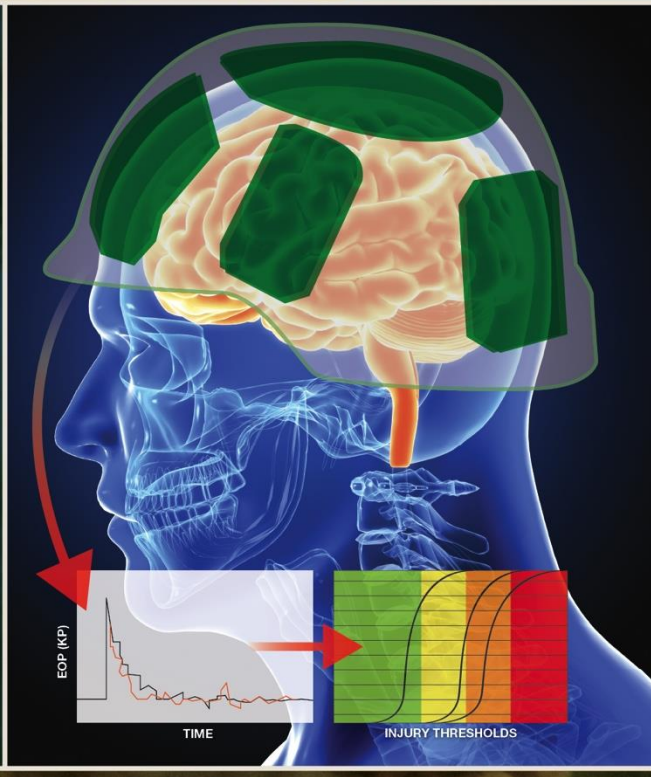
DoD Blast Injury Research Program Coordinating Office

International State-of-the-Science Meeting on the Biomedical Basis for Mild Traumatic Brain Injury (mTBI) Environmental Sensor Threshold Values

4-6 November 2014



Literature Review

National Institutes of Health

Foreword

The Blast Injury Research Program Coordinating Office was established within the U.S. Army Medical Command at the U.S. Army Medical Research and Materiel Command, Fort Detrick, Maryland, to assist the Executive Agent for the prevention, mitigation and treatment of blast injuries in coordinating and managing blast injury-related the Department of Defense (DoD) medical research efforts and programs. The Program Coordinating Office coordinates and manages relevant DoD medical research efforts and programs, identifies blast injury knowledge gaps, shapes medical research programs to fill identified gaps, facilitates collaboration among diverse communities both within and outside of the DoD, and widely disseminates blast injury research information.

The "State-of-the-Science Meeting Series" was established in 2009 to assist the DoD Blast Injury Research Program Executive Agent in identifying knowledge gaps pertaining to key blast injury research issues. The November 2014 International State-of-the-Science Meeting on the Biomedical Basis for Mild Traumatic Brain Injury Environmental Sensor Threshold Values will bring together subject matter experts from the DoD, other Federal agencies, academia, and industry to assess current state-of-the-science underlying the mild traumatic brain injury (mTBI)/concussion thresholds associated with environmental sensors. The objectives of this meeting are to:

- Assess the current state-of-the-science for the biomedical basis of environmental sensor threshold values and the relationship of these threshold values with the risk of the development of mTBI/concussion;
- Identify gaps in the development and utilization of current environmental sensor injury threshold values;
- Guide future research to gain understanding between varying blast forces and the development of traumatic brain injury; and to
- Improve protection, treatment, and mitigation for civilian and Warfigher communities.

The State-of-the-Science meeting will be a working session during which attendees will be expected to actively participate and share information and ideas. All attendees will be asked to participate in working groups to address the following questions:

- Are the existing environmental sensor threshold values suitable for predicting the development of mTBI/concussion?
- What are the challenges for developing biomedically valid standardized thresholds that accurately capture mTBI/concussion events?
- What are the appropriate parameters (e.g., linear/rotational acceleration, pressure, event duration) for which sensor threshold values need to be established?
- What biomedical research is needed to develop predictive models for association of sensor threshold values and development of mTBI/concussion?

This review of the literature serves to inform the meeting attendees on the current state-of-the-science regarding mTBI environmental sensor threshold values and to focus meeting discussions on associated knowledge gaps and to inform discussions that will guide future research efforts for preventing and mitigating injuries to the Warfighter and civilian populations.

Executive Summary

The DoD sponsors medical research programs aimed at advancing the DoD's capability to prevent, mitigate, and treat blast injuries. Established in 2007, the DoD Blast Injury Research Program Coordinating Office has played a key role in coordinating blast injury research by leveraging expertise from within and external to the DoD, nationally as well as internationally. Despite extensive research in the areas of mTBI/concussion and methods for detecting concussion events, our understanding of the biomedical basis for mTBI exposure sensor threshold values remains limited. This literature review provides a summary of the current state-of-the-science for mTBI/concussion thresholds associated with environmental sensors with an emphasis on the neuropathology, mechanisms, computational modeling, environmental sensor technology, the evaluation of sensor technology, as well as the validation and correlation of environmental threshold values to mTBI/concussion.

There are three main non-exclusive hypotheses for the mechanical mechanisms of blast-induced TBI: (1) thoracic pressure waves that transmit to the brain; (2) impact/head acceleration (both linear and rotational); and (3) direct cranial entry of blast waves. To determine the exact contribution of the thorax to structural changes in the brain following blast exposure, additional collaborative research efforts are needed. Flexion trauma appears to result in more serious injury than extension trauma and additional research may contribute to the development of more effective protective equipment. Further research on the effects of blast waves on neuronal cells to aid in the development of novel biomarkers for blast exposure is needed.

Advancements in animal modeling and neuroimaging have allowed for more detailed investigation into the pathophysiological (e.g., neuroanatomical, cellular, molecular) outcomes of mTBI. Despite such preclinical and clinical research to date, the exact outcomes and trajectory of TBI (blast and non-blast) remain unknown.

Advances in computational modeling allow the simultaneous simulation of the dynamic response of both fluids and solids to blast. Computer modeling may aid in elucidating the mechanisms of blast injury and identifying "regions of interest" for injury thresholds. The accuracy of computational modeling is limited by the ability to determine parameter values, which have varied over orders of magnitude in experiments. Several environmental sensors have been deployed in the field. No reports, however, have been published linking data from fielded sensors to known injury. Product developers are conducting their own *ad hoc* tests on the sensors to determine accuracy. There is a need for independent standardized testing to validate sensory accuracy. Additionally, sensors currently under development align to one of three categories: (1) packaged environmental sensors; (2) raw pressure sensors; and (3) burst sensors. Packaged environmental sensors can record pressure and acceleration (both linear and angular) along with vital signs such as electroencephalogram (EEG), heart rate, and oxygen saturation (SpO_2). Raw pressure sensors need further development before being packaged for fielding. Burst sensors are cheap, lightweight, and require no external power source; they, however, cannot report or accurately record environmental data.

Currently, there is no definitive experimental evidence for the existence of clinically relevant thresholds for mTBI. Current blast injury tolerance curves for humans are obtained by scaling from animal models. Published reports on the identification of proposed mTBI thresholds from impact have come largely from the civilian sector, specifically professional and collegiate athletics.

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I. Introduction

TBI is a significant health issue affecting large numbers of service members and Veterans. The DoD and Department of Veterans Affairs have classified TBI according to severity (e.g., mild, moderate, severe) based on specific injury criteria outlined below in Table 1 (U.S. Department of Veterans Affairs & U.S. Department of Defense, 2009).

Table 1. Classification of TBI Severity

Criteria	Mild	Moderate	Severe
Structural Imaging	*Normal*	*Normal or abnormal*	*Normal or abnormal*
Loss of consciousness	*0 to 30 minutes*	*> 30 minutes and < 24 hours*	*> 24 hours*
Alteration of consciousness	*a moment up to 24 hours*	*> 24 hours; Severity based on other criteria*	
Posttraumatic amnesia	*0 to 1 day*	*> 1 and < 7 days*	*> 7 days*
Glasgow Coma Scale	*13 to 15*	*9 to 12*	*< 9*

The number of reported TBIs has increased significantly among service members following recent military and combat operations in Iraq and Afghanistan. According to the Defense and Veterans Brain Injury Center, approximately 295,000 service members sustained a TBI between 2000 and 2013 with the vast majority (82.5 percent) classified as mTBI (U.S. Department of Veterans Affairs & U.S. Department of Defense, 2009). More specifically, service members are sustaining blast-related neurotrauma, with exposure to explosive blasts accounting for more than 60 percent of all combat causalities (Ling, Bandak, Armonda, Grant, & Ecklund, 2009). A survey of 3,952 U.S. Army infantry soldiers found that 587 (14.9 percent) of the soldiers met the criteria for having had mTBI during a year long deployment. Of the 587 soldiers identified with mTBI, 424 (72.2 percent) reported a blast-related mechanism, while 150 (25.6 percent) reported a nonblast-related mechanism (Wilk et al., 2010).

Due to its prevalence, blast-related mTBI is widely accepted as the "signature injury" of the Global War on Terror because of the preferred use of explosive devices by enemy combatants including improvised explosive devices (IEDs), vehicle borne IEDs, and improvised rocket assisted mortars during Operations Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND) (Kovacs, Leonessa, & Ling, 2014). Blast injuries are characterized by complex interactions between the primary blast wave, the environment, and the body.

As shown in Table 2, injuries caused by blast explosions have been defined as primary, secondary, tertiary, quaternary, and quinary (U.S. Department of Defense, 2014). Primary injuries are caused by exposure to blast overpressure (BOP), which can transmit directly through the skull or indirectly through blood vessels (Kobeissy et al., 2013). Secondary injuries are caused by penetrating fragments thrown from the explosive device. Tertiary injuries are caused by rapid displacement of the body that may cause impact with blunt objects; rapid acceleration/deceleration of the head can lead to coup contrecoup brain injuries. Quaternary injuries include flash burns, crush injuries, and inhalation injuries. Quinary injuries are caused by exposure to environmental contaminants associated with explosive blasts, such as bacteria, chemicals, and radiation. This review will focus on primary and tertiary injuries.

Table 2. Taxonomy of Injuries from Explosive Devices adapted from the (U.S. Department of Defense, 2014)

Taxonomy of Blast Injuries	
Primary	*BOP injury resulting in direct tissue damage from the shock wave coupling into the body*
Secondary	*Injury produced by primary fragments originating from the exploding device (preformed and natural (unformed) casing fragments, and other projectiles deliberately introduced into the device to enhance the fragment threat); and secondary fragments, which are projectiles from the environment (debris, vehicular metal, etc.)*
Tertiary	*Displacement of the body or part of body by the BOP causing acceleration/deceleration to the body or its parts, which may subsequently strike hard objects (impact) causing typical blunt injury (translational injury), avulsion (separation) of limbs, stripping of soft tissues, skin speckling with explosive product residue and building structural collapse with crush and blunt injuries, and crush syndrome development*
Quaternary	*Other "explosive products" effects – heat (radiant and convective), and toxic, toxidromes from fuel, metals, etc. – causing burn and inhalation injury.*
Quinary	*Clinical consequences of "post detonation environmental contaminants" including bacteria (deliberate and commensal, with or without sepsis), radiation (dirty bombs), tissue reactions to fuel, metals, etc.*

The precise underlying mechanisms of injury, as well as the neuropathological, pathophysiological, and functional consequences of both blast and non-blast mTBI, remain unknown despite the wealth of clinical and preclinical research. As explained above, "blast" injury entails a number of different kinds of injuries. With respect to mTBI, it is unknown if exposure to BOP or rapid acceleration due to impact is the leading transmission mode of injury. Research in the field is impeded by the rarity of isolated primary blast exposure cases (Chapman & Diaz-Arrastia, 2014).

Animal studies that immobilize subjects' heads have shown that BOP alone can induce TBI, but pressure levels must be higher to cause injury in head-restrained cases than in non-head-restrained cases. In the civilian population, impact in sports and automobile accidents can induce TBI as well. With respect to blast, research is still needed to understand which mode is the primary driver, if/how they interact, and whether blast- and impact- induced mTBI can be treated as the same disease. Recent studies have shown that blast- and impact-induced mTBI have similar clinical outcomes (Chapman & Diaz-Arrastia, 2014; C. L. Mac Donald et al., 2014).

Another major research gap is the identification of standardized, valid threshold values for detecting and predicting blast and non-blast mTBI/concussion. Technological advances in the development of helmet-mounted and head mounted dosimeters have allowed for the capture and analysis of real-time data on head impacts within the civilian (e.g., sports) and military (e.g., deployed, training) environments (Cobb, 2013; Dionne, 2010). Biomechanical data such as linear acceleration are being used to generate concussion risk curves or injury threshold values for the detection of mTBI/concussion, however, many gaps still exist especially regarding threshold for blast and impact-related mTBI. To address this need, the DoD Blast Injury Research Program Coordinating Office has commissioned the Biomedical Basis for Mild Traumatic Brain Injury (mTBI) Environmental Sensor Threshold Values literature review to describe the current state of the field regarding mTBI/concussion thresholds and to inform the expert working group attending the upcoming State-of-the-Science meeting. While recognizing that all severities of TBI and the entire spectrum of blast injuries are important to understand, this literature review is focused on mTBI/concussion and the primary injuries caused by blast explosion.

In addition to the published literature reviewed in this document, accomplishments and activities of several military organizations have been included to highlight the considerable efforts of the DoD to facilitate the development of environmental sensors and establishment of validated sensor threshold values. These efforts have been included in gray boxes throughout the document to distinguish this work from the peer-reviewed literature.

II. Literature Review Methodology

Table 3 lists the terms that were used for identifying potentially relevant literature to answer the following two research questions:

- What is the current state-of-the-science regarding threshold values for environmental sensors (e.g., acceleration and overpressure)?
- What is the relationship between acceleration and overpressure threshold values and the development of mTBI?

In Table 3, Column A addresses broad search terms for a high-level search on blast exposure events; Column B narrows the scope of the articles to capture articles specific to injury outcomes with a focus on TBI and more specifically, mTBI; Column C further refines the search to identify articles about environmental sensor systems (e.g., Defense Advanced Research Projects Agency [DARPA] blast gauge, Integrated Blast Effects Sensor Suite [IBESS], Headborne Energy Analysis and Diagnostic Systems™ [HEADS]); Column D contains additional search terms related to the organizations, manufacturers, and studies performed to validate sensor data. Search terms and search strings (when possible) were used to identify articles that reported on the mechanisms and neuropathology of TBI, environmental sensors in a variety of research settings, articles that attempted to determine TBI threshold values, and the validation of environmental sensors for predicting injury.

Table 3. Relevant Search Terms to Identify Literature on Blast Exposure, Validated Sensor Data, and mTBI

COLUMN A	COLUMN B	COLUMN C	COLUMN D
Blast	Concuss*	Blast gauge	Analysis
Blast event	Injury	Blast sensor	BlackBox Biometrics
Blast exposure	Injury outcomes	Computational models	Clinical
Blast induced	mTBI	Gauge	DARPA
Blast-induced	mTBI	Ground vehicle	DoD
BOP	TBI	Headborne Energy Analysis and Diagnostic System	Evaluat*
Blast wave	TBI	HEADS	Manufacturer
Blunt		Helmet-mounted	Natick Soldier Research, Development, and Education Center
Closed		Helmet sensor	Program Executive Office Soldier
Combat		HMSS	Quanti*
Explosi*		IBESS	Studies
IED		IBESS	Study
Impact		Models	Training
IED		Sensor	Trials
Non-impact		Sensor system	Valid*
Non-penetrating		SHIELD	
Overpressure		Shock Impact and Explosive Limits Dosimetry	

COLUMN A	COLUMN B	COLUMN C	COLUMN D
Rotational		Threshold	
		Threshold values	

In addition to the search terms listed in Table 3, *ad hoc* searches on key principal investigators or specific topics were performed. Pertinent articles identified in the bibliographies of relevant papers were reviewed for inclusion in the literature review. Potentially relevant articles identified from the literature search were reviewed for the following data for inclusion in the literature review:

- Environmental (acceleration/overpressure) sensor device/system evaluated
- Study design/type
- Study population
- Medical assessment used (e.g., biomarkers, imaging, histochemistry)
- Key results/include statistics (when available)
- Key conclusions/next steps

Few limits were set on the literature search to more broadly capture the state-of-the-science on environmental sensors and the pathophysiology of TBI. Only articles published in the English language were collected and reviewed. Articles reviewed were published between 2004 and 2014 with the exception of articles published prior to 2004 if an article was determined to be fundamental to understanding the subject matter within the context of the literature review. Additionally, studies that included in vitro and animal (small and large) models, and retrospective human studies as well as the use of physical surrogates were also considered in the literature review.

More than 300 potentially relevant articles were identified from the literature search. All articles were briefly reviewed and the most relevant articles are discussed in the literature review document. A table describing the results of the literature search can be found in Appendix B.

III. Results

A. Mild Traumatic Brain Injury (mTBI)

1. Mechanisms of mTBI

The precise mechanisms by which a blast pressure wave causes mTBI are still under investigation. Blast pressure waves resulting from penetrating ballistic projectiles or impacts to body armor have been shown to have damaging effects to the brain. There are three main hypotheses (Table 4) developed from research studies explaining the proposed mechanical mechanisms of TBI. These proposed mechanisms are not mutually exclusive and it is most likely some combination of two or more components of these mechanisms that result in TBI.

Table 4. Descriptions of the proposed mechanical mechanisms for mTBI

Mechanical Mechanism for Primary Blast-Induced TBI	Description
Thoracic mechanism	• *Blast pressure waves enter the thorax and lead to brain injury (Bhattacharjee, 2008; Cernak, I, 2005)* • *Pressure waves focused to the thoracic region could only cause brain injury through an internal mechanism – primarily compression of the thorax resulting in a vascular surge to the brain (Cernak, Wang, Jiang, Bian, & Savic, 2001a)*
Head acceleration/impact	• *Translational and rotational mechanisms have been well defined (Krave, Höjer, & Hansson, 2005; Zhang, Yang, & King, 2004)* • *Numerical modeling of head models exposed to blast waves have demonstrated the plausibility of primary acceleration-induced TBI (Stuhmiller, J.H. et al., 1998).The blast wave itself is thought to cause injurious head acceleration apart from potential secondary or tertiary blunt head force trauma (Finkel, 2006)*
Direct cranial entry of blast waves	• *Animal studies have shown that blast waves are unimpeded by the thin cranium of rats (Chavko, Koller, Prusaczyk, & McCarron, 2007). Blast waves retain two-thirds the magnitude passing through the thicker cranium of swine (Bauman et al., 2009)* • *The interaction of human craniums and blast waves is still under investigation. Finite Element Modeling of blast waves has illustrated the potential of blast waves to enter the cranium directly (Nyein, Jerusalem, Radovitzky, Moore, & Noels, 2008; Stuhmiller, J.H. et al., 1998; Taylor & Ford, 2009)* • *This mechanism may also include injury resulting from skull flexure (Moss, King, & Blackman, 2009)*

**Adapted from Courtney and Courtney, no date*

Thoracic mechanism of TBI: Early laboratory and clinical studies performed by Cernak et al. (2005; 1996, 2000, 2001), Cernak, Savic, Zunic, et al. (1999), Cernak, Savic, Lazarov, Joksimovic, and Markovic (1999), and Bhattacharjee (2008) laid the foundation for the proposed thoracic mechanism of mTBI from blast exposure. Using a rodent model, Cernak et al. (2011) reported that ultrastructural and biochemical changes in the brain were not limited to whole-body blast exposure, but that similar results were observed in localized (chest) blast exposure.

In addition to the observed structural and biochemical damage, the authors also reported cognitive deficits in the rats.

Recently, Simard et al. (2014) demonstrated that a non-lethal (451 ± 11 kilopascal [kPa]) blast wave directed at the thorax in rats resulted in a number of pathological changes to the lung and the brain. First, apnea was observed up to 60 seconds (sec) following blast exposure with accompanying reduction in oxygen saturation up to 30 minutes following blast. Twenty-four hours after injury diffuse patchy hemorrhages were observed in the lungs but no cerebral hemorrhages were detected in the rats. Second, perivenular inflammation was detected in the cortex, hippocampus, and hypothalamus by quantifying the amount of tumor necrosis factor-α and sulfonylurea receptor 1 in the vascular tissues throughout the brain. The most significant finding from this study was that a blast wave directed at the thorax results in a hydrodynamic pulse that is propagated to the brain via the jugular vein. Briefly, a sudden increase in pressure from the blast wave on the walls of the large blood vessels accelerates the fluid resulting in a rapid displacement of blood. The authors noted that as the hydrodynamic pulse radiates from the point of origin — the easiest route is the blood vessels that lack valves to slow the progress of the pulse — it enters the brain and ruptures blood vessels if the force remains strong enough. Even without the rupture of blood vessels, the pulse may still carry enough energy to damage endothelial cells, resulting in an inflammatory response in the brain. Simard et al. (2014) was the first study to provide direct evidence that blast waves directed at the thorax can induce a hydrodynamic pulse through the vascular system to the brain. Additional research is needed to identify the precise mechanism for the neuroinflammation observed in the study, and the authors recommend neuroimaging studies of humans exposed to similar blast waves to characterize the vascular damage and inflammation in the brain.

In contrast, studies performed by Säljö, Mayorga, Bolouri, Svensson, and Hamberger (2011) reported that it is the magnitude of the pressure waves in the air directly outside the head that cause TBI and not through a thoracic mechanism.

Head acceleration: TBI resulting from sudden acceleration (linear or rotational) is not exclusive to blast events. Impacts in sports and automobile accidents are known to elevate cranial pressures to levels that cause injury (Krave et al., 2005; Zhang et al., 2004). Preclinical research on the effects of rotational acceleration has produced similar effects as those seen in humans with TBI (Cernak, I, 2005; Kilbourne et al., 2009; Morales et al., 2005). Krave, Al-Olama, and Hansson (2011) investigated the effects of rotational acceleration on the head and neck of rabbits to determine if seemingly identical loads caused different types of injury depending on the orientation of the blast. Interestingly, a low-level flexion trauma was equal to or more severe than a high-level extension trauma in causing diffuse brain injury. In contrast, a low-level extension trauma only produced minor histopathological abnormalities.

A recent study by Gullotti et al. (2014) reported in a mouse model that restricting the movement of the head significantly increased survivability and decreased cognitive deficits following blast exposure. This approach was most effective against parallel exposure to the blast wave as opposed to a perpendicular orientation of the mouse to the blast wave.

Direct cranial entry of blast waves: The orientation of the head in relation to the direction of the blast wave affects the duration and magnitude of the resultant pressures in the brain. Exposure to BOP, depending on the proximity to the explosion can result in secondary injuries causing additional trauma unrelated to the blast wave. This further complicates determining the exact nature of the intracranial pressures (ICPs) caused by the blast wave itself (Chavko, M. et al., n.d.). Chavko, Koller, Prusaczyk, and McCarron (2007) exposed rats to BOPs between 30−40 kPa in various orientations in relation to the head. The results indicated that the dynamics of the blast wave changed in relation to the orientation of the head, and that the

highest pressure magnitude was observed from head-on exposure. This study also investigated whether whole-body protection (i.e., leaving the head and neck exposed) mitigated the pressures generated in the brain. The polyvinyl chloride cylinder used as the whole-body protection did little to reduce the pressures recorded in the brain. Additionally, considerable pressure was measured in the femoral artery and orientation to the blast did not change the pressures measured. This highlights the need for further study into the design of equipment and structures being used to provide protection from BOPs.

Skull flexure is also thought to be a contributing factor to the varying ICPs measured in the brain following exposure to a blast wave (Leonardi, Bir, Ritzel, & VandeVord, 2011; VandeVord, 2013). Results from animal studies vary depending on the model used due to the shape and thickness of the skull. The thinner skull of rats allow blast waves to pass more readily than in the thicker skulls of larger animals such as swine; ICP rise times are also prolonged in swine (Bauman et al., 2009). Bolander, Mathie, Bir, Ritzel, and VandeVord (2011) investigated skull flexure in a rat model and based on the results, the authors proposed a two-fold mechanism to account for the ICP gradients observed in the brain following blast exposure. The first, and possibly the most damaging, is the rapid compression of the skull, which generates additional waves in the brain — this transient phase is thought to be the leading contributor to neurotrauma due to the high strain rates. The second mechanism pertains to the energy transferred to the brain with the more uniform rate of decompression of the skull. The authors recommend in vitro studies to determine cellular vulnerability of the brain under the high stress rates observed in this study. These studies could lead to the development of neurological biomarkers as a result of blast wave exposure. Säljö et al. (2011) suggest that measuring ICP may be a more sensitive method for detecting mTBI than neuropathological markers based on the work of Teranishi, Chavko, Adeeb, Carroll, and McCarron (2009).

Key findings for the mechanisms of mTBI

- *Additional collaborative research efforts are necessary to determine the exact contribution of the thorax to structural changes in the brain following blast exposure*
- *Flexion trauma appears to result in more serious injury than extension trauma and this research may contribute to the development of more effective protective equipment*
- *More research is needed into the effects of blast waves on neuronal cells to aid in the development of novel biomarkers for blast exposure*

2. Neuropathology of mTBI: evidence from clinical and preclinical research

Blast-related TBI is widely accepted as the “signature injury” of the Global War on Terror because of the preferred use of explosive devices by enemy combatants including IEDs, vehicle borne IEDs, and improvised rocket assisted mortars during OEF/OIF/OND (Kovacs et al., 2014). Hoge et al. (2008) published their seminal paper on psychological health outcomes in U.S. Army soldiers with combat-related mTBI; since its publication, the mTBI population has been the focus of a vast number of research studies. Despite the growing numbers of military personnel sustaining injuries and living with TBI, little is known regarding the long-term consequences of mTBI (blast or non-blast-related) and much of what is known comes from preclinical research. Additionally, there is considerable debate surrounding the pathophysiological and clinical outcomes of blast versus non-blast-related mTBI. While moderate and severe TBI is fairly well characterized, the field is saturated with published studies on the underlying mechanisms and outcomes of mTBI, including anatomical, cellular, molecular, and functional consequences.

Basic research, especially the development of clinically- and military-relevant animal models of TBI, is critical to understanding TBI across a continuum of care, from the underlying mechanisms of injury and pathophysiology to functional consequences and therapeutics. The use of animal models allows for investigation in a controlled setting, thereby eliminating many confounding variables present in the clinical (i.e., human) population. The field of animal models, particularly of blast mTBI, has grown exponentially in the years since OEF/OIF/OND and continues to evolve to improve model validity and reliability. Several different types of TBI models exist to study consequences across the range of TBI severity, including those for non-blast and blast TBI (bTBI) (for review see [McCabe et al., 2010]). There is a particular interest in elucidating the complex mechanisms and neuropathological sequelae of the primary, secondary, tertiary, quaternary, and quinary injuries characteristic of blast-related TBI. Animals are particularly useful for the study of blast-related TBI as these component mechanisms and associated injuries can be isolated, which rarely occurs in the real-world setting (Calabrese et al., 2014). In reviews by Risling and Davidsson (2012) and Kovacs et al. (2014), the various animal models of bTBI (e.g., open field exposure, blast tube, shock tube, penetrating) are discussed, including their experimental design and clinical relevance. Regardless of the specific model employed, the goal of all animal studies is to increase understanding of TBI and ultimately improve health outcomes for the Warfigher by improving prevention, detection and treatment.

Evidence from clinical research: Conventional anatomical imaging tools such as computed tomography (CT) and magnetic resonance imaging (MRI), while sufficient to detect gross morphological defects caused by moderate and severe TBI, fail to detect the more subtle and microscopic brain defects associated with blast and non-blast mTBI. Advances in neuroimaging tools, including functional MRI and diffusion tensor imaging (DTI) allow for the visualization of the potential anatomical correlates of mTBI and there is a growing interest and reliance upon neuroimaging to identify biomarkers for mTBI (Graner et al., 2013). Evidence suggests that mTBI, at a pathological level, is characterized by diffuse, micropscopic axonal (i.e., white matter) damage in the absence of gross tissue damage (Hulkower et al., 2013).

Recent Review Articles on the Neuropathology of mTBI: Evidence from clinical studies

- *Kobeissy et al., (2013). Assessing neuro-systemic & behavioral components in the pathophysiology of blast-related brain injury. Frontiers in Neurology, 4, Article 186.*
- *Cernak and Noble-Haeusslein (2010).Traumatic brain injury: an overview of pathobiology with emphasis on military populations. Journal of Cerebral Blood Flow & Metabolism, 30, 255-266.*
- *Graner et al. (2013). Functional MRI in the investigation of blast-related traumatic brain injury. Frontiers in Neurology, 4, Article 16.*
- *Hulkower et al. (2013). A decade of DTI in traumatic brain injury: 10 years and 100 articles later. American Journal of Neuroradiology, 34, 2064-74.*

One promising area of neuroimaging research uses DTI to investigate such white matter abnormalities by providing a measure of the integrity of the axonal membranes and myelin sheaths comprising white matter tracts. Jorge et al. (2012) conducted one of the largest DTI studies of mTBI to date using a sample of male Veterans of the Iraq and Afghanistan wars. Of the 93 enrolled subjects, 77.4 percent (n = 72) had a deployment-related blast mTBI. The primary outcome measure was number of white matter "potholes," which were defined as small regions of white matter with abnormally low fractional anisotropy. The blast mTBI group had significantly greater numbers of potholes than the uninjured control group (n = 21). Within the injury group, the total number of potholes was correlated with TBI severity and functional impairment, as measured by performance on an executive function task, such that increasing number of potholes were associated with greater severity and worse performance. Results suggest that

such white matter potholes may serve as discreet biomarkers of blast mTBI-related axonal injury (Jorge et al., 2012).

In another DTI study, a sample of U.S. Service members who met DoD criteria for mTBI and had a history of a single blast exposure event (n = 4) underwent DTI and were compared to a control group (n = 18) of Service members who were not exposed to blast and had no history of TBI. The two groups did not significantly differ in neuropsychological test performance. Although cerebellar-mediated cognitive and motor functions remained intact in the blast exposure group, abnormalities in the cerebellar white matter were detected suggesting the presence of sub-clinical lesions. The results of this study suggest that the cerebellum may be susceptible to blast-related TBI and should be considered a region of interest for further investigation (Mac Donald et al., 2013). In a smaller DTI study, Yallampalli et al. (2013) failed to detect any DTI abnormalities in a sample of OEF/OIF/OND Veterans with mild to moderate blast-related TBI.

Large scale post-mortem studies that allow for microscopic analysis of brain tissue are lacking. A recent study performed a histopathological examination of an Iraqi war Veteran (age 27 years, male), after the individual committed suicide. According to Omalu et al. (2011), the patient had a history of repeated deployment and non-deployment related mTBIs and suffered from posttraumatic stress disorder as well as persistent headache, dizziness, sleep disturbances, tinnitus, and irritability. Upon examination, his brain revealed pathology consistent with chronic traumatic encephalopathy (CTE), a condition most notably associated with professional athletes with repeated head trauma due to impact (Stein, Alvarez, & McKee, 2014). Pathology included nonspecific, microscopic white matter lesions accompanied by tauopathy (e.g., neurofibrillary tangles, neuritic threads) and astrogliosis (Omalu et al., 2011). Two additional studies investigating clinical CTE also reported similar pathology in a cohort of military Veterans with a history of repetitive mTBI, including blast-related injuries (Goldstein et al., 2012; McKee et al., 2013). Additional post-mortem research is required before definitive conclusions regarding the presence of CTE in military personnel with histories of repeated mTBI (e.g., blast or non-blast) can be made.

Evidence from preclinical research: The neuropathological and pathophysiological consequences of mTBI, including blast exposure, have also been studied using animal models with a growing number focused on blast-specific models (for review, [Kovacs et al., 2014; Risling & Davidsson, 2012]). While the vast majority of studies have been conducted in rodents, there are limited studies using non-human primate models. One such study investigated the neuroanatomical and pathophysiological effects of exposure to primary BOP. Neuroimaging and post-mortem analysis revealed white matter damage, cell death, astrogliosis, and selective structural damage to the cerebellum and hippocampus — results similar to the human studies previously discussed (Lu et al., 2012). Using a rodent blast neurotrauma model, CTE-like tau neuropathology, in the absence of gross macroscopic tissue damage was recreated in mice following a single blast exposure (Goldstein et al., 2012). Multiple independent research groups, exposing rodents to sub-lethal BOP, have demonstrated a range of neuropathological changes including white matter and vascular damage, apoptotic cell death, and neuroinflammation (Budde et al., 2013; Calabrese et al., 2014; Gama Sosa et al., 2014; Goldstein et al., 2012; Pun et al., 2011). A novel experimental rodent model of blast injury that

Review Articles on the Neuropathology of mTBI: Evidence from preclinical studies

- *Kovacs et al. (2014). Blast TBI models, neuropathology, and implications for seizure risk. Frontiers in Neurology, 5, Article 47.*
- *Risling and Davidsson (2012). Experimental animal models for studies on the mechanisms of blast-induced neurotrauma. Frontiers in Neurology, 3, Article 30.*

utilizes a more complex shock tube delivery system to better replicate blast conditions in theater has been developed and used to identify changes at the cellular and molecular level. A gene expression study by Cernak et al. (2011) identified up-regulation of several key neuroinflammatory mediators in the hippocampus and brainstem at different time points after blast exposure, suggesting the presence of ongoing and prolonged inflammation in the brain.

Key findings for the neuropathology of mTBI

- *Advances in animal modeling as well as neuroimaging have allowed for further investigation into the pathophysiological (e.g., neuroanatomical, cellular, molecular) outcomes of mTBI*
- *Despite such preclinical and clinical research, the exact pathophysiological and clinical outcomes of blast and non-blast mTBI remain unknown*

B. Computational modeling of TBI

Due to the difficulty, cost, and ethical concerns of performing blast experiments, computational modeling of blast has become an important companion to traditional laboratory blast and impact research (for a review see [Gupta & Przekwas, 2013]). Simulating blast and impact is a complicated endeavor, involving a wide range of time and length scales. A hypothetically realistic model of bTBI would include: (1) a model to simulate the motion of fluids, both gases and liquids, in order to capture the dynamics of blast pressure waves and body fluids; (2) a model to simulate the mechanical properties and anatomical details of the human body (or at least the head, skull, and brain); (3) a model of the biological cascade that leads to secondary brain injury; and (4) a way to couple models together.

Generally, the first two models are accomplished through the solution of partial differential equations using discretization of space and time. Blast waves and the motion of liquids can be simulated using methods from computational fluid dynamics (CFD) — a branch of fluid mechanics that applies numerical methods to solve fluid flow problems. The structural dynamics of the head, including the internal vasculature of the brain, is usually represented through the use of the finite element method (FEM), which breaks down materials into a mesh of smaller constituent pieces (elements). A detailed model of secondary brain injury is a monumental task and does not exist yet (for recent steps towards that goal see [Gupta & Przekwas, 2013]). Recent advances, however, in computational modeling have made it possible to study primary brain injury through simulations of blast and the concomitant head/brain response by coupling CFD and FEM models (Chafi, Karami, & Ziejewski, 2010; Moore et al., 2009; M. K. Nyein et al., 2010; Panzer, Myers, Capehart, & Bass, 2012; Zhang, Makwana, & Sharma, 2013).

Many challenges still exist in the computational modeling of blast. Converting head forms into mesh models is a challenge on its own, even though it is accessible non-invasively. Describing the intracranial space, with all of the different types of biological tissues, blood vessels, fibers, and sulci is a laborious task. Usually, a representative head is used in simulations, individual variability, however, in both head forms and neuroanatomy may affect the results of simulations.

Another challenge is modeling the structural dynamics of materials in biological tissue; some materials are linear elastic, others nonlinear elastic or nonlinear viscoelastic. Even within a particular kind of model, there is no agreement on parameter values, such as material properties, which must be measured experimentally. Environmental conditions such as temperature can greatly influence measurements of mechanical properties; equally, experimental conditions such as the amount of compression applied to samples before testing can influence measurements. Material property measurements can differ by orders of magnitude (Hrapko, van Dommelen, Peters, & Wismans, 2008).

These challenges represent only *some* of the issues in modeling the structural dynamics of the head and brain. Modeling the fluid dynamics of blast has its own set of challenges. Moreover, validating computational models *in vivo* is not possible with the human head. Cadaver heads have been used (Bir et al., 2011); modeling a *specific* head form, however, is difficult and capturing internal anatomy would be even more so.

Despite the many challenges in the field of computational modeling, simulation remains a vital tool in understanding blast and blast injury. Simulations allow for tests that are completely impossible in the laboratory setting. Due to the many uncertainties inherent to simulating blast, computer modeling should not be thought of as providing precise and quantitative predictions. Rather, simulation can help elucidate phenomena of blast injury that would be otherwise difficult to detect in experiments, such as skull flexure (Ganpule, Alai, Plougonven, & Chandra, 2013; Moss et al., 2009), cavitation (Ganpule et al., 2013; Goeller, Wardlaw, Treichler, O'Bruba, & Weiss, 2012; Panzer et al., 2012), even piezoelectricity (Lee et al., 2011). Computational studies can inform experiments on mechanisms that need examining and provide "regions of interest" for impact and blast parameters; computational modeling needs to have a constant back and forth dialog with experiments.

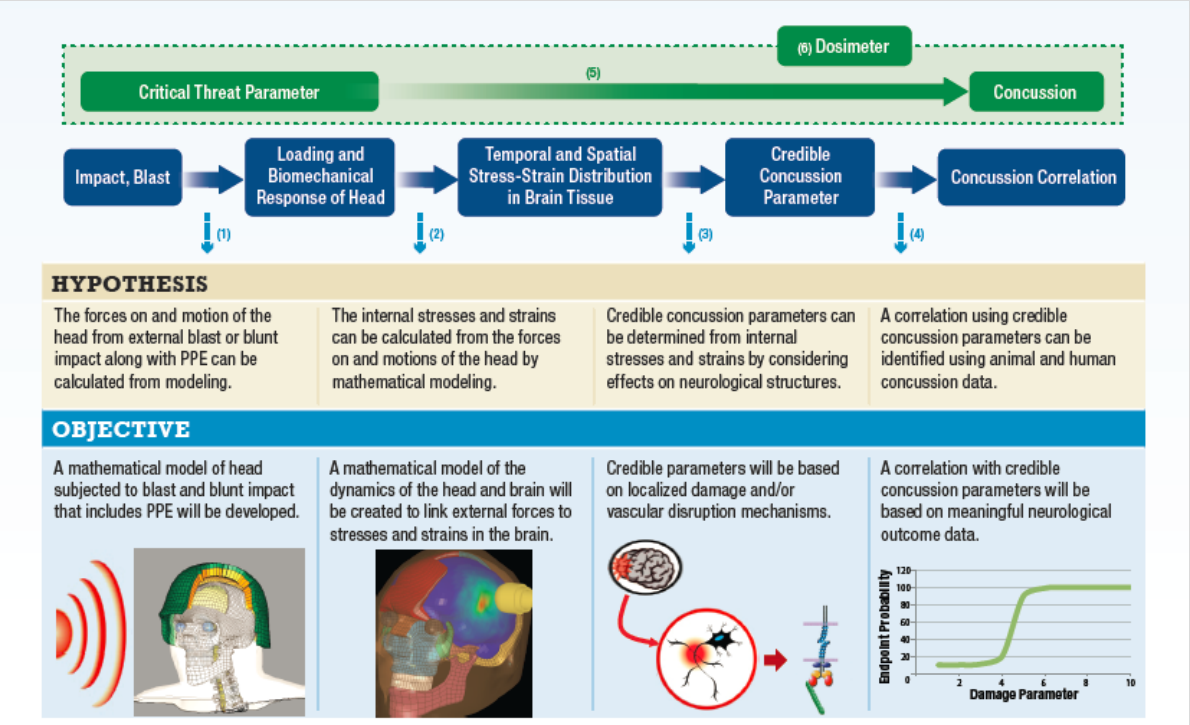
With regard to sensors and thresholds, given the ability to record pressure and acceleration inside the helmet of Warfighers, it may one day be possible to make gross "reconstructions" of blasts in computer simulations from the recorded data. Examining blast events from multiple individuals may help elucidate the mechanisms and conditions under which primary blast injury occurs. Zhang, Yang, and King (2004) have recreated simulated impacts from football videos where two players were involved, but only one had a confirmed concussion. By performing video analysis of impacts, they recreated collisions using Hybrid III dummies and then fed the impact data into a simulation. By comparing the strains and stresses experienced by the non-injured player versus the injured player, the authors concluded that high stress concentrations were localized to the upper brainstem and thalamus regions and that this stress was the best predictor of head injury. In another computational study of both collegiate football impacts and automobile side impact collisions, Takhounts et al. (2008) found that angular acceleration injury criteria may predict TBI better than linear acceleration injury criteria.

Key findings for computational modeling of mTBI

- *Advances in computational modeling allow the simultaneous simulation of the dynamic response of both fluids and solids to blast*
- *Simulation can help elucidate the mechanisms of blast injury and help identify "regions of interest" for injury thresholds*
- *The accuracy of computational modeling is limited by the ability to determine parameter values, which have varied over orders of magnitude in experiments*

mTBI Dosimetry Modeling

The U.S. Army Medical Research and Materiel Command sponsors the Technology-Enabled Capabilities Demonstration (TECD) Brain in Combat. As part of the TECD, the U.S. Army's Military Operational Medicine Research Program is sponsoring research by L-3 Communications in collaboration with others to understand the sequence of mechanisms that lead to concussion in order to build a model that can accurately predict credible damage parameters that correlate with concussion indicators. Mathematical modeling is being used to link the external forces with stresses and strains in the brain. The model being developed is not specific to a particular exposure sensor.



**Adapted from the U.S. Department of Defense (2013)*

C. Environmental sensors

1. Fielded sensors

Several commercial sensors have been deployed in the field, but few studies of them have been published. Helmet-mounted blast sensors such as British Aerospace Systems' HEADS™, Allen Vanguard's blast dosimeter, BlackBox Biometrics' Blast Gauge™, and Georgia Tech Research Institute's IBESS™ have been deployed, but there have been no published reports based on field data. All of the above sensors collect data on overpressure and acceleration (both linear and rotational, except for Blast Gauge, which captures only linear) measured by the helmet. Simbex's Head Impact Telemetry System (HITS) has many published reports in the context of sport injuries (e.g., concussions), but no studies have examined its use in the military. HITS measures linear and angular acceleration only; on its own, it would be unable to predict the presence of head injuries associated with overpressure.

Other sensors such as Reebok's CHECKLIGHT™ and X2's xPatch™ are also designed to detect sports-related impacts. CHECKLIGHT is currently available as a skull cap and does not transmit detailed recorded data. Instead, CHECKLIGHT displays a light to indicate the

presence of a potential injury-causing impact. xPatch is a wearable electronic device that can be taped behind the ear. It has six-degree-of-freedom accelerometers, allowing it to measure linear and rotational impacts; it can also determine impact location and direction using software algorithms. There are no published studies benchmarking either CHECKLIGHT or xPatch.

Currently, there are no published studies on HEADS or IBESS. Dionne et al. (2010) conducted a proof-of-concept test on the Allen Vanguard helmet-mounted blast dosimeter using a Hybrid III anthropomorphic mannequin and compared results to reference laboratory-type sensors. Allen Vanguard's device consists of six accelerometers, which are capable of capturing linear and angular accelerations in three dimensions each, and a pressure sensor that fits inside a combat helmet underneath the padding. To keep the unit operating for entire tours of duties (6–12 months) without battery replacement or recharging, the device is kept in sleep mode until acceleration and pressure levels of sufficient size are sensed (threshold values not reported). When the helmet mounted blast device is triggered (mean wake-up times not reported), it records 30 milliseconds (msec) of data at 30 kilohertz on 7 channels (e.g., 6 acceleration, 1 pressure). The device continues to record if acceleration and pressure levels are above threshold levels after 30 msec.

Sample traces for resultant acceleration and overpressure showed that the helmet dosimeter outputs tracked reasonably well with reference sensors by visual assessment; a more systematic evaluation of performance was not demonstrated. Using multiple tests on the Hybrid III mannequin, peak accelerations recorded by the helmet dosimeter correlated linearly with peak head accelerations. The degree of correlation, however, depends upon the direction of the blast. The authors report that in proof-of-concept calculations, it was possible to determine blast direction from recorded data; the results of the analysis were not reported.

Combat Fielded Sensor Systems

DARPA Blast Gauge: *This sensor was deployed in July 2011 and linking of the sensor event to medical encounter and operational data has begun. DARPA receives gauges in theater or by mail from units and downloads the data which is then transferred to the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) or DARPA partners for analysis. A Service member's chain is typically notified of events via medical personnel, or the gauge can be accessed locally by command. In FY13, JTAPIC was working with DARPA on strategies to receive data from all Services.*

Gen II HS / HEADS: *This sensor was deployed in June 2012 and the effort has progressed to the dose-response model development stage. Data is collected by Brigade Combat Team (BCT)-embedded field service technicians following known events (or every 30 days) and transferred to Program Executive Office Soldier electronically. BCT data collectors notify the Service member's chain of command of blast exposure events.*

IBESS: *This sensor system was deployed in September 2012 and data collection is underway. Data is stored in the vehicle data recorder and is removed by data collectors for transfer via the Army's Test and Evaluation Vision Digital Library System to the JTAPIC program for analysis. There is currently no chain of command notification of events.*

**Adapted from the U.S. Department of Defense (2013)*

The only other published study of a commercial sensor deployed to the military was performed by Ostertag et al. (2013). They examined the possibility of using the Blast Gauge sensor to test blast pressures in complex environments, adding validity to the sensor as blast studies are commonly performed in free-field conditions (i.e., no reflecting walls or objects) that are not representative of the real world environment in theater.

Preventing Violent Explosive Neurologic Trauma (PREVENT)

The overall aim of DARPA PREVENT was to construct a model of blast brain injury relevant to the Warfighter, with the objective of gaining an understanding of this disease so that meaningful effective therapies could be identified. The program aimed to develop a large animal model (swine) and small animal model (rodent) of blast mTBI to study mechanisms of injury, neuropathology, molecular biomarkers, and neurocognitive changes. The program also sought to develop novel non-invasive diagnostic tools to detect and study explosive blast mTBI in human and large animal models sufficient to detect and identify extent, distribution, and severity of mTBI from explosive blast in Warfighters. Additionally, the program aimed to identify likely candidates among the Food and Drug Administration's approved drugs for therapeutic treatment of explosive blast mTBI.

Advanced magnetic resonance spectroscopic imaging techniques were developed to study alterations in brain metabolites resulting from explosive blast exposures in both the Warfighter and the large animal model. These techniques involved the development of sophisticated hardware on a 7 Tesla magnet to produce a capability to conduct increased signal to noise ratio spectroscopic imaging of the human hippocampus. Using these techniques, DARPA PREVENT discovered for the first time unequivocal evidence of organic brain injury in the hippocampus due to explosive blast in Warfighters as well as clear differentiation of injury to this brain area from blast compared to the injury in posttraumatic stress disorder without blast, providing an objective method for differential diagnosis.

DARPA PREVENT provided additional evidence that single exposures are associated with less hippocampal injury than multiple exposures. Large animal imaging studies revealed injury in the hippocampus similar to that in the Warfighter. This injury was detected only 6-8 months after a blast event suggesting an ongoing amplification of an initial injury. Multiple blast exposures resulted in enhanced injury. This PREVENT swine model produced neuropathological signs of injury and produced several critical pieces of evidence such as significant astrocyte activation more in multiple exposure animals than single exposures. Activated astrocytes can be involved in a number of other pathological functions, one in particular being the release of inflammatory and pro-inflammatory molecules.

DARPA PREVENT proteomic studies revealed the upregulation of several inflammatory molecules in the hippocampus raising the possibility that explosive blasts may trigger an initial inflammatory response in the brain which secondarily triggers slow neuronal injury and death. Another unique finding of PREVENT is a pattern of axonal injury around the ventricles (periventricular axonal injury) which differs from the classical patterns of diffuse axonal injury reported for TBI in the literature.

PREVENT Screening of the Food and Drug Administration's-approved drugs for treatment of mTBI and mTBI with hemorrhagic shock has identified minocycline as a promising therapeutic agent. Cognitive and neuropathological assessments in models show significant improvement from injury with treatment.

This study tested an entry charge (0.26 pounds trinitrotoluene-equivalent) in a hallway with several obstacles placed along the hallway. The charge was placed on a door hinge located on the front wall of the hallway. Blast Gauge sensors were placed along the side walls and center of the hallway at various distances. On the left side wall, sensors were placed at 5, 10, 15, and 20 feet (ft) (as measured from the front wall where the charge was placed). On the right side wall, sensors were placed at 5, 15, and 20 ft. In the center of the hall, four sensors were placed at different distances; one was placed facing the charge at 11.5 ft (the theoretical minimum safe distance for a free-field explosion as calculated with the *k*-equation); a second sensor was placed at 11.5 ft but facing the right wall; a third sensor was placed just past 15 ft (exact distance not provided) in between two objects; and a fourth sensor was placed before the second object at 20 ft. In complex interior environments, blast pressure waves may reflect and

combine to increase overpressure beyond safe levels at the free-field minimum safe distance. The logic of placing a sensor at the minimum safe distance was to examine whether free-field calculations of the minimum safe distance applied in complex environments such as hallways.

The study assumed that the safe overpressure threshold was 4 pounds per square inch (psi). Results from only a single blast test were reported. All 11 sensors recorded peak overpressures higher than the safe overpressure threshold (range, 4.6–13.3 psi), even those beyond the theoretically calculated minimum safe distance of 11.5 ft. The study claimed that Blast Gauge sensors allowed for tests in complex environments to be performed with less expense and more convenience than with conventional laboratory sensors. The study did not compare the accuracy of Blast Gauge sensors with reference sensors.

Outside of the military, Simbex's HITS has been widely used in collegiate and high school football settings (Duma et al., 2004). It employs six accelerometers and one temperature sensor, a wireless transceiver, and on-board memory. The helmet communicates wirelessly with a data collection system on the sideline. Whenever acceleration crosses a user-selected threshold, HITS collects data for 40 msec. HITS was tested on a Hybrid III dummy, which was treated as the reference sensors. Duma et al. (2004) found the data from HITS correlated well with the reference data (R^2 = 0.97) and was within ± 4 percent error for linear and rotational accelerations and HIC.

Currently, there is a large gap in published reports on deployed sensor technology. Other than Allen Vanguard and Simbex, no other manufacturer has published a report that has even benchmarked their products against reference sensors. There is a current need for independent investigators to perform a standardized blast test suite on commercial blast sensors; DARPA's PREVENT program (see box) will fill this gap. There is also a need to analyze and publish data from field tests.

Key findings for fielded sensor systems

- *There are currently no publicly published reports that link data recorded from fielded sensors to observed brain injuries*
- *Validation of sensor accuracy is currently being performed ad hoc by the sensor developers. There is a need for an independent test lab that can perform a standard battery of tests*

2. Technologies in development

There are a number of blast and/or acceleration sensors currently in development. They fall into three categories: (1) packaged sensors that are ready for deployment, (2) powered bare sensors that can record blast events by outputting pressure as a function of time, and (3) burst sensors that detect when the sensor has been exposed to superthreshold blast pressure levels. Only a single instance of a ready-to-deploy sensor being developed could be found in the literature (Cheriyan et al., 2009). Powered bare sensors have the benefit of recording data that can be used to identify exposures requiring medical attention, at the expense of needing memory, power, and additional support circuits which add to their cost, weight, and potential for failure (e.g., malfunction, power loss, failure to recharge). Burst sensors are generally cheaper, lighter, and easier to deploy; they, however, lack the ability to record precise data.

Packaged sensors: Cheriyan et al. (2009) designed a sensor system capable of monitoring EEG, blast pressure, head acceleration, SpO_2, and heart rate that can be embedded within the padding of an ACH.

The sensor can record frontal EEG from at least four electrodes (precise number not specified): between frontal and parietal 1 (FP1), FP2, central 4 (C4), and occipital 1 (O1) as per the International 10−20 naming standard. The frontal location was chosen due to its accessibility and because "it is well known that the frontal lobe is involved significantly in TBI"; no rationale for the choice of other locations were given (reference not reported).

The sensor monitors and stores EEG, SpO_2, and heart rate data continuously (maximum recording time and sampling rate not specified). The blast pressure accelerometer is placed in a "low power 25 microsecond (µsec) monitoring mode." When blast pressure rises above a programmable threshold all channels record head acceleration (both linear and rotational) along with physiological variables (EEG, SpO_2, and heart rate) for three continuous minutes.

Recorded data is analyzed by the device which outputs one of three levels of alert: red (potentially moderate brain injury), yellow (mild brain injury), and green (no apparent injury). The method for determining the alert output was not reported. The study did not indicate whether the sensor can be programmed to trigger on impact only.

Unlike most sensors currently in development, the sensor system from Cheriyan et al. (2009) is packaged into a device that is ready to deploy in an ACH. The device needs to be benchmarked against reference sensors to determine its accuracy. Moreover, practical considerations such as weight, power consumption (time between recharging), and cost need to be considered for deployment.

Powered sensors: Chu et al. (2012) described and tested a combined impact and over-pressurization sensor that can be used to detect blast and impact exposure. The custom sensor was tested simultaneously against a reference sensor in three different configurations: (1) exposed bare to a shock tube, (2) covered by a cut out from an ACH and helmet padding, and (3) exposed to drop tower.

The sensor was manufactured from a flexible electret (i.e., a material that holds excess charge) film that releases electrostatic charge proportional to the amount of compression and deflection applied to it. The sensor is 1 centimeter (cm) wide and 15 cm long and has conductive silver ink printed on both sides to act as electrodes for readout to analog electronics.

In all three test configurations (e.g., bare sensor, in-helmet, drop tower), measurements of peak charge from the custom sensor were well fit to measurements of peak pressure (bare sensor and in-helmet) or peak force (drop tower) from the reference sensors with a second degree polynomial (R^2 = 0.972, 0.987, 0.998, respectively). Mean cross-correlation values between custom and reference time series data were 0.913 ± 0.054, 0.902 ± 0.045, and 0.957 ± 0.004 for bare sensor, in-helmet, and drop tower test, respectively (mean ± standard deviation).

Due to the differences in response frequencies between blast and blunt loading, the authors were able to distinguish blunt loading events from blast loading events by appropriate choice of complimentary low and high pass filters. They found that blunt loading events could be characterized by filtering out signals above 80 hertz (Hz), while blast loading events could be characterized by filtering out signals below 80 Hz. Though this cutoff filter does distinguish blunt and blast events, there is some signal loss especially in blunt events; the use of filters has the advantage of not requiring separate transducers for blunt and blast events.

MacPherson et al. (2000) designed a fiber optic blast pressure sensor using the Fabry-Pérot interferometer principle, which uses interference from reflected light to measure changes in light paths. The sensor uses a single mode optical fiber whose end is enclosed in an air cavity that is capped with a copper diaphragm. By sending laser light (30 milliWatt laser diode at 780 nanometer wavelength) down the fiber, the light reflecting from the end of the fiber will interfere

with the light reflecting from the diaphragm. Pressure changes cause the diaphragm to bend, which changes the distance of the air gap (20 micrometers [µm]) between the end of the fiber and the diaphragm. This change in distance will, in turn, change the amount of interference, which can be detected at the opposite end of the fiber. By knowing the relationship between pressure changes and diaphragm deflection and the relationship between diaphragm deflection to interference, it is possible to measure pressure changes by measuring the amount of interference.

The sensor was calibrated in a blast tube, but further details were not provided. It was then tested in outdoor blast tests using standard plastic explosives (e.g., PE4) alongside five other commercial reference sensors. The sensor can theoretically handle BOPs of up to 1 megapascal (MPa); however, 1 kPa was the maximum value tested. The optical sensor had relatively low noise (0.2 kPa root mean square) and fast rise times (defined as the time difference between 10 percent and 90 percent of the peak overpressure, 2.8 versus 7.6–37.5 µsec for reference sensors). The optical sensor did exhibit some ringing after the initial overpressure peak due to the resonance of the diaphragm (calculated to be 1 megahertz [MHz]); they did not, however, suffer from acceleration artifacts that three of the five reference sensors did — a known limitation to piezoelectric pressure sensors.

While an optical sensor has many potential benefits (e.g., fast rise times, insensitivity to temperature and acceleration, excellent spatial resolution), there remain additional concerns including whether the optical sensors can be packaged into a portable sensor as well as weighing the benefits of this technology against the potential drawbacks that they present in a portable version.

Wu et al., (2011) described the design, fabrication, and testing of a novel fiber optic blast sensor. The main components of the sensor consisted of a v-shaped channel that was covered with a silicon nitride diaphragm and a fiber optic fiber placed inside the ‘v’. The fiber was cut to a 45 degree angle at its end and the v-channel was slightly larger where the end of the fiber was located. This design allows light rays (provided by a laser) reflecting on the fiber-air boundary to interfere with light rays reflecting on the air-diaphragm boundary. The diaphragm moved with changing pressure, hence altering the interference pattern with the movement. Therefore, measuring changes in the interference pattern allowed for the measurement of pressure. Measuring changes in the fringe pattern is generally slow (on the order of a few Hz). For monochromatic light, however, it is possible to simply measure the change in intensity, which can rapidly measure changes with a photodetector (on the order of MHz). The sensor was tested against a commercial pressure sensor in two configurations: (1) a pressure chamber where pressure was adjusted slowly and (2) a blast chamber.

The fiber optic blast sensor has a sensitivity of 3.1 nanometers per kPa and the diaphragm deflection was linearly correlated to pressure with a correlation coefficient of 0.9999. Using the distance between peaks in intensity (free spectral range, 26.5 nanometers), it is possible to calculate the length of the v-shaped cavity. This was calculated to be 43.8 µm, which was very close to the goal value of 44.1 µm. The ability to produce cavities of consistent length is important for the reliability of the device.

For blast tube tests, the fiber optic blast sensor was placed on the blast tube end plate alongside a commercial reference sensor. The fiber optic blast sensor performed similarly to the reference sensor. Because of the slight difference in location between the sensors, the signal was delayed in the reference sensor. The authors made no attempt to quantify the agreement between the reference sensor and the fiber optic sensor.

Zou et al. (2013) describes the design, fabrication, and testing of a novel fiber optic pressure sensor. Like a similar design published by the same group, the sensor is based on the Fabry-Pérot interferometer design, which uses light reflected from two different surfaces to observe interference patterns (Wu et al., 2011). Changes to the light path (e.g., due to changes in refractive index, distance, etc.) cause the interference patterns to change, with high sensitivity. In the case of blast, pressure changes cause the diaphragm to vibrate, which shortens or lengthens the reflective path and allows changes in the interference pattern to measure the pressure. Changes in interference pattern can be read by a photodetector. The blast sensor was calibrated in a chamber where pressure could be controlled precisely using a pressure controller. The blast sensor was tested against commercial reference sensors in a blast tube using two different media (air and water) separated by a rubber membrane.

In the controlled pressure chamber, the pressure was adjusted from 0 psi (above atmospheric) to 15 psi in steps of 3 psi. This was done three times consecutively to test the history dependence of the sensor. The sensor output (voltage from a photodetector) was well-fit to the applied pressure by a second degree polynomial (adjusted $R^2 = 0.999$) and showed no effect due to history. Four different sensors were tested, and each required its own calibration.

In the shock tube, four different fiber optic sensors were placed at different lengths along the tube. Two sensors were placed in air before a rubber membrane, and two were placed in water after the rubber membrane. That is, the shock wave traveled along the tube in air first, hit the rubber membrane, and then traveled in water. A commercial reference sensor was placed opposite each fiber optic sensor. The fiber optic sensor had very good agreement with the reference sensors by visual inspection (no quantification reported). The fiber optic sensors appear to have a higher cutoff frequency; that is, they can capture very fast events that are filtered out by the slower responding piezoelectric reference sensors. It was not clear whether these high frequency events would be clinically relevant.

The sensor in the Zou, Wu, Tian, Niezrecki, et al. (2013) publication is identical to that found in Zou, Wu, Tian, Zhang, et al., (2013) publication, except in the former study, instead of testing the sensor in a blast tube, the sensor was tested using a starter pistol firing blanks and compared to reference sensors. The sensor has a rise time of 0.2 µsec, as compared to the reference sensors rise time of 10 µsec.

Daniel et al. (2010) designed and tested a printed flexible piezoelectric pressure sensor. The sensor was designed such that roll-to-roll processing methods could be employed, which can substantially reduce manufacturing costs. The sensor was made from polymers (i.e., polyvinylidene fluoride - trifluoroethylene) that were printed into a thin film over a cavity. Pressure changes induce strain in the film that in turn induce a charge, which is measured as a voltage across the film. To reduce the pyroelectric effect (i.e., temperature induced charge) of piezoelectric devices, an elastomer layer was placed over the film to act as a thermal mass.

To calibrate the printed piezoelectric sensor, it was placed inside a pressure chamber alongside a reference sensor. Pressure pulses of duration 10 msec were applied at target values of 5, 10, 15, 25, 50, and 100 psi. The voltage output for each of these pulses were recorded along with the pressure reading on the reference sensor. A second order polynomial was fit to the pressure versus sensor voltage curve (goodness-of-fit values were not reported, visual inspection of a single calibration curve had a suitable fit with a bias towards underreporting higher pressures). Blind testing of a small sample of calibrated devices ($n = 4$) showed that the pressure error was within ± 10 percent for pressure ranges between 5 and 100 psi. The printed sensor was tested alongside a reference sensor in a blast tube. Visual inspection of a single example had agreement between the printed and reference sensor (statistics not reported).

Printing piezoelectric sensors presents a low-cost opportunity to outfit helmets with a flexible, lightweight, low energy consumption device. Piezoelectric devices have sensitivities to acceleration, which should be characterized before being deployed. Other details, such as power management, data storage, and communication need to be developed before the sensor is ready to be deployed. The sensor's low cost and lightweight may offer the opportunity to outfit soldiers with multiple sensors.

Burst sensors: Cullen et al., (2011) developed a novel blast dosimeter that reports blast exposure through irreversible color changes. The blast dosimeter was fabricated from a photoresist (i.e., light sensitive) material (SU-8) using multibeam interference lithography. SU-8 is normally transparent to near-ultraviolet and visible light. By forming crystalline films with the right periodicity (~1 µm), samples can selectively reflect light of a particular color through constructive interference. When exposed to blast, the crystalline structure changes, hence, altering the color reflected by the sample. Fabrication of the crystalline structure can be calibrated to adjust the threshold at which the sensor changes color. Importantly, the crystalline structure is thermally stable up to 300˚ Celsius, chemically inert, and is durable to physical impact (data not reported) . Therefore, any color changes found in the dosimeter should be due solely to blast exposure. The dosimeters are also small (diameter, 1.0–6.5 millimeter [mm]), lightweight, and cheap to manufacture. Unlike electronic sensors, the dosimeters require no power source and can easily be deployed throughout a Warfigher's uniform.

To test the dosimeter, it was exposed to two different sources of overpressure: (1) a single pulse ultrasonic irradiation and (2) an explosive driven shocktube. The ultrasound pulse was capable of generating extremely rapid pressure fluctuations that lasted 100–200 msec and reached peak overpressures of 1–10 MPa, which can be controlled based on the power output. The study exposed dosimeters to two different power densities (i.e., 320 kilowatts/meter^2 [kW/m^2] or 960 kW/m^2, associated peak overpressure not reported). Exposure to both power density levels induced a color change from a yellow/green color to a gray/green color, indicating a break in the structure and exposure to superthreshold pressure levels. The higher power density level also had material loss (i.e., visible as black spots under light microscopy) at the edges and center of the dosimeter, whereas the lower power density observed material loss only at the edges. The study showed data for only a single sample for each power density level; therefore, the consistency of these findings could not be confirmed.

The dosimeters were exposed to different BOPs using a cylindrical shocktube driven by ignition of gaseous hydrogen-oxygen mixture. Overpressure was monitored using piezoelectric reference sensors placed along the shocktube. In the first shocktube experiment, two dosimeters with different initial colorimetric properties were manufactured and exposed to the same blast. The first dosimeter, which was a mélange of orange, red, tan, and yellow, became mostly bright red and yellow after exposure to 410 kPa overpressure. The second dosimeter, which was a mixture of yellow, orange, and green, became almost completely translucent when exposed to the same blast. The experiment demonstrated the ability to calibrate the dosimeter to respond differently to the same BOP exposure. In the second experiment, two different dosimeters fabricated with the same properties were exposed to two different BOPs (i.e., 655 kPa or 1090 kPa) . In experiments with either BOP, the dosimeters had clear color changes. The color change in the dosimeter exposed to the lower overpressure was indistinguishable from the color change in the dosimeter exposed to the higher overpressure.

To determine the dosimeter's sensitivity to repeated subthreshold insults, the experimenters repeatedly exposed the dosimeter to multiple blasts (method and parameters not reported). The dosimeter did not display any visible color changes until after the fourth insult, when focal color loss appeared on the surface. After the fifth insult, the dosimeter darkened completely. Therefore, the dosimeter may be able to detect cumulative subthreshold blast exposures. The

color of the dosimeter for this experiment was blue and green, presumably fabricated with different properties from the dosimeters used in previous experiments. It was not clear from the reported data whether the same set of dosimeters could measure both cumulative and superthreshold blasts. Because the dosimeters are lightweight and low cost, sensors with different properties (i.e., thresholds) could be placed into an array.

One limitation with the colorimetric dosimeter was that, unlike electronic dosimeters, it may be difficult to accurately gauge BOP levels from the color or pattern changes. Each dosimeter, even when fabricated with the same properties, looks unique; each having its own "fingerprint" of color fringes. It was not reported whether manufacturing the sensors with a more uniform appearance is possible. One possibility is to apply a machine learning algorithm to determine the BOP by analyzing an image of the dosimeter after exposure. The algorithm would have to be trained with a large number of examples beforehand.

Judge and Matthews (2010) developed and tested a burst sensor for detection of superthreshold blast detection. The sensor is made of a glass coverslip (square, 22 mm in width, 0.155 mm in thickness) that is designed to break when exposed to BOPs exceeding a value that can be adjusted at fabrication time.

In order to adjust the blast sensor threshold, the glass coverslip is laser etched with a circle of diameter 5.6 mm at various depths. Etching weakens the glass by thinning it at the location of the etching; deeper etches make the glass more vulnerable to blast. The depth of the etching can be controlled with the number of passes (revolutions) performed by the laser (2 Watt, 266 nanometer laser microfabrication system). Etching depth is adjustable in units of approximately 1 μm, as each pass of the laser etches approximately 1 μm into the glass.

To test the sensor, samples were placed into a blast tube fitted with reference pressure sensors. Detonations were performed using a custom explosive charge made from smokeless black powder, a precisely machined steel cap, and an igniter. To vary the peak overpressure applied to the sensor, the distance between the charge and sensor was varied. Peak BOPs were found to vary by less than 10 percent at a given distance.

To test the consistency of the sensor's burst threshold, blast experiments were repeated at a given etching depth and BOP exposure. At 3 μm etching depth, 0 percent of the sensors burst for BOP ranges up to 1000 kPa. At 5 μm etching depth, 80 percent of the sensors burst at pressure ranges between 900–1000 kPa, but blast pressures as low as 200–399 kPa burst 17 percent of the dosimeters. At 7 μm etching depth, 100 percent of the dosimeters burst at pressures between 800–1000 kPa, but blast pressures between 400–599 kPa still burst 69 percent of the sensors. At 10+ μm, 100 percent of the dosimeters burst at pressures between 400–1000 kPa, but 18 percent of sensors burst at BOPs between 200–399 kPa.

The fact that the sensor bursts with some probability rather than consistently at a specific overpressure is a reflection of the variability in its fabrication. Glass coverslips were purchased from a vendor and have variability in thickness and structural integrity. The etching process can lead to variability in the actual etching depth. Depth is not the only variable that accounts for the breaking point of the sensor; factors such as the width of the etching may matter too. Also, measurement of BOP may be different at the reference sensor than at the burst sensor. To minimize this, the two sensors are placed close together and placed far enough away from the explosive charge to improve homogeneity across the blast front; nevertheless, some variability is inevitable. It is also possible that the threshold is sensitive to not only BOP but some combination of overpressure and blast duration; this was not tested by the researchers. The researchers aggregated results into arbitrary pressure ranges. It would be interesting to instead

apply a generalized linear model to determine a fitted relationship between etch depth, measured overpressure, and burst rate.

The variability of the sensor's burst threshold limits the applicability of any single sensor being used as a overpressure dosimeter (provided the sensor could not be fabricated with better consistency). An array of sensors with multiple copies at various etch depths, however, could allow for a probabilistic assignment for the BOP experienced. The low cost and relative ease in manufacturing the sensors would make this a feasible solution, likely more cost effective than improving the consistency of individual sensors.

The study did not test the ability of the sensor to measure cumulative insults. That is, the study did not report whether the sensor is more likely to burst at a given BOP on subsequent exposures. The study also did not report the sensor's sensitivity to impact.

Lakamraju et al. (2010) develop a flexible blast pressure sensor based on a collapsible membrane suspended above a fixed electrode. Upon exposure to blast, the membrane contacts the fixed electrode and is held there by van der Waals forces. The change in resistance across the electrodes upon contact is used to drive a low power electrophoretic display element, which retains its change in state for later readout, even without power. Medical staff can later check for blast exposure by examining the electrophoretic display state.

The bottom electrode is made from aluminum and the collapsible membrane is made from amorphous silicon. The pressure threshold at which the sensor collapses can be tuned at fabrication time by adjusting the distance between the membrane and the electrode and by changing the membrane thickness.

Preliminary tests indicated that after activation due to exposure to overpressure, the resistance of the sensors dropped five or six orders magnitude (methods not reported). No other detailed blast tests were reported. The paper states "testing of devices in a calibrated shock tube are under way at U.S. Army Natick Soldier Research, Development, and Engineering Center in Natick, MA." At the time of this review, no reports of the sensor's testing were found.

A collapsible electronic overpressure sensor is a promising technology for a light-weight, low power consumption, low cost device. Blast tests, however, must be performed to confirm that the sensors have a consistent collapse threshold and that the threshold is indeed adjustable at fabrication time.

Key findings for sensors in development

- *There are three categories of sensors under development: (1) packaged environmental sensors, (2) raw pressure sensors, and (3) burst sensors*
- *Packaged environmental sensors can record pressure and acceleration (both linear and angular) along with vitals such as EEG, heart rate, and SpO_2*
- *Raw pressure sensors need further engineering to prove that they can be packed for fielding*
- *Burst sensors are cheap, lightweight, and require no power. They cannot, however, report or record accurate environmental data.*
- *Current sensors in development are focused on overpressure, further development of impact sensors are needed.*

D. Evaluation of environmental sensors (blast and non-blast)

1. *In vitro*

To date, there has been little, if any, environmental sensors evaluated in an in vitro setting. Research in vitro methods have focused on assessing the damage dynamics to brain cells that were embedded in gelatin and exposed to various blast pressures and distances. The cells were then evaluated for physiological damage.

2. Animal

Cullen et al. (2011) tested a blast injury dosimeter (BID) already discussed earlier. In brief, the BID irreversibly changes color upon exposure to blast. The BOP threshold at which the BID changes color can be adjusted at fabrication time.

The structural/colorimetric alterations of the BID arrays were evaluated following exposure to surrogate blast conditions using a compressed air-driven shock tube with anesthetized Sprague Dawley (250–300 grams) rats. Light images were taken for each BID before and after surrogate blast or control conditions in addition to neuropathological assessment of the rats equipped with BID arrays, as well as other rats exposed to identical blast conditions but not wearing BID arrays.

After blast exposure, the BID arrays remained on the rats and the photonic crystal dots remained adhered to the substrate, which was not overtly damaged. A range of neuropathologies were noted including prominent neuronal degeneration in aspects of the cerebral cortex and hippocampus, and substantial reactive astrocytosis in the dentate gyrus and the cerebellum. Corresponding with pathological changes, a set of the BIDs affixed to the rats exposed to blast shockwave demonstrated overt color changes. Over 80 percent of the BIDs tested in this study changed color following BOP of 140 kPa, but less than 60 percent of the BIDs changed color following 120 kPa exposure. These findings establish the use of arrays consisting of BIDs with various thresholds to establish an accurate range of blast shockwave exposure levels.

3. Human

Duma et al. (2005) described recordings of impacts taken from HITS placed inside helmets (around the crown) of select collegiate (Virginia Tech) football players (n = 38) for the entire 2003 season (10 games, 35 practices).

Head Impact Telemetry System *(HITS) is an integrated sensor and software system designed to detect potential concussion type collisions (based on detection of linear and rotational acceleration) of American football players and is the first of its kind that can measure the impacts of players in real game time.*

A total of 3312 valid head impacts were recorded, with 1198 occurring during games and 2114 occurring during practices.

HITS records linear and angular acceleration using an array of six accelerometers, and transmits accelerations greater than 10 g (as recorded by a single reference accelerometer) wirelessly to a sideline laptop. The system also records the location of impact and calculates commonly used collision indexes including the Head Injury Criterion (HIC) and Gadd Severity Index (GSI).

The accuracy of the HITS sensor was validated in a series of tests with a helmeted Hybrid III mannequin instrumented with reference accelerometers. HITS had a correlation of R^2 = 0.97

with data from the reference sensor (variables used in correlation not specified). It also agreed with reference sensors within ± 4 percent for linear and angular accelerations as well as HIC scores (precise conditions not described). Impact location error was ± 1.20 cm.

For all recorded impacts, average peak head acceleration was 32 ± 25 *g* (range, 1–200 *g*). The majority, 89 percent, of impacts had peak accelerations lower than 60 *g*. The distribution of peak accelerations had positive skew (long tail to the right). Mean GSI was 36 ± 91 (range, 1–1599). Mean HIC was 26 ± 64 (range, 1–956). Mean rotational acceleration was 905 ± 1075 radians/sec^2 (rad/sec^2; range, 1–11,348 rad/sec^2) about an axis normal to the plane of the face and 2020 ± 2042 rad/sec^2 (range, 1–18,477 rad/sec^2) about an axis going through the ears.

A single concussion was recorded in an instrumented player. The player was not diagnosed with the concussion until the following day and the injury was retrospectively assigned as a grade 1 or grade 2 concussion. The putative impact that caused the concussion had a peak linear acceleration of 81 *g* (267 GSI, 200 HIC), which is consistent with an earlier study that found concussive impacts had mean peak linear accelerations of 98 ± 28 *g* using video and dummy reconstructions. In the present study, 583 impacts had peak linear accelerations greater than 70 *g*, but only a single instance resulted in concussion.

The authors report that in a previous study (as cited in Duma et al., 2005), nominal tolerance of concussion was estimated to be GSI = 300 and HIC = 250. The present study found, however, that 71 impacts had GSI higher than 300 and 55 impacts had HIC higher than 250 without a single reported concussion for those specific impacts.

Another previous study (as cited in Duma et al., 2005) estimated a 75 percent chance of mTBI for HIC greater than 333, peak linear acceleration of 98 *g*, and peak resultant angular acceleration of 7130 rad/sec^2. HITS recorded 25 impacts over the entire 2003 season that met all three of these criteria; not a single one resulted in a reported concussion. The single concussion recorded by HITS had a HIC of 200, peak linear acceleration of 81 *g*, and resultant (two-dimensional) angular acceleration of 7912 rad/sec^2.

Discrepancies from previous studies may be due to underreporting of concussions in the present study. Previous studies examined measurements given concussion. The current study (Duma et al., 2005) measured concussions given measurements. Agreement between the two is sensitive to underreporting of concussions.

4. Physical Surrogates (e.g., mannequins)

Christopher et al. (2013) investigated the skull-coupling of a tri-axial accelerometer mounted to a back molar and compared it with a tri-axial accelerometer inserted in the boney ear canal. The tri-axial accelerometers were mounted to three post-mortem human surrogate skulls, and compared with a rigid, skull-mounted laboratory sensor reference cube. Each specimen was subjected to both a high-*g* impact loading from a vertical drop tower and a low frequency cyclic loading from a shaker device. The specimens were subjected to an approximate 150 *g* impact acceleration on the drop tower, and up to 10 *g* at a frequency of 9 Hz on the shaker device. Each specimen was tested on all three of the anatomical axes on both the drop tower and the cyclic shaker. Both the tooth-mounted accelerometer and the ear-mounted accelerometer were in close agreement with each other, and compared favorably with the rigid reference accelerometers. The coupling of the tooth with the skull did produce an amplification of the resultant acceleration, but maintains enough fidelity to develop a simple transfer function for the sensor data.

Rigby et al. (2011) constructed an FEM model of the complete helmet and head assembly including pads and straps to develop a transfer function that, when supplied with the motion data from the helmet mounted sensors, would calculate the motion the head experiences during blast wave situations. The helmet contained pads between the head and the helmet that cushion the impact experienced by the head. In order to determine the motion of the head, a transfer function was needed that takes the helmet motion and calculates the corresponding head motion that would give inference to mTBI.

The FEM consisted of three main steps: (1) helmet system geometry definition; (2) material modelling; and (3) laboratory validation. A series of CT scans were conducted to create the ACH and Team Wendy Pads and the FEM model was created with HyperWorks. For accurate configuration guidance, a plastic ISO full-faced headform was fabricated to allow scanning of the complete helmet system. It was important to have the correct material models when developing a FEM to have accurate measurements of blast conditions. Due to the different strain rates experienced by the pads when the helmet is subjected to various stimuli, Team Wendy Pad material validations were done for both drop and shock tests. FEMs were created to reproduce the hysteresis curves for Team Wendy pads in both cases.

With the right material properties for each component of the helmet-head system, the FEM was able to: (1) reproduce similar results to the experimental data; (2) provide a better understanding of how individual pads deliver loads to the head; and (3) verify pad distribution, magnitude, and timing. The FEM can accurately predict head motion across a wide spectrum of insults to the helmet and can be used as a transfer function to characterize the complicated interaction between the helmet, pads, and head. The knowledge gained from the FEM about the complex helmet, pad, and head interaction helped guide the construction of a simple model that can accurately predict head motion using helmet sensor data.

Environmental Sensors in Training (ESiT)

The Training and Doctrine Command was tasked to review environmental sensors to be fielded to Army Soldiers in various training environments. One goal of the project was to obtain data from exposure to either blast overpressure or blunt impacts. The head response to the exposure (acceleration or pressure) combined with documented mTBI could then be used to establish a reliable dose-response relationship between exposure and mTBI. The effort was focused on both accelerative environments (Airborne Training and Modern Army Combatives Program training) and overpressure environments (Heavy Artillery and Shoulder Fired Weapons). The U.S. Army's Aeromedical Research Laboratory (USAARL) and Walter Reed Army Institute of Research (WRAIR) have been involved in the review of environmental sensors and fielding them to Soldiers in training.

USAARL has been conducting laboratory evaluations of sensors, developing a methodology for fielding sensors, and will be performing concussion assessments on trainees in blunt impact environments. WRAIR has been involved with several blast environments. At this time, the sensors of interest include the PEO-S PM SPE-sponsored Gen II HMSS, the DARPA Blast Gauge (manufactured by BlackBox Biometrics), the SIMBEX Head Impact Dosimeter (a USAARL-sponsored Small Business Innovation Research effort), the Reebok Checklight, and the X2 XPatch. New environmental sensors will be considered for inclusion as they are made available.

USAARL performed a laboratory evaluation of the above sensors. The purpose of these evaluations was to (1) validate the technical performance of the sensors against the lab grade instrumentation in a variety of controlled exposure conditions and (2) determine whether they provide sufficient information to employ existing head injury metrics. Several tests were performed, including indirect impacts using a minisled and a drop tower, as well as measurement of mass properties (center of gravity, moments of inertia, etc.). Additionally, the environmental sensors were evaluated to determine whether it is possible to correlate the output they provide with any known head injury metrics (i.e., HIC, GSI, accurate peak linear acceleration, peak rotational velocity, etc.).

Following laboratory evaluations, USAARL conducted a form and fit pilot test of the sensors using the Training Cadre from each of the accelerative environments (Basic Airborne Training and Combatives training). This allowed the cadre to gain familiarity with the sensors in order to assess any potential interference with the training environment or their normal operating procedures. USAARL also determined best approaches for access to the trainees for distribution and recovery of the sensors.

A second planned pilot study will instrument a small population of trainees (n = 10–20) in both environments with sensors to (1) determine appropriate sensor trigger levels and the incidence of false triggers and missed impacts, (2) perform a comparison between different sensors, and (3) provide information to support developing best practices for the logistics of incorporating environmental sensors into military training environments (e.g., Soldier access, sensor distribution/recovery, data recovery). WRAIR has conducted several pilot tests of the sensors in blast environments (Heavy Artillery and Shoulder Fired Weapons) with the same goals.

Future activity being planned includes incorporating techniques for assessing concussion (i.e., the Military Acute Concussion Evaluation Exam, the Automated Neuropsychological Assessment Metrics, and other neurocognitive, vestibular, and vision assessments) into larger scale studies. The culmination of the project combined with other ongoing research should result in the development of a robust injury threshold for environmental sensor(s) (measuring exposure severity from a blast or impact) allowing them to be transitioned to a dosimeter capable of identifying the likelihood of injury based solely on exposure level.

**Adapted from the U.S. Department of Defense (2013)*

E. Validation of blast environmental threshold values

Exposure to blast entails a number of injury mechanisms that can contribute to injury (e.g., primary overpressure, linear/rotational acceleration, skull flexure, brain deformation, impact, thoracic mechanisms). Any one of these factors can induce TBI in isolation. Determining the existence and location of a threshold for any single factor can be difficult in itself: some factors (e.g., overpressure, acceleration) are easily parametrized, while others (e.g., skull flexure, brain deformation) are not. Additionally, individual physical differences (e.g., weight, skull thickness, musculature, biochemical) may smear or completely obscure thresholds. To further complicate matters, factors may interact with one another. For instance, an overpressure level that is safe at one value of head acceleration may not be at another value. Because human prospective trials are not feasible, determination of these thresholds would have to be extrapolated from animal studies, which are costly, time consuming, and carry their own ethical and political issues. Moreover, animal studies are performed under anesthesia, complicating the extrapolation of results.

Most research examining brain injury thresholds come from sports medicine, injuries which are mostly due to accelerations and impact. Despite the intensive study of injury criterion in sports-related impact, the issue is hardly a settled matter (Guskiewicz & Mihalik, 2011). Although some of the difficulty may be attributable to the inaccuracy of HITS in measuring accelerations during impact (Jadischke, Viano, Dau, King, & McCarthy, 2013).

> *"One of two areas of greatest need is an appropriate physiologically based injury tolerance curve for primary blast- induced TBI so that manufacturers, academics, governments, and end users can base new protective equipment designs on valid injury criteria and help to develop appropriate personal protective equipment standards."*
>
> Desmoulin & Dionne (2009)

In blast research, the concept of exposure tolerances was synthesized by Bowen et al. (1968). The study accumulated and analyzed data from a number of studies where different species, ranging from mice (mass ~ 0.02 kilograms) to steer (mass ~ 180 kilograms), were exposed to blasts under similar conditions. The 24-hour mortality rates were recorded for each animal species, which were fit as a function of scaled blast duration and scaled peak reflected overpressure; scaling from animal species to humans was based on mass. From these fits, curves that define the lines of constant mortality rates could be defined; these have come to be known as the "Bowen curves." That is, given a mortality rate, say 50 percent, the Bowen curve for this rate defines the combination of peak pressure and blast duration at which 50 percent of subjects will survive. Bowen et al. also derived a threshold curve for lung damage. There have also been recent attempts to update the Bowen curves, but these still apply to pulmonary injury and mortality (Bass, Rafaels, & Salzar, 2008; K. A. Rafaels, Bass, Panzer, & Salzar, 2010).

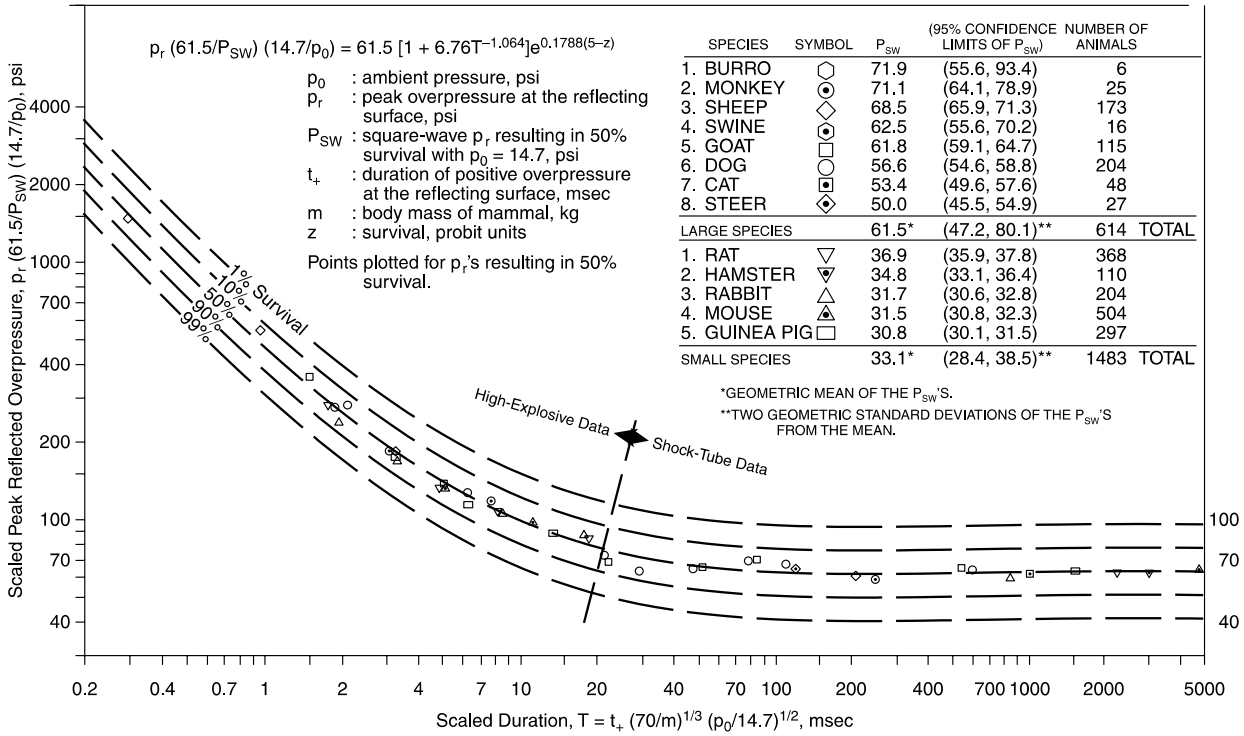


Figure 1. Pulmonary blast tolerance curves show the estimated combination of scaled blast duration and scaled peak reflected overpressure at a fixed survival percentage. Adapted from IOM (2014), which is adapted from Bowen et al. (1968)

Attempts to determine tolerance curves in the context of head injury have been attempted in non-human primates and human cadaver skulls subjected to impacts (Ono, Kikuchi, Nakamura, Kobayashi, & Nakamura, 1980). Using simple dimensional arguments, Courtney and Courtney (2011) adapted the threshold curve from Ono et al. (1980) to locate a "region of interest" where blast thresholds should be studied. In brief, they used the acceleration threshold curve reported by Ono, converted them to force using Newton's law and a typical head mass (4.3 kilograms), and converted force to pressure using a typical head cross sectional area (0.035 meters^2); in other words, they found the pressure required to push a typically-sized head at threshold acceleration levels. They then defined the region of interest by considering an area that encompasses twice the values and one-half the values in the derived curve. Plotting this region of interest together with an adapted Bowen curve, they found that the entire region of interest lies below the Bowen curve for the threshold of lung damage (Figure 1). This hypothetical region of interest only accounts for the threshold due to linear acceleration alone; it does not account for rotational acceleration or overpressure.

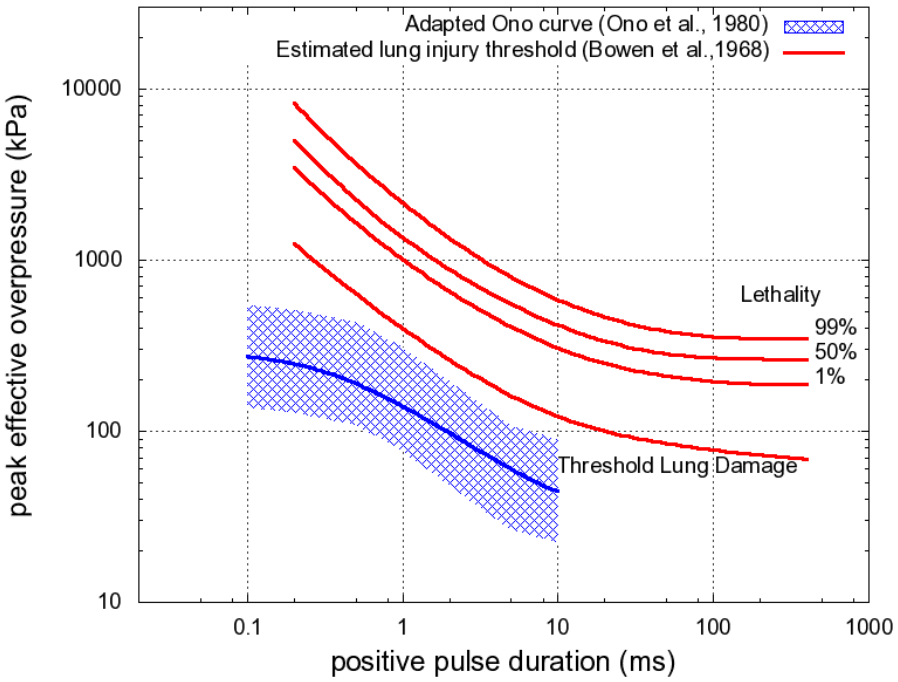


Figure 2. By converting an acceleration tolerance curve into a pressure tolerance curve, a region of interest for brain injury tolerances (blue curve and shaded region) was derived. Adapted from Courtney and Courtney (2011)

Rafaels et al. (2011; 2012) have also attempted to produce blast tolerance curves. In Rafaels et al. (2011), the researchers subjected rabbits (anesthetized and restrained) to varying levels of shock (via a shocktube) focused on the head, while simultaneously protecting the thorax. They fit logistic regression curves to the fatality data to determine a lethality threshold (i.e., the incident blast pressure at which there was 50 percent mortality). They found, comparing to the earlier work on pulmonary thresholds (Bass et al., 2008), that the overpressure threshold was higher for brain lethality than for pulmonary lethality (750 kPa versus 305 kPa, statistics not reported). The authors also used scaling arguments to derive a tolerance curve for brain injury survival (Figure 2).

Seeing the value in producing a brain injury threshold curve, as opposed to a brain lethality curve, Rafaels et al. (2012) used a similar methodology to their previous work (K. Rafaels et al., 2011), except they used ferrets — because of their gyrencephalic brains — rather than rabbits. Instead of regressing to lethality, the researchers regressed to the presence of mild or greater hemorrhaging — hemorrhages that covered ≥ 3 percent of the surface area of the extracted brain (Figure 3). Again, they found that brain injury threshold curves are higher relative to pulmonary injury threshold curves; this finding contradicts the analysis performed by Courtney and Courtney (2011). Given the large differences in methodology and assumptions, this should come as no surprise. In particular, Courtney and Courtney (2011) derived their threshold line by considering the acceleration of the head due to blast pressures. Rafaels et al. (2012) considers primary blast exposure only.

Several papers have experimentally searched for the existence of a blast threshold. VandeVord (2013) exposed anesthetized and restrained rats to different levels of BOP using a blast tube. Rats were exposed to 0 kPa (sham), 97 kPa, 117 kPa, or 153 kPa of overpressure due to a single blast (except for sham rats who underwent all surgical procedures but experienced no blast). VandeVord then tested rats for motor coordination (horizontal ladder test) and

neurocognitive deficits (Morris water maze). Rats were preselected to be tested at 3, 6, 48, or 72 hours after blast exposure. VandeVord found that mean measures of motor coordination were not significantly different at any time period (p = .826). Both 117 kPa and 153 kPa exposed groups demonstrated significant mean deficits in the Morris water maze (p < .05) compared to sham, but only at 48 hours after exposure.

After testing, subjects were sacrificed and brains were sliced to record histological damage. In particular, VandeVord examined astrocyte reactivity as measured by glial fibrillary acidic protein, the number of apoptotic cells as measured by the number of cleaved caspase-3 positive cells, and the number of degenerating neurons as measured by the number of Fluor-Jade B positive cells. They examined the histology in pre-selected areas: primary motor cortex, dentate gyrus, and posteromedial cortical amygdala; these areas were selected for their important role in cognitive and behavioral deficits in TBI. Surprisingly, VandeVord found that most measures of histological damage were much worse in the 117 kPa exposed group than for the 153 kPa exposed group. VandeVord speculate that this may be due to resonance effects at 117 kPa that are not observed at 153 kPa and could lead to efficient energy transfer of the shockwave to the brain. This result does cast doubt on the existence of single blast threshold, beyond which, TBI is imminent.

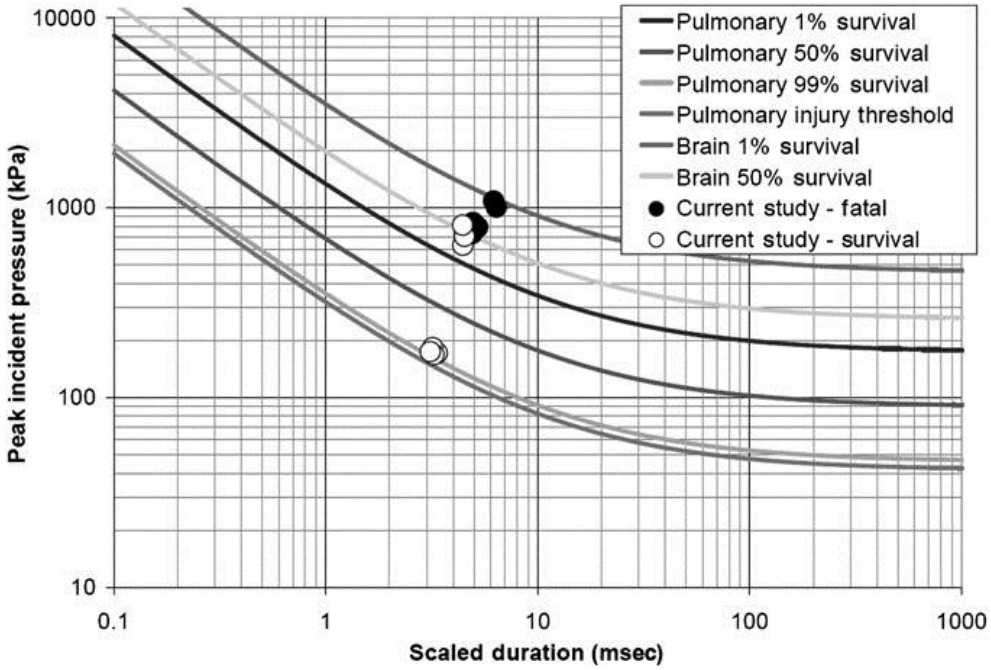


Figure 3. A brain injury tolerance curve adapted from Rafaels et al. (2011)

Standard injury criteria such as the HIC and GSI also use linear acceleration to predict head injuries due to impact. Both of these standards are based on the Wayne State University tolerance curve, which were derived from animal concussion and cadaveric skull fracture tests. Recent attempts have been made to redefine head injury criteria in the context of American football. Greenwald et al. (2008) examined data from the HITS sensor implanted in collegiate and high school football players. The researchers used principal components analysis to derive a weighted index of linear and rotational head acceleration, HIC, GSI, impact duration, and impact location. Their weighted principal components score performed better at classifying impacts that caused an impact than any of the measurements alone, as assessed by receiver operating characteristic curves.

Zhang et al. (2004) used a computational modeling approach to propose a new injury criterion. Through video analysis of 12 National Football League two-player helmet-to-helmet collisions where only one of the players had a confirmed concussion, the researchers reconstructed the impacts using Hybrid III Anthropomorphic Test Devices. The results from the reconstructed impacts fed into an finite element computer model of the brain, which could calculate a number of quantities such as brain acceleration (both linear and rotational), ICP, shear stress, etc. at different locations. By applying a logistic regression model to predict the presence of the concussive impact, they determined that shear stress at the brain stem was the best predictor of concussion, outperforming both HIC and GSI. Shear stress at the brainstem was also found to correlate with resultant rotational acceleration with a value of 0.78, but did not have a significant correlation with resultant linear acceleration (statistics not reported).

Takhounts, Craig, Moorhouse, McFadden, and Hasija (2013) used the Simulated Injury Monitor (SIMon) and the Global Human Body Models Consortium finite element models to develop the Brain Injury Criterion (BrIC) (Bandak, F. A. et al., 2001; Thompson et al., 2012). By scaling loading parameters from animal impact experiments to humans, the researchers simulated human head response to various impact conditions. They assumed that injury thresholds would be identical for humans and animals given the scaled kinematic conditions. From the simulation data, they developed BrIC. In the study, angular velocity was found to be the best predictor of impact injury; angular acceleration did not correlate well and was therefore left out from the definition of BrIC.

Desmoulin and Dionne (2009) argue that injury thresholds designed for automobile accident research, such as HIC and GSI, are likely to have limited applicability in blast research because of the differences in mechanisms of energy transference. They point out that only head accelerations of duration >20 msec are validated for HIC in automotive accidents. Blast tests performed on manikins suggest that durations of head accelerations can be in the range of 5–12 msec. They also performed several tests, subjecting the Hybrid III head form to blast tube exposure (92.4 ± 6.1 kPa). Head accelerations were on the order of 40 *g* and had a duration of 3.22 msec ± 0.14 msec. High speed video confirmed that BOP interacts with the head before any initiation of acceleration by approximately 7 msec. Therefore, theoretically, overpressure has the first chance to cause injury. Desmoulin and Dionne also suggest that the viscoelastic response of the brain may provide good mechanical criteria for developing blast related thresholds. As such, they call for the development of a brain simulant inside of a surrogate skull to test this possibility.

Key findings for validation of environmental sensors threshold values

- *Currently there is a lack of definitive experimental evidence for the existence of a clear clinically-relevant threshold for mTBI*
- *Current blast injury tolerance curves for humans are obtained by scaling from animal models*
- *Published proposed mTBI thresholds have come largely from sports-related impact injuries*
- *Modern machine learning methods should be adopted*

F. Correlation of blast environmental threshold values to injury

There is a need for quantifiable and reliable and valid brain injury prediction metrics, or concussion injury thresholds, based on kinematic parameters of the head. Monitoring of head injuries and utilizing injury prediction models will be invaluable for the identification of individuals at risk for experiencing a mTBI/concussion. There is a growing body of published literature on proposed concussion threshold values using data (e.g., linear and rotational accelerations) collected from sports-related head impacts, however, there is much variability and to date, no

reliable threshold for diagnosing concussive injury exists. An even bigger research gap exists in the field of blast mTBI-related injury thresholds — an area particularly relevant for the DoD and the deployed military personnel subject to repetitive blast exposures in theater. The majority of injury threshold studies rely on HITS for the real-time, in vivo recording and subsequent analysis of biomechanical head impact data, which includes peak linear acceleration, rotational acceleration, impact duration, location, time stamp, GSI and HIC (Broglio, Surma, & Ashton-Miller, 2012; Cobb, 2013). To date, over two million data points have been collected using HITS and the system at a cost of approximately $1,000 per helmet is relatively affordable for widespread use compared to the one other commercially-available helmet sensor system, the six degrees of freedom system, which is cost prohibitive and not widely used (Cobb, 2013). Nearly all proposed mTBI/concussion thresholds are derived from data collected from athletes wearing the HITS helmet-mounted accelerometer, data from which is presented below and can be used to inform the understanding of blast-related threshold values.

Because mTBI/concussion is caused by biomechanical forces acting on the body and brain, threshold values can theoretically be derived from analyzing biomechanical parameters associated with head impact and correlate them with occurrence of a clinically-defined mTBI/concussion (Funk, Rowson, Daniel, & Duma, 2012). The National Football League were the first to propose injury threshold values by recreating concussive impacts in mannequin crash test dummies. The seminal paper by Pellman, Viano, Tucker, Casson, and Waeckerle (2003) showed a threshold of linear head acceleration of 98 ± 28 *g* and HIC of 381 ± 197.

The first published mTBI/concussion injury threshold using data collected from impacts recorded by HITS, suggested that concussion was associated with linear acceleration of at least 81 *g* and rotational acceleration of 5590 rad/sec^2 (Duma et al., 2005). Additional studies of collegiate football athletes indicate linear acceleration concussion threshold values ranging from 55.7 *g* to 136.7 *g* (Brolinson et al., 2006). One of the first studies to generate predictive threshold levels used data collected from the HITS in concussed high school football players concluded that there was a 6.9 percent chance for concussion with impacts with peak linear acceleration greater than 96.1 *g* and 1.9 percent chance for concussion with impacts with a peak rotational acceleration of 5582 rad/sec^2 (Broglio, Eckner, & Kutcher, 2012).

Two additional studies of high school (Broglio, Eckner, Surma, & Kutcher, 2011) and collegiate (Guskiewicz et al., 2007) football players suggest a concussion threshold based on linear acceleration of 86.3 and 102.8 *g*, respectively, and a threshold based on rotational acceleration of 5311.6 and 6111.4 rad/sec^2, respectively — indicating a lower threshold for high school athletes compared to their older counterparts. According to Greenwald et al. (2008), a linear acceleration of at least 96 *g* and rotational acceleration of 7235 rad/sec^2 is the threshold for concussive injury in high school and collegiate athletes, whereas Broglio, Surma, and Ashton-Miller (2012) and Eckner, Sabin, Kutcher, & Broglio (2011)report a threshold of linear acceleration of 105 *g* and rotational acceleration of 7229.5 rad/sec^2. A study by Eckner, Sabin, Kutcher, and Broglio (2011) reported concussions occurring over a wide range of impacts with linear accelerations ranging from 74 to 146 *g* and rotational accelerations ranging from 5582.6 rad/sec^2 to 9515.6 rad/sec^2. A recent study by Funk, Rowson, Daniel, and Duma (2012) used head impact data collected from collegiate football athletes (*n* = 98 athletes; *n* = 37,128 head impacts) fitted with HITS showed a linear acceleration threshold value of 145 ± 35 *g* and HIC threshold value of 615 ± 309, results of which were consistent with previous studies.

Together this body of literature clearly indicate that a reliable, meaningful threshold value remains to be determined and that this gap must be addressed.

The vast majority of prediction models and associated risk curves and kinematic-based injury metrics are based on either linear (associated with a transient ICP gradient) acceleration or rotational (associated with a strain response) acceleration-related modes of brain injury; these models that fail to incorporate both modes of injury may not be reflective of real world head impact in which both linear and rotational acceleration occur concurrently. A recent study by Rowson and Duma (2013) developed a novel injury prediction metric, the combined probability of concussion, which computes the overall risk for concussion by accounting for both linear and rotational accelerations experienced by the head during impact. Risk curves using multivariate logistic regression analysis of data drawn from two separate datasets were generated. The HITS dataset included peak linear and rotational accelerations from 62,974 sub-concussive impacts and 37 diagnosed concussive impacts and the National Football League dataset included peak linear and rotational accelerations from 58 impacts including 25 concussions. For each dataset, predictive measures of concussion were quantified using receiver operating characteristic (ROC) curves for linear acceleration, rotational acceleration and the combined probability (i.e., both linear and rotational) and the area under the ROC curve (AUC) was compared to the predictive capability of random guessing. For both datasets the AUC for all three parameters (e.g., linear acceleration, rotational acceleration and the combined probability of concussion) were significantly better at predicting concussion than the AUC associated with random guessing. For both datasets, the AUC for the combined parameter was the largest, suggesting that it had the greatest predictive value, although linear acceleration alone was no worse at predicting concussion. The authors suggest that this new metric is more valuable than other metrics based solely on linear acceleration data because the model accounts for all components of head impact.

Key findings for the correlation of blast environmental threshold values to injury

- *There is an emphasis on determining predictive markers of mTBI, specifically injury threshold values that can be used diagnostically*
- *Most of what is known comes from the civilian athletic sector using data derived from football athletes fitted with helmet-mounted dosimeters*
- *Concussion risk curves and threshold values have been proposed, however, additional validation studies are required*
- *A large gap exists in the validation of threshold values for blast-induced mTBI*

IV. Summary and Conclusions

This literature review summarized the current state-of-the-science for mTBI/concussion thresholds associated with environmental sensors. The literature review discussed the neuropathology, underlying mechanisms, and computational modeling of both blast and non-blast induced mTBI, as well as environmental sensor technology, the evaluation of sensor technology, and the validation and correlation of environmental threshold values related to mTBI/concussion. The findings from this literature review will serve to inform discussions at the November 2014 International State-of-the-Science Meeting on the Biomedical Basis for Mild Traumatic Brain Injury Environmental Sensor Threshold Values.

Currently, the proportion of mTBI due to blast versus non-blast mechanisms (i.e., impact) is not fully understood. Moreover, the lack of isolated primary blast exposure cases make it difficult to study the different contributions of mTBI. Currently, it is believed that BOP can contribute to injury through two mechanisms: (1) thoracic transmission of pressure waves and (2) direct cranial entry of blast waves. Head acceleration (both linear and rotational) due primarily to impact are also believed to be a major contributing factor to mTBI. Recent evidence suggests that blast and non-blast induced TBI have similar clinical outcomes. Nevertheless, it currently not known whether they are indeed the same disease requiring identical treatment courses. Further research is needed to understand the differential contributions of blast and impact to mTBI and also to understand their interaction.

Advancements in animal modeling and neuroimaging have allowed for more detailed investigation into the pathophysiological (e.g., neuroanatomical, cellular, molecular) outcomes of mTBI (including both primary blast and non-blast-induced). Neuroimaging tools such as functional MRI and DTI have found correlations between mTBI and diffuse, microscopic white matter damage in the absence of gross tissue damage. In the Veteran population, there have been conflicting reports on the clinical relevance of DTI in detecting lesions related to TBI. DTI represents a promising new method for the study of TBI; further investigations in the Veteran population may help elucidate the outcomes and trajectory of TBI (both blast and non-blast).

Computer models can simulate the movement of both head and brain in response to blast loading, which makes it possible to study phenomena and conditions not feasible in traditional laboratory experiments. Simulations can calculate the strain, stress, and acceleration experienced by the brain during blast exposure, which helps elucidate the mechanisms of blast-induced TBI. The accuracy of computational modeling is limited by the ability to determine parameter values, which have varied over orders of magnitude in experiments. Nevertheless, computer models are low-cost and rapid turnaround making them complimentary to lab experiments.

There are currently several environmental sensors deployed in the field; however, there are no published reports linking data from fielded sensors to known injury. Product developers are conducting *ad hoc* tests on the sensors to determine accuracy. Additionally, there are sensors under development that align to one of three categories: (1) packaged environmental sensors, (2) raw pressure sensors, and (3) burst sensors. Packaged environmental sensors record pressure and acceleration (both linear and angular) along with vital signs such as EEG, heart rate, and SpO_2. Raw pressure sensors need further development before being packaged for fielding. Burst sensors are cheap, lightweight, and do not require an energy source, but cannot report or accurately record environmental data.

Currently, there is no definitive experimental evidence for the existence of clinically relevant thresholds for TBI. Current blast injury tolerance curves for humans are obtained by scaling from animal models. Published reports searching for mTBI thresholds have come largely from sports research. Research into current sensor technology and evaluating their ability to detect mTBI is underway.

Next steps include convening the State-of-the-Science meeting where experts will gather and discuss the research gaps in the field of environmental sensor threshold values for mTBI and identify best practices for development of threshold technology ultimately for the advancement of prevention and mitigation of injuries to the Warfighter and civilian populations.

V. Appendices

A. References

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B. Literature Search Results

Search term(s)	Search Engine/Database	Number of hits	Number of relevant hits	Number of reviews
blast gauge	Pubmed	12	5	0
"blast gauge"	Google Scholar	149	9	2
blast sensor	Pubmed	49	12	0
"blast sensor"	Google Scholar	78	7	1
blast computational models	Pubmed	297	N/A	N/A
blast computational models brain	Pubmed	21	15	2
blast computational brain	Pubmed	36	22	2
blast sensor TBI	Pubmed	3	3	0
blast TBI	Pubmed	255	N/A	N/A
blast TBI helmet	Pubmed	5	5	1
blast helmet sensor	Pubmed	1	1	0
explosi* TBI sensor	Pubmed	2	2	0
explosi* TBI gauge	Pubmed	2	2	1
"Headborne Energy Analysis and Diagnostic System"	Google Scholar	1	0	0
HMSS	Pubmed	32	0	0
helmet-mounted brain	Pubmed	10	5	0
blast helmet-mounted	Pubmed	0	0	0
TBI helmet-mounted	Pubmed	0	0	0
helmet-mounted sensor	Pubmed	5	0	0
helmet sensor brain	Pubmed	22	3	1
blast sensor TBI	Google Scholar	1600	100+	
helmet sensor	Pubmed	45	4	0
helmet-mounted blast sensor	Pubmed	0		

Search term(s)	Search Engine/Database	Number of hits	Number of relevant hits	Number of reviews
helmet-mounted blast sensor	Google Scholar	457	2	
helmet-mounted "blast sensor"	Google Scholar	5	4	
tbi threshold	Pubmed	161	4	
blast threshold	Pubmed	210		
blast sensor TBI	DTIC	356		
blast sensor	DTIC	1070		
"helmet sensor"	Google Scholar	128		
"blast gauge" tbi	Google Scholar	12		
overpressure tbi	Pubmed	32		
tbi threshold	Pubmed	161		
blast dosimeter	Pubmed	4	3	
"blast dosimeter"	Google Scholar	37		
overpressure threshold tbi	Pubmed	3		
blast threshold tbi	Pubmed	8		
blast threshold brain	Pubmed	25		
blast threshold brain	Google Scholar	51600		

C. Acronyms and Abbreviations

Acronym or Abbreviation	Full Name
ACH	Advanced Combat Helmet
AUC	Area Under the ROC Curve
BOP	Blast Overpressure
BID	Blast Injury Dosimeter
BrIC	Brain Injury Criterion
bTBI	Blast-Induced Traumatic Brain Injury
BCT	Brigade Combat Team
CFD	Computational Fluid Dynamics
cm	Centimeter
CT	Computed Tomography
CTE	Chronic Traumatic Encephalopathy
DARPA	Defense Advanced Research Projects Agency
DoD	Department of Defense
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
FEM	Finite Element Method
ft	Feet
GSI	Gadd Severity Index
HEADS	Headborne Energy Analysis and Diagnostic Systems™
HIC	Head Injury Criterion
HITS	Head Impact Telemetry System
Hz	Hertz
IBESS	Integrated Blast Effect Sensor Suite
ICP	Intracranial Pressure
IEDs	Improvised Explosive Devices
JTAPIC	Joint Trauma Analysis and Prevention of Injury in Combat

Acronym or Abbreviation	Full Name
kPa	Kilopascal
kW	Killowatt
m	meter
MHz	Megahertz
µm	Micrometer
µsec	Microsecond
mm	Millimeter
MPa	Megapascal
MRI	Magnetic Resonance Imaging
msec	Milliseconds
mTBI	Mild Traumatic Brain Injury
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
PREVENT	Preventing Violent Explosive Neurologic Trauma
Psi	Pound Per Square Inch
Rad	Radians
ROC	Receiver Operating Characteristic
sec	Seconds
SIMon	Simulated Injury Monitor
SpO_2	Oxygen Saturation
TECD	Technology-Enabled Capabilities Demonstration
TBI	Traumatic Brain Injury
USAARL	U.S. Army's Aeromedical Research Laboratory
WRAIR	Walter Reed Army Institute of Research