see Figure 15). The disparate observations of tau aggregation in these case studies and other findings indicate a need for scientific progress and consensus among experts on the interpretation of tau signal in PET imaging.

Treatment Strategies

Although neuropathological and clinical features of CTE have not been definitively established, investigators have made advances in exploring potential treatment strategies for chronic neurodegeneration, including CTE.

Dr. Kun Ping Lu, Beth Israel Deaconess Medical Center at Harvard Medical School, reviewed research about the role of tauopathy in TBI, CTE, and AD and the development of novel antibodies that specifically recognize the early driver of neurodegeneration, *cis* pTau. TBI is a potential risk factor for CTE and AD. Tauopathy is a primary neuropathological characteristic of CTE and AD. However, pathogenic processes linking TBI exposure to the development of tauopathy remain largely unknown.

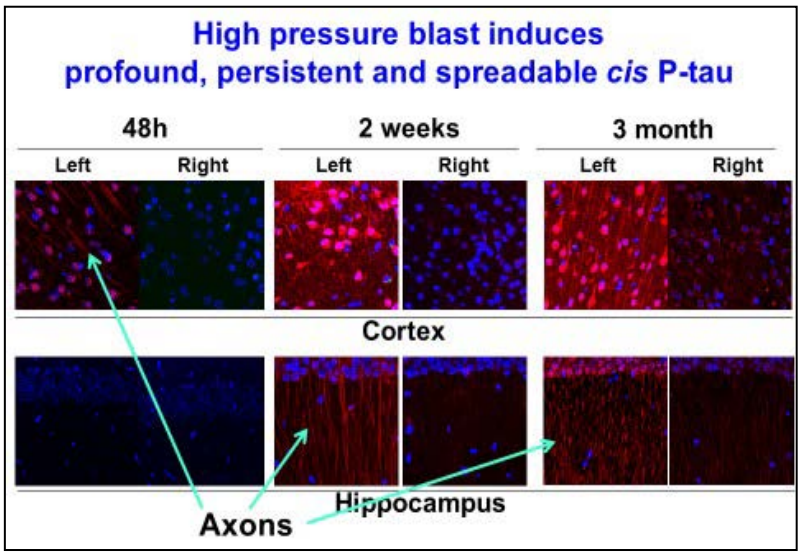

Figure 16: Localization of Cis *pTau in Cortex and Hippocampus*

In AD studies, the *cis* isomer of pTau is predominantly localized to axons and has been implicated in the pathogenesis of AD in rodents and human brain tissue (Nakamura et al., 2012). Unlike *trans* pTau, the *cis* isomer cannot promote microtubule assembly, is more resistant to dephosphorylation and degradation, and is more prone to aggregation. When *cis* pTau is converted to the *trans* conformation, through Pin1, a peptidyl-prolyl *cis-trans* isomerase, the progression of tauopathy in AD is inhibited, suggesting that the *cis* isomer of pTau may be a promising biomarker and therapeutic target of AD.

Recent neuropathological studies indicate the presence of *cis* pTau in human CTE brains following TBI. The *cis* isoform appears at early time points in mouse brain tissue after exposure to blast- and impact-induced TBI (Kondo et al., 2015). Forty-eight hours after blast, *cis* pTau is localized in neurons of the cortex in the damaged side of the brain and spreads to hippocampal neurons in the ipsilateral hemisphere by two weeks and then to the cortex in the contralateral hemisphere by three months (see Figure 16). Follow-on experiments in cell culture found that repeated TBI brain lysates potently induce cell death in 22 percent of neurons by apoptosis; when *cis* pTau is depleted from the TBI brain lysates by *cis* pTau antibody, neuron apoptosis is inhibited. In addition, *cis* pTau antibody blocks the ability of neuronal stress, such as hypoxia, to induce *cis* pTau and apoptosis in cultured neurons.

The *cis* pTau-induced pathogenic process termed “cistauosis” is thought to mediate disease progression of tauopathy through disruption of axonal microtubule networks and mitochondrial transport, ultimately leading to apoptosis; these events are blocked by *cis* pTau antibody in neuron cultures and rodents (Kondo et al., 2015). Blockade of cistauosis in mice exposed to TBI through administration of *cis* pTau antibody prevents tauopathy; prevents neuron loss and brain atrophy; and restores TBI-related functional outcomes, including risk-taking behavior, urinary dysfunction, and sensorimotor imbalance. Cistauosis is thought to represent a pathogenic mechanism linking TBI to AD and CTE (see Figure 17); *cis* pTau antibody may be used to target this mechanism for the development of early diagnosis, prevention, and therapeutic strategies for these conditions.

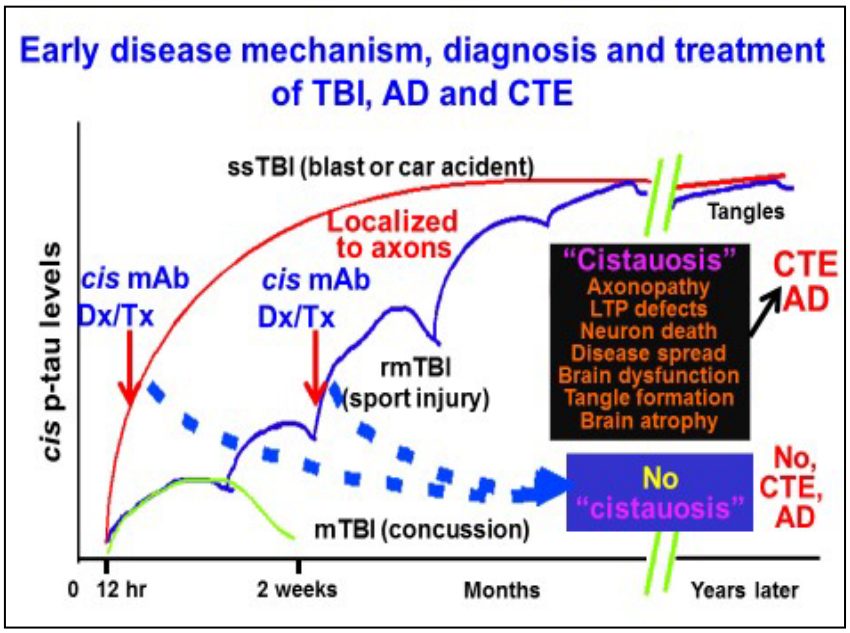

Figure 17: Cistauosis Disease Mechanism

WORKING GROUP SUMMARY

On the second and third days of the meeting, participants divided into six working groups, with each group chaired by an Expert Panel member. Each working group discussed and answered the same set of five specific questions based on their expertise, findings from the literature review, and information from the topic and research presentations. Following the working group discussions, participants reconvened and Expert Panel members presented the conclusions from their working groups. Findings and recommendations from the working groups are described below.

Working Group Question #1

What are the definitive pathological characteristics of neurodegeneration from repeated blast-induced trauma?

- What specific features could be used to characterize CTE as a unique neurodegenerative condition?

The working groups agreed that no definitive neuropathological characteristics specific to blast-induced neurodegeneration have been identified, which is largely attributed to a lack of blast-induced trauma cases available for study. The working groups supported existing NINDS consensus statements identifying diagnostic criteria for CTE (e.g., perivascular accumulation of tau in deep cortical sulci). However, this work was acknowledged as preliminary, given that the neuropathology described by consensus criteria had weak, if any, correlation with clinical phenotypes. Additionally, the cohort examined to create this consensus criteria consisted of professional football players, not individuals exposed to blast-induced trauma.

Neuropathological characteristics of repeated blast-induced trauma are unknown.

The working groups acknowledged that CTE may be part of a neurodegenerative spectrum of disease. Tau deposition was considered the most likely feature capable of uniquely characterizing CTE and associated neurodegeneration. Additional neuropathological analysis of brain tissues exposed to blunt (e.g., boxing, football) and blast injury is needed to determine whether the pathology of neurodegeneration following blast TBI is in the spectrum of CTE.

Tau deposition is the most promising neuropathological feature that could uniquely identify and characterize CTE.

Exploration of other neuropathological characteristics potentially associated with blast-related neurodegeneration and CTE is needed, including neuroinflammation, astrogliosis, microgliosis, axonal pathologies, amyloid deposition, cerebrovascular changes, alterations in deep sulci, and changes in cortical density and thickness.

The lack of human brain tissue available for analysis limits characterization and diagnosis of CTE.

A challenge to definitively identifying a neuropathological characteristic to diagnose blast-associated neurodegeneration and CTE is the lack of human brain tissue available for analysis. To move the field forward, it is critical to encourage brain donation for existing and future clinical trials; donated tissue should have well-characterized clinical, symptom, and exposure history with appropriate age-matched controls. Brain samples should be shared across laboratories for neuropathological analyses. When a solid understanding of the pathology of neurodegeneration from TBI is elucidated, then the field can move forward to create appropriate animal models of TBI that recapitulates what is observed in humans.

Working Group Question #2

What risk factors, both traumatic and nontraumatic, are predictive of CTE?

- What types of traumatic risk factors contribute to the development of CTE and at what frequency?
- How do factors such as overall resiliency, stress, age, genetics, and history of mental illness contribute to CTE development?
- How do blast exposure (e.g., frequency, severity) and other head trauma (e.g., impact, acceleration/deceleration, linear/rotational acceleration) correlate with progressive neurodegeneration?

Exposure to TBI can be considered a known risk factor for CTE; severity of trauma, frequency of trauma, and the time interval between multiple trauma exposures are potentially relevant characteristics of this risk factor. While clinically evident injuries are recognized to be a potential risk for neurodegeneration and CTE, it is also possible that frequent subconcussive injuries have meaningful consequences. More frequent exposure to mTBI and shorter time intervals between injuries are suggested to be associated with greater risk of neurodegeneration. However, additional research is needed to investigate the role of multiple (high frequency), subconcussive (low severity) exposures and the risk developing of CTE. Existing evidence is insufficient to definitively identify risk factors for CTE other than TBI. The working groups identified recommendations for future research of CTE risk factors, including 1) a better understanding of the physics of blast exposure; 2) improved linking of sensor data with blast physics; 3) prospective studies that adequately capture exposure data, lifetime medical and injury histories, and biological samples; and 4) animal models with physiologically relevant scaling of blast exposure characteristics and longer-term follow-up for measurement of outcomes.

Other than TBI, there is insufficient evidence to identify definitive risk factors for CTE.

The working groups highlighted potential traumatic and nontraumatic risk factors predictive of CTE. Traumatic risk factors, in addition to TBI exposure, include physical properties of blast, such as intensity or orientation. Potential nontraumatic contributing risk factors for CTE include 1) genetic predisposition, 2) peri-injury factors (e.g., nutrition, hydration), 3) comorbid psychological or health factors (e.g., stress, sleep deprivation, substance abuse), 4) age at time of injury (first exposure as a younger age is more problematic), 5) comorbid psychological disorders, and 6) environmental factors. Studies demonstrating a greater susceptibility to concussions in female athletes compared to male athletes and observations that Service Members generally take longer than athletes to recover from brain injury suggest further investigation is needed into the roles of gender and occupation as risk factors for CTE and neurodegeneration. Risk factors may contribute to neurodegeneration though pathological mechanisms including 1) acceleration of normal aging processes, 2) induction of neuronal death, 3) DAI combined with tau and cerebrovascular pathology, 4) initiation of inflammatory responses, 5) hypoxia/ischemia, and 6) neuroendocrine disturbances.

Working Group Question #3

What research is needed to explore the putative spatiotemporal development of CTE resulting from repeated blast exposure?

- What is the mechanism of injury in repeated exposure?
- Can dose-response curves be developed to establish a link between the dose of blast and brain injury, including frequency and severity of injury and rate of neurodegeneration?
- What retrospective and prospective human studies are required and what are the limitations of such studies?

The working groups agreed that large prospective longitudinal clinical studies of military Service Members and/or Veterans with, or at risk of, blast injury are needed to characterize the association between repeated blast exposure and the development of CTE. Cohorts of contact sport athletes could illuminate differences between impact- and blast-related exposures. Studies targeting specific military populations with well-controlled or well-known exposure environments could also be useful for assessment of long-term exposure risk. Comparison between combat blast-exposed military personnel and training-exposed control groups without combat experience could potentially identify the contribution of psychological factors to combat-related injury.

Large prospective clinical studies are needed to characterize the development of CTE.

In addition to a commitment from funding agencies that is commensurate with the resources and time intrinsic to prospective studies, several policy-level actions for facilitating CTE-related research were identified. First, clinical data generated by VA, likely the largest source of subjects who have been exposed to repeated blast injuries, should be made available for collaborative analysis. Second, because of a critical need for clinical neuropathological data, physician and military communities should encourage and enable brain donation and biospecimen collection in

There is a critical need for clinical neuropathological data; brain donation and biospecimen collection should be encouraged.

longitudinal studies that include subjects with TBI, neurodegenerative disorders, and mental health disorders. Third, data sharing of brain bank and biospecimen repositories should be strongly encouraged if not mandated for participation.

The working groups also agreed that the development of standardized, properly scaled animal models is needed to better understand blast injury mechanisms and characterize dose-response curves. Preclinical approaches should emphasize clinical relevance, and seek to replicate human pathology to the extent possible. Animal model studies should be conducted over longer time points compared to current experimental approaches to observe changes associated with chronic neurodegeneration. Given that the vast majority of preclinical work is carried out in rodents, models using larger species with gyrencephalic brains should be adopted; existing findings observed in rodents also need to be validated in these larger models.

The working groups agreed that mechanisms underlying repeated exposure to blast injury are largely unknown; multiple biological mechanisms (e.g., neurotransmitter release, vascular injury, blood–brain barrier disruption, endoplasmic reticulum stress, white matter deformation, seizure activity), which may be associated with a particular blast feature (e.g., primary through quinary, force, duration, direction, frequency, reflection), are likely drivers of the neurodegenerative processes. Research into the relationship between physical load and the mechanisms of biological response is needed. Existing physical modeling efforts are often oversimplified, rely on untested assumptions, and do not fully reflect complex biological processes (e.g., effects across solid–fluid interfaces of the brain). Current research gaps relevant to mechanism of injury include 1) determining whether tau and/or amyloid beta accumulation drive disease progression or if they represent biological responses to injury; 2) understanding the pathophysiology priming responses to initial injury that result in increased vulnerability to subsequent injuries; and 3) determining mechanistic differences between multiple subconcussive events and a single traumatic event.

Mechanisms underlying repeated exposure to blast injury are largely unknown.

Development of dose-response curves is possible, but only over a longer term timeframe. The potential for new clinical dose-response studies is challenged by a lack of definitive dose measurement in humans, limited methods for quantitative assessment of neurodegeneration, as well as the reduction of deployment-related exposure among Service Members in recent years following OEF/OIF. Animal models represent a substantive opportunity to characterize dose-response relationships and interrogate potential dosage variables, including exposure force, duration, directionality, and frequency.

The working groups identified several outstanding research questions that need to be addressed by future clinical studies that seek to better understand and characterize the development of CTE: 1) Study design should consider and accommodate the latency of neurodegenerative pathological cascades and progression of clinical symptoms following blast exposures; 2) Research needs to assess the influence of comorbidities (e.g., sleep disturbances, mental health conditions [e.g., PTSD], diabetes, metabolic conditions, substance abuse) on CTE progression; 3) Designing future longitudinal studies according to common frameworks (e.g., sample size requirements, outcome measures, biomarkers) and common data elements would enable data to be compared between studies; and 4) Existing research limitations need to be addressed, including recollection bias in current datasets and regulatory burdens (e.g., multiple, at times conflicting, institutional review boards [IRBs]).

The working groups noted that retrospective studies inherently convey limited information about exposure variables (e.g., severity, frequency), the natural history of symptoms, and comorbidities potentially contributing neuropathology and/or symptoms. Future retrospective studies should use all available military medical records, although it was acknowledged that they are limited by a general lack of TBI data.

Future prospective studies should collect imaging data, blood, and CSF biomarker samples; development of biomarkers capable of identifying subconcussive injuries is particularly needed. For CSF biomarkers, methods for detecting nonsteroidal anti-inflammatory drugs (NSAIDs) and serotonin-selective reuptake inhibitors (SSRIs) in patients would be valuable. Investigators also need to consider the limitations of lumbar CSF sampling and recognize differences in sampling ventricular CSF. Developing neuroimaging biomarkers also requires improved PET and better quantitative analysis methods. Prospective studies should also incorporate sensors to measure the physical properties of blast exposure; the existing limitations of sensor technology creates a need for the development of new sensor-based approaches.

Working Group Question #4

What approaches can be used to detect early stages of blast-related neurodegeneration and evaluate the progression to CTE to support the screening, detection, diagnosis, prognosis, assessment of therapeutic interventions, and determination of return to duty status?

- Is there a specific structure-function profile that can be established using a combination of imaging (DTI and/or PET) and clinical measures that would definitively identify CTE premortem?

Detection of blast-associated CTE development is not currently possible.

The working groups noted that detection of blast-associated CTE development is not possible given the existing state of knowledge. Neuropathological abnormalities and clinical presentation are poorly defined at early stages of CTE. Additionally, differentiating between CTE and other neurodegenerative disorders (e.g., AD) is difficult. Given these realities, the validation of diagnostics is implausible. The working groups identified a number of potential approaches to support screening, detection, diagnosis, prognosis and treatment of early-stage CTE (e.g., imaging, registries, electrophysiology, neuropsychological testing, genomic assessment) that need standardization and validation for stable use over longer term research timeframes and clinical applications. Furthermore, there is no scientific evidence that existing DoD RTD guidelines, which are based on clinical symptoms, are protective against the risk of neurodegeneration.

Biomarkers are needed for detection of early-stage CTE in living persons.

The working groups agreed that development of premorbid biomarkers is needed for detection of blast-related neurodegeneration and early-stage CTE. Potential neuroimaging biomarkers would be further enabled by standardization of imaging acquisition protocols, establishment of normative datasets, and the development of innovative analytic approaches. Working groups indicated that improvement of PET ligands to image amyloid, tau, inflammation, and related pathways are needed. While effective and tolerable CSF biomarkers exist for AD and severe TBI, a widespread search for CSF biomarkers of CTE (including microRNA) is needed. Current blood plasma biomarker techniques do not distinguish tau from other nonbrain

sources of the protein (e.g., muscle), so methods for detection of proteins derived from the central nervous system (e.g., exosomes) are needed.

The working groups agreed that determining structure-function relationships specific to early-stage CTE using imaging and clinical measures is not possible at this time given existing gaps. Current neuroimaging modalities do not reliably distinguish CTE from AD or TBI. Ongoing efforts to develop additional PET ligands, improve analytic techniques, and establish new physiological targets (e.g., neuroinflammation, vascular damage) could potentially enable identification of CTE with neuroimaging. Neurodegeneration in the cerebellum may be particularly relevant to CTE, so a focus on neuroimaging in this region in addition to assessment of cerebellar-mediated functional outcomes was suggested.

Working Group Question #5

What are the strategies that can be used to prevent, mitigate, or treat neurodegeneration following repeated blast exposure?

The working groups agreed that a better understanding of the progression of neurodegeneration following repeated blast exposure is crucial to developing prevention, mitigation, and treatment strategies. Continued study of blast-induced neurophysiological injury cascades leading to neurodegeneration, including neuroinflammatory processes, apoptosis, gliosis, autoimmune effects, and protein aggregation (tau, amyloid beta), will inform identification of targets for these strategies. Research of the processes should include developing animal models with standardized, scaled blast exposures and long-term follow-up.

Improving personal protective equipment and establishing blast exposure limitations are the most promising areas for preventing blast-induced neurodegeneration.

The working groups also agreed that among existing efforts to develop strategies that would prevent blast-related injury, the most promising include improving personal protective equipment (PPE) and vehicle design, providing additional training, and establishing limits (number, frequency) for blast exposure. Several areas of research are needed to identify factors predicting neurodegeneration and development that can be targeted by prevention development efforts. An improved understanding of blast physics and how physical forces measured by sensors relate to brain injury is needed. This understanding can be accomplished by enhancing field measurements of environmental exposure and developing additional

computational and empirical tools for estimating biomechanical injury risk. Better characterization of biological dosimetry measures and improved surveillance and reporting of exposures during training and in the field (including the use of sensors) will inform development of new and existing protocols that limit blast exposure. Materials science approaches should be pursued to develop new and advanced solutions for PPE and vehicle design. Researchers should also examine the potential for altering training procedures and engagement tactics in order to maximize the ability of PPE to protect Service Members from blast exposure.

Currently, blast injury can be best mitigated by enhancing communication up and down the chain and by maximizing the rest period during the acute injury stage.

Although more work is needed to understand how injuries might be mitigated postexposure and prior to the onset of neurodegeneration, several mitigation strategies were suggested. Working groups indicated that communication efforts within the military line that promote maximization of recovery time during the acute stage of injury (as much as possible given mission requirements) are an effective mitigation strategy. Communication strategies are needed to change attitudes about reporting TBI, to improve reporting of TBI, and to enable line leaders to comply with guidelines for reporting potentially potential compensable events (PCEs). Steps to maximize recovery at the acute stage of injury may include: 1) encouraging the longest period of rest following that is possible, given mission requirements; 2) assisting Service Members with lifestyle management; 3) researching the influence of exercise, diet, drug and alcohol use, and cognitive exercises on brain recovery following blast injury; 4) improving sleep/sleep hygiene, particularly during the early recovery period; 5) developing standards for progressive RTD; and 6) researching biological markers that might identify the onset and end of the risk period.

The working groups noted that more research is needed before treatments for blast-related neurodegeneration can be offered. Recommended lines of research include pharmacological targeting of specific molecular pathologies (e.g., tau, inflammation, apoptosis, glutamate excitotoxicity, amyloid beta, astrogliosis, microgliosis), improving data sharing access across agencies and resolving conflicts that arise as a result of having multiple IRBs, investigating the benefits of cognitive behavioral therapy tailored to specific symptom constellations, and promoting the benefit a healthy lifestyle to maximize improvements in brain health following injury.

SOS EXPERT PANEL FINDINGS AND RECOMMENDATIONS

Following the SoS Meeting, the Expert Panel convened during a closed session to identify key findings and recommendations that encapsulate the major discussion points from the topic presentations, the poster sessions, and the working group sessions.

Expert Panel Findings

The Expert Panel noted that the majority of blast-related TBIs within the military population arise from a mixed exposure to both blast overpressure and impact as opposed to blast overpressure alone; this complicates the meaning of "blast" when discussing blast-related trauma. The pathology of TBIs and any subsequent neurodegenerative outcomes arising from either of these exposure types is largely unknown. As a result, the overarching finding identified by the Expert Panel is that existing scientific evidence is insufficient to link blast-related TBI with CTE. The Expert Panel identified thirteen findings describing research and knowledge gaps, clinical gaps, and research opportunities that, if addressed with focused effort, would further the understanding of the potential relationship between blast-related trauma and CTE.

Research and Knowledge Gaps

There is a lack of blast exposed clinical tissue, with well-annotated medical and blast exposure histories, available for neuropathological analysis. Limited opportunity to gather neuropathological evidence with historical data impedes the ability to explore the association between neuropathology and lifetime risk factors or clinical features. Better understanding of the human neuropathology of blast and any associated neurodegeneration is needed to develop informative animal models.

Standard definitions of "blast" and "blast exposure" are needed. Blast-related exposures can encompass all types of blast injury, from primary to quinary. However, different preclinical and clinical investigations model or define blast differently, which introduces variability across studies and limits reproduction and validation of findings.

Existing animal models are inadequate to study blast-related TBI and neurodegeneration. Validated and clinically-relevant animal models are needed to identify underlying mechanisms of acute and chronic blast injury. Absent an understanding of injury mechanisms, the discovery of diagnostics and treatments is greatly inhibited.

Longitudinal and prospective studies, both having a strong neuropathological component, are needed to characterize the risk factors and spatiotemporal development of CTE. Informed by the current state-of-the-science, well designed studies that collect detailed medical histories and exposures (frequency, magnitude) from Service Members and Veterans, and obtain consent for brain donation by these

individuals, can help establish the role of blast-related trauma in the development of CTE.

Limitations to data access and data sharing impose significant barriers to research. Legal, ethical, and logistical barriers to use of Service Member and civilian health data, exposure history, and medical records prevent analysis of potentially useful clinical information. Promoting broader access and use of these extant data could result in rapid answers to outstanding questions on the potential relationship between blast exposure and chronic TBI.

Substantiated risk factors for CTE are unknown, with the exception of exposure to head trauma. Studies of other potential risk factors, including gender, age, psychological health, drug or alcohol abuse, and genetics, have not been conclusive.

Evidence-based RTD protocols are lacking. There is no existing scientific evidence establishing parameters of existing DoD RTD guidelines, which are based on clinical symptoms, as protective against the risk of neurodegeneration.

Clinical Gaps

Clear and standardized clinical criteria for CTE are lacking, impeding progress in development of premortem diagnosis and screening approaches. Because the clinical features associated with CTE overlap with other neurodegenerative conditions such as AD, identification of specific or unique clinical diagnostic criteria has been difficult. Standardized neuropsychological and behavioral assessments relevant to CTE are also lacking. Definition and diagnosis of CTE should ultimately be driven by clinicopathological approaches that incorporate clinical and pathological information. Defining and describing CTE as a spectrum disease, rather than as a binary condition, should also be considered.

Development of fluid and imaging biomarkers are needed for diagnosis and treatment of CTE. Non-invasive biomarkers of CTE would enable premortem diagnosis and serve to assess the efficacy of therapeutic strategies.

Current neuroimaging approaches cannot diagnose CTE, or distinguish CTE from other neurodegenerative disorders. Neuropathological abnormalities associated with CTE, such as tau or Aβ protein aggregation, cannot be characterized reliably with existing neuroimaging technology. Spatial resolution of existing neuroimaging modalities is also insufficient to image neuropathology at the scale observed in CTE studies.

Potential Research Opportunities

Extant data can be used to investigate CTE risk factors. Clinical correlation studies of electronic health record data and/or concussion care clinics should be explored.

Populations exposed to blast should be continuously monitored. Monitoring may help to determine a dose-response relationship between blast intensity and frequency, and severity of human injury. Once a dose-response curve is established in humans, it will become easier to create more accurate animal models of blast injury.

Sensor technology development and materials science offer significant research and prevention opportunities. PPE-embedded blast wave sensors could allow objective measurement to supplement, or replace, exposure documentation. Sensor-enabled detection of rotational acceleration, which may play a role in blast-related mid-brain and cerebellar injury, may be valuable. Advanced materials research can benefit sensor technology development, as well as personal and vehicular protection.

Expert Panel Recommendations

The Expert Panel identified six recommendation describing specific actions needed to advance research exploring the potential relationship between blast-related trauma and CTE. Table 5 describes Expert Panel recommendations, including immediate (< 1 year), short term (1-2 years), midterm (3-4 years), and long term (5+ years) timeframes for addressing necessary components of these recommendations.

Among the six recommendations, the Expert Panel identified the first four as highest priority for addressing pressing research needs. These four high-priority recommendations include, in order of priority: 1) more collection and study of clinical neuropathology samples, 2) standardization of clinical diagnostic criteria, 3) development of clinically-appropriate and standardized animal models, and 4) development of non-invasive serial assessment strategies (i.e., imaging or biospecimen biomarkers).

Table 5: Expert Panel Recommendations

Recommendation	Timeframe	Components
1. Create a coordinated brain bank/ repository system, accessible to the research community	Immediate (< 1 year)	• Educate researchers on the importance of neuropathology and provide communication strategies that would enable them to advocate for brain donation with participants and families • Address logistical barriers of brain donation to promote rapid acquisition of brain tissue and facilitate sharing within research community
	Short Term (1-2 years)	• Establish a central repository and laboratory for storing, processing, and analyzing brains o Collect 100 brains
	Mid Term (3-4 years)	• Develop definitive criteria for establishing the pathology of blast exposure
	Long Term (5+ years)	• Collect 1,000 brains, including medical and blast exposure history o For brains acquired <48 hours postmortem, fix one hemisphere (e.g., for immunostaining) and freeze the other hemisphere (e.g., for *in situ* hybridization) o For brains acquired >48 hours postmortem, fix both hemispheres
2. Develop standardized clinical diagnostic criteria	Short Term (1-2 years)	• Gather exposure data from pre-enlistment and pre- and post-deployment time periods • Use standardized neuropsychological/behavioral assessments validated for serial use in subjects with suspected blast-related neurodegeneration • Continue development of biospecimen biomarkers of injury to complement exposure histories
	Long Term (5+ years)	• Follow subjects with blast exposure, with potential exposure, and age-matched controls long term to determine the incidence of blast-induced neurodegeneration
3. Develop and validate animal models clinically relevant to blast injury and chronic neurodegeneration	Short Term (1-2 years)	• Develop standardized protocols with blast exposure characteristics • Measure outcomes at longer time points following blast exposure that more appropriately reflect chronic effects • Share protocols across the research community
4. Develop a strategy for development of next-generation biospecimen and imaging biomarkers	Immediate (< 1 year)	• Convene an expert panel to assess current biomarkers and make recommendations for future development of technologies, protocols, and analytics
	Short Term (1-2 years)	• Develop a long-term plan for standardizing biomarker measurement
	Mid Term (3-4 years)	• Explore combinatorial imaging modalities for differential diagnosis
	Long Term (5+ years)	• Develop high spatial resolution neuroimaging approaches to detect potential neuroanatomical characteristics specific to CTE

Table 5: Expert Panel Recommendations (continued)

Recommendation	Timeframe	Components
5. Strengthen ongoing longitudinal and prospective studies, or initiate new studies, to explore the spatiotemporal development of CTE and candidate risk factors, respectively; emphasize neuropathological analysis of blast-exposed tissue	Immediate (< 1 year)	• Convene an objective expert panel to: o Identify gaps in current longitudinal studies that can be addressed with additional data (e.g., neuropathological tissue) o Review current prospective studies to determine if risk factors are adequately addressed • Plan a prospective study using candidate risk factors, potential biomarkers, and tissues that would address remaining gaps • Identify additional potential risk factors for analysis which may include genetic susceptibility, gender, age, drug abuse, and performance-enhancing drugs
	Short Term (1-2 years)	• Initiate recruitment and data collection, with an emphasis on neuropathological analysis of blast-exposed tissue
	Long Term (5+ years)	• Analyze prospective data to determine which candidate risk factors and biomarkers can be quantified
6. Implement prevention and mitigation strategies until treatment strategies become available	Immediate (< 1 year)	• Modify training protocols to reduce exposure (without reducing training time) • Educate military instructors about long term exposure risks • Maintain optimal brain health in Service Members (e.g., sleep, etc.) • Re-inforce existing guidelines for management of mTBI
	Long Term (5+ years)	• Improve equipment (PPE and vehicles) to mitigate injury • Determine extent to which RTD guidelines mitigate risk of neurodegeneration

CONCLUSIONS

The 2015 International SoS Meeting sought to comprehensively survey existing evidence and gaps in knowledge about the potential relationship between blast-related trauma and CTE. The Expert Panel identified one overarching finding, followed by thirteen findings, to include research and knowledge gaps, clinical gaps, and potential research opportunities. The overarching finding is that existing scientific evidence is insufficient to link blast-related TBI with CTE. Seven subsequent Expert Panel findings described research and knowledge gaps, which include a lack of 1) standard definitions of blast and blast exposure, 2) adequate access to blast-exposed clinical tissue with well-annotated medical and exposure information, 3) validated and clinically-relevant animal models, 4) longitudinal and prospective studies with neuropathological components to characterize the risk factors and spatiotemporal development of CTE, 5) data access and data sharing within the scientific community, 6) substantiated risk factors for CTE, other than head trauma, and 7) evidence-based RTD guidelines. Three Expert Panel findings identified clinical gaps which include a lack of 1) clear and standardized clinical diagnostic criteria for CTE, 2) fluid and imaging biomarkers for diagnosis and treatment of CTE, and 3) neuroimaging approaches capable of diagnosing CTE or distinguishing CTE from other neurodegenerative disorders. Finally, three Expert Panel findings identified potential research opportunities, including 1) use

of extant data to investigate CTE risk factors, 2) continuous monitoring of populations exposed to blast, to explore dose-response relationships between blast intensity and injury severity, and 3) sensor technology development and materials science to advance data gathering and prevention strategies.

An additional goal of the 2015 International SoS Meeting was to develop recommendations to advance the state-of-the-science on the potential relationship between blast-related trauma and CTE. The Expert Panel identified six recommendations, the first four of which were determined as highest priority for addressing pressing research needs.

- First, **creation of a coordinated brain bank and tissue repository** system, is recommended with a robust plan for donation of clinical specimens that are annotated with medical and blast exposure data; this would enable exploration of the relationship between neuropathology and risk factors or clinical features.
- Second, **development of standardized clinical diagnostic criteria for CTE** is recommended to enable premortem identification of the condition, ideally in concert with neuropathological information.
- Third, **development and validation of clinically-relevant animal models** is recommended to explore potential biological mechanisms linking blast injury and development of CTE.
- Fourth, **development of biomarkers** is recommended to enable premortem diagnosis and study of CTE in living persons.
- Fifth, **strengthening of ongoing longitudinal studies** and **initiation of new prospective studies** to assess candidate risk factors of CTE as well as spatiotemporal development of CTE and other candidate neuropathological changes linked to long-term sequelae resulting from blast exposure.
- Sixth, **implementation of existing prevention and mitigation strategies** in at-risk or exposed populations, given that treatment strategies for CTE are not yet available.

Findings and recommendations identified by the 2015 International SoS Meeting can help develop methods and tools for achieving a better understanding of the potential relationship between blast-related trauma and CTE. This knowledge could translate into enhanced strategies for prevention, mitigation, diagnosis and treatment of CTE or other blast-induced neurodegeneration experienced by Service Members.

APPENDICES

Appendix A. References

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Appendix B. Acronyms

Aβ	Beta-amyloid
AD	Alzheimer's disease
APP	Amyloid precursor protein
Blast PCO	DoD Blast Injury Research Program Coordinating Office
CARE	Concussion Assessment, Research and Education Consortium
CENC	Chronic Effects of Neurotrauma Consortium
CHOP	C/EBP homologous protein
CNRM	Center for Neuroscience and Regenerative Medicine
CSF	Cerebrospinal fluid
CTE	Chronic traumatic encephalopathy
DAI	Diffuse axonal injury
DHA	Defense Health Agency
DNA	Deoxyribonucleic acid
DoD	Department of Defense
DoDI	Department of Defense Instruction
DTI	Diffusion tensor imaging
DVBIC	Defense and Veterans Brain Injury Center
ENIGMA	Enhancing Neuro Imaging Genetics Through Meta Analysis
ER	Endoplasmic reticulum
ERP	Event-related potentials
FDG-PET	Flurodeoxyglucose PET
FITBIR	Federal Interagency Traumatic Brain Injury Research
HA	Health Affairs
HDFT	High definition fiber tracking
HHS	Department of Health and Human Services
IRE1	Inositol-requiring enzyme 1
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
NAA	N-acetylaspartate
NCAA	National Collegiate Athletic Association
NFL	National Football League
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NIH	National Institutes of Health
NINDS	National Institute for Neurological Disorders and Stroke
NRAP	National Research Action Plan
NSAIDS	Non-steroidal anti-inflammatory drugs
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
PERK	PRKR-like endoplasmic reticulum kinase
PET	Positron emission tomography
PiB	Pittsburgh Compound B

PPE	Personal protective equipment
pTau	Phosphorylated tau
PTSD	Posttraumatic stress disorder
RTD	Return to duty
SoS	State-of-the-Science
SSRI	Serotonin-selective reuptake inhibitor
TBI	Traumatic brain injury
TNAP	Tissue nonspecific alkaline phosphatase
TRACTS	Translational Research Center for TBI and Stress Disorders
USAMRMC	US Army Medical Research and Materiel Command
USUHS	Uniformed Services University of the Health Sciences
VA	Department of Veterans Affairs
WRAMC	Walter Reed Army Medical Center
WRNMMC	Walter Reed National Military Medical Center

Appendix C. Meeting Planning Committee Members

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COL Ladd Tremaine
Armed Forces Medical Examiner System

Dr. James Zheng
PEO Soldier

Appendix D. Expert Panel Biographies

COL Jamie Grimes, Chair

COL Jamie Grimes, MD, MC, USA was the National Director of the Defense and Veterans Brain Injury Center from July 2010 until July 2013. As national director, COL Grimes oversaw all aspects of the organization's mission to serve Service Members and Veterans with traumatic brain injury through state-of-the-art medical care and care coordination, and clinical research and educational programs. COL Grimes is board certified in vascular neurology, neurology, and psychiatry. COL Grimes oversaw standardization of care at 11 concussion care centers while deployed to Afghanistan in 2011, serving as theater neurology consultant. During her deployment, she performed site visits to ensure that staff had appropriate training and resources. She reviewed cases, shared best practices, and worked with theater providers to close gaps in care. COL Grimes has held multiple appointments and academic posts, including former neurology consultant for the Army Office of The Surgeon General and currently is the Chief of the Neurology Department at Walter Reed National Military Medical Center and the Chair of Neurology at the Uniformed Services University of the Health Sciences.

Dr. Stephen Ahlers

Dr. Stephen Ahlers has been performing basic and applied research for the Navy since 1986. He was a Program Officer at the Office of Naval Research managing the Undersea Medicine, Stress Physiology and Casualty Prevention programs. Since 2003, he has served as the Director of the Combat Casualty Care and Operational Directorate, which was renamed as the Operational Undersea Medicine Directorate. His current research interests are related to traumatic brain injury from blast exposure. In response to operational need, Dr. Ahlers initiated research to develop an animal model assessing the effects of repeated exposure to low-intensity blast overpressure, research that paralleled studies assessing the effects of multiple low-intensity blast exposures in operational personnel, e.g., Breachers. Dr. Ahlers has published numerous articles on the effects of blast. He is the principal investigator of a large, multicenter, collaborative effort to develop occupational standards to guide exposure to multiple blast events.

Dr. Kelley Brix

Dr. Kelley Brix is the program director for the Department of Defense (DoD) and Department of Veterans Affairs (VA) Research Coordination Defense Health Agency, Research, Development, and Acquisition Directorate. She provides expertise as a physician epidemiologist in the oversight of the Defense Health Program medical research portfolios, a research investment of $1.6 billion annually. Additionally, she manages the DoD/VA Research Business Line, which coordinates research, including the identification of emerging research priorities and development of interagency research collaborations. She also manages the 10-year National Research Action Plan on Mental Health, which was mandated by the White House. Dr. Brix holds a BS in Biology from Purdue University, an MS in Zoology, an MD from the University of Michigan, and an MPH in Environmental and Occupational Health Sciences from the

University of Illinois. She is Board Certified in Preventive and Occupational Medicine and is a Fellow of the American College of Preventive Medicine.

Dr. David Brody
Dr. David Brody is currently a tenured associate professor in the Department of Neurology at Washington University in St. Louis. Dr. Brody treats patients with subacute and chronic sequelae of traumatic brain injury in the Traumatic Brain Injury Clinic. The Brody laboratory and collaborative group is focused on the development of novel therapeutic and diagnostic strategies for traumatic brain injury. The laboratory is funded by grants from the National Institutes of Health, the Department of Defense, Cure Alzheimer's Fund, and the National Football League (NFL). Dr. Brody is the Washington University site director for the NFL Neurological player care program. He received both an MD and PhD from the Johns Hopkins University in 2000 and completed an internship in Internal Medicine in 2001 and a Neurology residency in 2004 at Barnes-Jewish Hospital. He has advised the US Army Vice Chief of Staff and assisted the Medical Advisor to the Chairman of the Joint Chiefs of Staff.

Dr. William Stewart
Dr. William Stewart is Consultant and Lead Neuropathologist at the Queen Elizabeth University Hospital, Glasgow and Honorary Associate Professor at the University of Glasgow and the University of Pennsylvania. He has an internationally recognized research program in traumatic brain injury directing studies using the resources of the unique Glasgow TBI Archive to characterize the complex pathologies of human TBI, with particular focus on the link between TBI and late neurodegenerative disease. This work attracts research funding from a variety of agencies, including the US National Institutes of Health and Department of Defense, NHS Research Scotland, and the European community. Reflecting his insight into the biology and pathology of traumatic brain injury, Dr Stewart acts as an external advisor to multiple national and international sports and government organizations.

LTC Avraham Yitzhak
Dr. Avi Yitzhak is currently head of the Trauma and Combat branch of the Israeli defense forces. Dr. Yitzhak received his MD from the Ben-Gurion University School of medicine in 1999, after which he served as a field physician in the 101 battalion, the paratroopers unit, and was the chief physician of the Special Forces. Dr. Yitzhak completed his residency in general surgery in Soroka Medical Center (affiliated to Ben-Gurion University at the Negev). Being the only level one trauma center in southern Israel, the Soroka Medical Center has taken care of all the wounded from the last major conflicts in the Gaza strip. After completing his residency, Dr. Yitzhak served as the Chief Medical Officer of the Gaza division of the southern command, during which he was in charge of the medical aid to the combat zone during operation "Protective Edge." Dr. Yitzhak's research interests include treatment and rehabilitation of trauma patients after army conflicts, including head trauma with a special focus on developing protective helmets.

Appendix E. Meeting Participants

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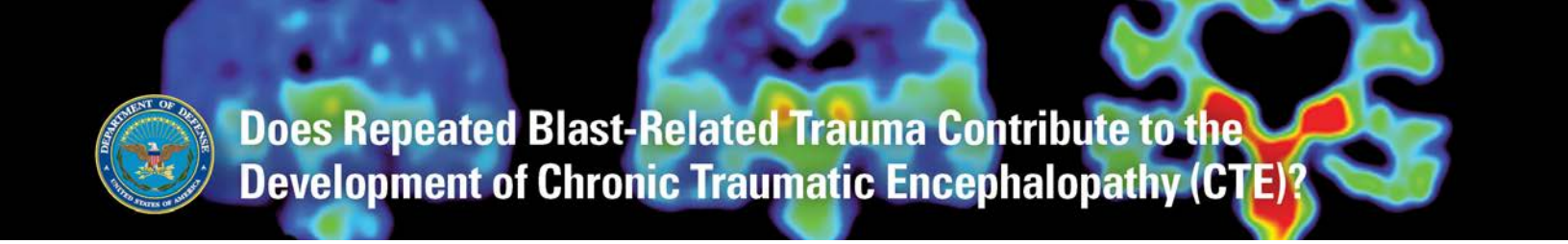
North Dakota State University

Appendix F. Meeting Agenda

Tuesday, 3 November 2015

Time	Schedule	Presenter
8:00 am	***Registration***	
8:30 am	***Welcome and Meeting Overview***	***Mr. Michael Leggieri, DoD Blast Injury Research Program Coordinating Office***
9:00 am	Keynote Address	Dr. John F. Glenn, Principal Assistant for Research and Technology, US Army Medical Research and Materiel Command
9:20 am	***Requirements and Defining the Problem***	***Mr. Michael Leggieri***
9:25 am	Prevalence of TBI and Chronic Effects of Blast-Related Trauma In the Military	COL Sidney Hinds, Defense and Veterans Brain Injury Center
9:45 am	Annual Blast Overpressure Exposure of Mortar and Artillery Men	LT Uade Olaghere da Silva, Naval Medical Research Center
10:05 am	Future Policy Considerations for Managing Chronic Effects of TBI in Service Members	Ms. Elizabeth Fudge, Office of the Assistant Secretary of Defense, Health Affairs
10:25 am	Q&A for all Speakers	
10:40 am	***AM Break***	
10:55 am	***Requirements and Defining the Problem (continued)***	***Mr. Michael Leggieri***
11:00 am	VA Perspective on Current State of the Science and Policy Considerations: Past, Present, and Future	Dr. Stuart Hoffman, Department of Veterans Affairs
11:20 am	NIH-Public Health Perspective on the Relationship between Head Trauma and CTE	Dr. Patrick Bellgowan, National Institute of Neurological Disorders and Stroke
11:40 am	NCAA Perspective on the Relationship Between Head Trauma and CTE	Dr. Steven Broglio, University of Michigan
12:00 pm	Q&A for all Speakers	
12:15 pm	***Lunch and Poster Set-up***	
1:15 pm	***Current State of the Science and What's Next***	***Mr. Michael Leggieri***
1:20 pm	Literature Review Summary: the Biological Basis of Chronic Traumatic Encephalopathy Following Blast Injury	Dr. Matt Aldag, Booz Allen Hamilton
1:40 pm	Q&A/Discussion	



Time	Schedule	Presenter
1:55 pm	***Scientific Session I: Pathological Characteristics of Blast-Induced TBI***	***Mr. Michael Leggieri***
2:00 pm	Why Do We Know So Little About the Neuropathology of Blast TBI?	Professor Douglas Smith, University of Pennsylvania
2:20 pm	Neuropathology Studies of Acute and Chronic Blast TBI, Evidence of an Unique Pattern of Damage to the Human Brain Following Blast Exposure	Dr. Daniel Perl, Uniformed Services University of the Health Sciences, The Center for Neuroscience and Regenerative Medicine
2:40 pm	***PM Break***	
2:55 pm	***Scientific Session II: Risk Factors and CTE***	***Mr. Michael Leggieri***
3:00 pm	Clinicopathologic Phenotypes of Chronic Traumatic Encephalopathy: Distinct Risk Factors	Dr. Robert Cantu, Boston University School of Medicine
3:20 pm	***Scientific Session III: Blast-Induced Neurodegenerative Mechanisms***	***Mr. Michael Leggieri***
3:25 pm	Vascular and Inflammatory Factors in the Chronic Pathophysiology of Blast-Induced Brain Injury	Dr. Gregory Elder, James J. Peters VA Medical Center
3:45 pm	Repeated Blast Exposures Cause Neuropathological Underpinnings of CTE and Alzheimer's Disease	Dr. Peethambaran Arun, Walter Reed Army Institute of Research
4:05 pm	Measuring Changes in Brain Chemistry after Repetitive Brain Trauma using MR Spectroscopy	Dr. Alexander Lin, Brigham and Women's Hospital, Harvard Medical School
4:30 pm	***Closing Remarks and Adjourn***	***Mr. Michael Leggieri***

Wednesday, 4 November 2015

Time	Schedule	Presentation
8:00 am	***Registration***	
8:30 am	***Welcome and Topic Introduction***	***Mr. Michael Leggieri***
8:40 am	Chronic Traumatic Encephalopathy: Contact Sports and Blast Injuries	Dr. Joseph Maroon, University of Pittsburgh Medical Center
9:00 am	Q&A for the Speaker	
9:15 am	***Scientific Session III: Blast-Induced Neurodegenerative Mechanisms (continued)***	***Mr. Michael Leggieri***
9:20 am	The Role of Aberrant Phospho-Tau in Blast-Induced Mild Traumatic Brain Injury	Dr. David Cook, VA Puget Sound Health Care System
9:40 am	A Novel Investigation into the Underlying Mechanisms Linking Neurotrauma to Neurodegeneration	Dr. Charles Rosen, Department of Neurosurgery, West Virginia University
10:00 am	***AM Break***	
10:15 am	***Scientific Session IV: Neuroimaging and Biomarkers***	***Mr. Michael Leggieri***
10:20 am	High-Fidelity Animal Modeling of Blast-Induced Neurodegeneration: A Longitudinal Study to Identify Mechanisms and Biomarkers	Professor Denes Agoston, Uniformed Services University of the Health Sciences
10:40 am	Neuroimaging of Non-Concussive Blast Exposure in OEF/OIF/OND Veterans	Dr. Meghan Robinson, VA Boston Healthcare System
11:00 am	Blast TBIs are Associated with Higher Concentrations of Amyloid Beta in Peripheral Blood	Dr. Jessica Gill, National Institutes of Health
11:20 am	PET Imaging with Pittsburgh Compound B of Amyloid Deposition in White Matter in Chronic TBI: An Exploratory Analysis	Dr. David Okonkwo, University of Pittsburgh Medical Center
11:40 am	Cortical Gray Matter-White Junction Pattern of Retention of the Tauopathy Ligand ^{18}F-T807 (Avid 1451) in Clinically Probable CTE	Professor Sam Gandy, James J. Peters VA Medical Center and Icahn School of Medicine at Mount Sinai
12:00 pm	***Scientific Session V: Treatment Strategies***	***Mr. Michael Leggieri***
12:05 pm	Cis-P-Tau Directly Links TBI to CTE and AD, But Can Be Blocked by Antibody	Dr. Kun Ping Lu, Beth Israel Deaconess Medical Center, Harvard Medical School

Time	Schedule	Presentation
12:25 pm	***Lunch and Poster Session***	
2:25 pm	***Roles and Responsibilities of Working Groups****	***Mr. Michael Leggieri***
2:35 pm	Working Group* Deliberations	
5:00 pm	***ADJOURN directly from Working Groups***	

Thursday, 5 November 2016

Time	Schedule	Presentation
8:00 am	***Registration***	
8:30 am	Working Group* Deliberations	
11:30 am	***Lunch and Poster Session***	
1:00 pm	Working Group* Deliberations	
2:00 pm	Working Groups Report Out	Working Group Chairs/ Expert Panelist
4:00 pm	***Closing***	***Mr. Michael Leggieri***

Appendix G. Taxonomy of Injuries from Explosive Devices

Injury Type	Description
Primary Blast Injuries • Blast lung • Ear drum rupture and middle ear damage • Abdominal hemorrhage and perforation • Eye rupture • Nonimpact-induced mTBI	Primary blast injuries result from the high pressures the blast creates. These high pressures, known as blast overpressure, can crush the body and cause internal injuries. Primary blast injuries are the only category of blast injuries that are unique to blast.
Secondary Blast Injuries • Penetrating ballistic (fragmentation or blunt injuries) • Eye penetration	Secondary blast injuries result when strong blast winds behind the pressure front propel fragments and debris against the body and cause blunt force and penetrating injuries.
Tertiary Blast Injuries • Fracture and traumatic amputation • Closed and open brain injury • Blunt injuries • Crush injuries	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.
Quaternary Blast Injuries • Burns • Injury or incapacitation from inhaled toxic fire gases	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.
Quinary Blast Injuries • Illnesses, injuries, or disease caused by chemical, biological, or radiological substances (e.g., “dirty bombs”)	Quinary blast injuries refer to the clinical consequences of “post-detonation environmental contaminants,” including chemical, biological, and radiological (e.g., dirty bombs) substances.

From DoD Directive 6025.21E

The term “blast injury” includes the entire spectrum of injuries that can result from exposure to explosive weapons, ranging from nonimpact-induced mTBI and ear damage to penetrating wounds, heat and chemical burns, and/or loss of limbs. 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. The *Taxonomy of Injuries from Explosive Devices* assigns blast injuries to five categories—Primary, Secondary, Tertiary, Quaternary, and Quinary—based on the mechanism of injury.

Appendix H. Welcome Letter

Dear Colleague:

On behalf of the DoD Executive Agent for Medical Research for Prevention, Mitigation, and Treatment of Blast Injury, welcome to the 2015 International State-of-the-Science Meeting addressing the question, “Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?” We have assembled approximately 140 subject matter experts, who have volunteered their time to participate in this meeting in order to answer this important question. The ultimate objective of this meeting is to gain knowledge that will help shape medical research to deliver timely and effective prevention, mitigation, and treatment strategies for our Service Members.

Over 300,000 US Service Members have been diagnosed with a traumatic brain injury (TBI) since 2000. Most of these are non-combat related (motor vehicle accidents, falls, training, sports) and the vast majority are mild. Blast-related, mild TBI is the most common injury encountered by Service Members in the combat settings of Iraq and Afghanistan, which leads to the following question: What are the long term impacts of such injuries, especially if there are multiple exposures? The question of the possible association between head impacts and CTE in the military has a well-publicized parallel within the contact sports community who, together with the DoD, has made considerable investments to establish multi-institutional and multi-disciplinary collaborative research programs focused on CTE. Thus far, findings from CTE studies have resulted in some controversies due to the conclusions drawn, as well as the research methodologies employed; these controversies are well documented in the scientific literature.

During this meeting, experts from the scientific, medical, and operational communities within the DoD, other Federal agencies, academia, and industry, as well as our international partners, will present their research and participate in working groups to discuss, challenge, and seek consensus about the link between repeated blast-related trauma, neurodegeneration, and CTE. Your active participation will help to achieve the following meeting objectives:

1. Discuss the evidence linking repeated blast exposure to neurodegeneration
2. Assess the pathophysiology, underlying mechanisms of injury, and progression of blast-induced neurodegeneration
3. Identify specific features that can contribute to the characterization of CTE as a unique neurodegenerative condition
4. Examine relevant animal injury models for blast-induced neurodegeneration

5. Discuss strategies for prevention, mitigation, early diagnosis, and treatment of blast-induced neurodegeneration
6. Explore the link between blast-induced neurodegeneration and CTE
7. Identify knowledge gaps that will inform future research directions

Over the next three days, I encourage you to take every opportunity to engage with your colleagues and actively participate in working group discussions. I am especially looking forward to the dialogue during the working group sessions, as we seek to answer the following questions:

1. What are the definitive pathological characteristics of neurodegeneration from repeated blast-induced trauma?
2. What risk factors, both traumatic and non-traumatic, are predictive of CTE?
3. What research is needed to explore the putative spatiotemporal development of CTE resulting from repeated blast exposure?
4. What approaches can be used to detect early stages of blast-related neurodegeneration and evaluate the progression to CTE to support screening, detection, diagnosis, prognosis, assessment of therapeutic interventions, and determination of return to duty status?
5. What are the strategies that can be used to prevent, mitigate, or treat neurodegeneration following repeated blast exposure?

Together, our efforts during this meeting can serve to achieve the ultimate objective of gaining the knowledge needed in order to identify critical knowledge gaps and provide recommendations on the pivotal research required to improve the safety and well-being of our Service Members.

I look forward to working with all of you on this very important topic, and I am grateful for your participation in this meeting.

Michael J. Leggieri, Jr.
Director, DoD Blast Injury
Research Program Coordinating Office

Appendix I. Poster Presentations

Submitter	Title
Professor Michel Audette	Model-Based Approaches for Descriptive Subject-Specific Head Models for Blast-Induced Traumatic Brain and Ear Injury Simulation and Shock Wave Studies
Professor Carey Balaban	Remodeling and Lipidomic Responses to Local Vascular Injury in Mild Blast Wave TBI: Possible Paths to Chronic Degenerative Disorders
Dr. Rohan Banton	Understanding the Effects of Repeated Primary Blast Impact on Dissociated Neuron Cells
Dr. Elizabeth Brokaw	Visuomotor Tracking for Evaluation of Sub-Concussive Brain Injury
MAJ Walter Carr	Environmental Sensors in Training: Pilot Field Studies
Dr. Douglas DeWitt	Blast-Induced Cerebral Vascular & Behavioral Dysfunction & Neuronal Injury
Dr. Gary Fiskum	Underbody Blast-Induced Traumatic Brain Injury: Reduction of Acceleration Dependent Neurologic Impairment and Mortality by Advanced Vehicle Hull Design
Dr. Lee Goldstein	Blast and Impact Neurotrauma: Neuropathology and Mechanisms of Mild Traumatic Brain Injury (TBI) and Chronic Traumatic Encephalopathy (CTE)
Professor Ghodrat Karami	Blast-Induced Brain Injury: A Study on the Directionality of Blast, Helmet Protection and Helmet Underwash Effect
Dr. Laurel Ng	mTBI from Accumulation of Rapid Low-Level Repeated Blast
Dr. Thuvan Piehler	Compounded Primary-Explosive–Blast-Loading Impacts on Neurons and Hippocampal Slice Cultures
Ms. Julie Proctor	Aeromedical Evacuation-Relevant Hypobaria Worsens Axonal, Cerebrovascular, and Neurologic Injury in Rats Following Underbody Blast- or Impact-induced Traumatic Brain Injury
Dr. Paul Rigby	Analysis of Known Events from Theatre using Helmet Mounted Sensor System
Dr. Marten Risling	Experimental Studies on Repeated Blast Induced TBI
Dr. David Tweedie	Blast TBI-Induced Cognitive Deficits are Attenuated by Pre- or Post-Injury Treatment with the Glucagon-like Peptide-1 Receptor Agonist Exendin-4
Maj Adam Willis	Skull dynamics of TBI (topic area, not title)
Dr. Nikki Zander	In Vitro Studies of Primary Explosive Blast Loading on Neurons, Glia and 3D Aggregates

Appendix J. Keynote Speaker Biography

Dr. John F. Glenn, SES
Principal Assistant for Research and Technology,
US Army Medical Research and Materiel Command

Dr. John Frazier Glenn was selected to the Senior Executive Service in November 2005. He serves as the Principal Assistant for Research & Technology at the US Army Medical Research and Materiel Command at Fort Detrick, Maryland, where he exercises scientific oversight and direction of the command's Science and Technology programs ($1.7 billion in fiscal year 2010) in military infectious diseases, military operational medicine, combat casualty care, clinical and rehabilitative medicine, advanced technology, medical chemical and biological defense, and congressional directed special interest research programs, as well as in oversight of the command's worldwide laboratory system of laboratories, six in the continental United States and three outside the continental United States.

Prior to his current appointment, Dr. Glenn was the Technical Director, Headquarters, US Army Medical Research and Materiel Command from 2004 to 2005. Before retiring at the rank of Colonel with 30 years of military service, he served as the Deputy for Research and Development from 2000 to 2004 and Director, Plans Programs, Analysis, and Evaluation from 1998 to 2000 at Headquarters, US Army Medical Research and Materiel Command. Prior to these positions, Dr. Glenn also served as the Director, Medical Systems Integration Office from 1996 to 1998 and the Executive Assistant to the Commanding General from 1992 to 1996 at Headquarters, US Army Medical Research and Materiel Command. Dr. Glenn was also the Deputy Commander, Headquarters, US Army Research Institute of Environmental Medicine, Natick, MA, from 1989 to 1992. Prior to this assignment, he was the Senior Army Technology Staff Officer for Medical Research, Office of the Assistant Secretary of the Army for Research, Development and Acquisition, Washington, DC, from 1988 to 1989 and the Liaison Officer, Office of the Program Executive Officer for Combat Medical Systems, U.S. Army Medical Materiel Development Activity with duty at the Pentagon Office of the Assistant Secretary of the Army for Research, Development & Acquisition, Washington, DC, from 1987 to 1988. Dr. Glenn also served as the Senior Staff Officer, Medical Chemical Defense Research Program, Headquarters, US Army Medical Research and Materiel Command, Fort Detrick, MD, from 1986 to 1987 and the Chief, Neurotoxicology Branch, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD, from 1982 to 1986. Prior to these assignments, he also was the Deputy Chief, Neurotoxicology and Experimental Therapeutics Branch from 1981 to 1982 and a Research Psychologist, Physiology and Neurotoxicology and Experimental Therapeutics Branches from 1980 to 1981 at the US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD. He also was a Research Psychologist, Behavioral Research Directorate, US Army Human Engineering Laboratory, Aberdeen Area, Aberdeen Proving Ground, MD, from 1975 to 1979.

Appendix K. DoD Blast Injury Research PCO Contact Information

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