Spring 2016

CONCUSSION: A NATIONAL CHALLENGE

The BRIDGE

LINKING ENGINEERING AND SOCIETY

A Multidisciplinary Approach to Concussion Management — *Jay L. Alberts*

Can Serum Brain Proteins Aid in Concussion Identification? — *Jeffrey J. Bazarian*

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Medical Imaging to Recharacterize Concussion for Improved Diagnosis in Asymptomatic Athletes — *Thomas M. Talavage*

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The BRIDGE

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The National Academies of
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Editors' Note

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Concussion

Status and Next Steps

The rising incidence of brain trauma from sports, military blasts, vehicle collisions, and falls prompted the faculties of Case Western Reserve University and its associated medical care programs in Ohio to convene a symposium, with the National Academy of Engineering and National Academy of Medicine, on all facets of concussion. In June 2015 experts and representatives in engineering, clinical medicine, military medicine, athletics, animal research, physics, and government engaged 650 participants at the Global Center for Health Innovation in Cleveland. This issue presents 14 short scientific papers based on their presentations—covering brain trauma epidemiology, mechanisms, diagnosis, treatment, and prevention—following a longer, comprehensive overview of concussion.[1]

[1] *Managing editor's note:* Publication of this substantially larger issue was supported by a special contribution from Cleveland area NAE members and Case Western Reserve University.

The information in this issue can enhance understanding of the nature and mechanisms of concussion. Years of experimental studies, initially focused on vehicle collisions, have evolved from crash simulations, animal experiments, tissue biophysics, and computer simulations to investigations of physical parameters of head impact through instrumented helmets, objective measures of cognitive function changes before and after sports engagement, and noninvasive imaging (e.g., functional magnetic resonance imaging, fMRI).

Over the last 10 years the neuropathology associated with symptoms of brain dysfunction has been revealed. Fortunately, these pathology diagnoses, at first done through postmortem assessments, can now be made by imaging methods (e.g., positron emission tomography, PET) in living athletes, veterans, and crash victims.

This information can be used to address a national problem that needs far more attention to prevention, diagnosis, and treatment, particularly concerning the risks to young athletes and servicemembers—and females in particular, as a paucity of data exists to address gender differences—of developing long-term behavioral and cognitive problems from multiple impacts.

The Way Forward: Potential Strategies

Compelling evidence presented at this symposium shows the urgent need for engineers, neuroscientists, and medical professionals to develop more precise information about how blunt trauma leads to brain tissue injury, how the effects of repeated trauma may accumulate over time, and how this accumulation results in long-term and progressive brain tissue damage and human behavior dysfunction.

Following are potential strategies to meet the challenges of concussion diagnosis and prevention and to determine optimal methods for treatment.

1. Establish a registry to track head injuries in pre–high school and high school sports, as is done for collegiate sports. A long-term medical history record, based on objective and quantitative measures, may enhance understanding of medical and academic outcomes for concussive events at all ages. A successful start of such a registry has been made by a consortium of colleges and the military service schools (cf. papers

by Hack and Hainline). Pathological information is a critical part of this registry (cf. papers by Kovacs, McKee, and Perl).
2. Incorporate objective methods of assessment of cognitive changes before and during impact sport activities, as has been done in pilot programs for high school players (cf. Talavage paper).
3. Extend objective and easily implemented measures of neuromotor function (such as those developed by the Cleveland Clinic Concussion Center; cf. Alberts paper) to other athletic programs around the country.
4. Add to the blood biomarker research program (cf. Bazarian paper) assessments of pituitary function (cf. Budinger overview).
5. Investigate the sensitivity of a simple test of olfaction function (odor detection) to predict long-term consequences of brain trauma (cf. Ruff paper).
6. Engage bioengineers in computer simulations with accurate representation of material properties to demonstrate brain tissue strain fields associated with blasts and impacts over a range of stress rates, accelerations, and angular directions (cf. papers by Radovitzky et al. and Margulies).
7. Improve vehicle collision tests by incorporating heavily instrumented anthropomorphic dummies and other test devices to measure head and brain accelerations in automobile barrier test impacts (cf. Michael paper).
8. At the national level, encourage research to determine the efficacy of anti-inflammatory drugs as well as other agents to aid in the recovery of concussion as well as approaches to aid in treating axon and mitochondrial injury (cf. Smith paper and Budinger overview).

Acknowledgments

Case Western Reserve University hosted the June 2015 Regional Meeting on which this issue is based.[2] The objective of the meeting was to bring together leaders from a variety of disciplines to present to the scientifically inclined public the knowledge available about concussions. This was the fifth such meeting organized by local members of the National Academies to provide information to the public on a topical issue where scientific clarification of issues has been important. The previous events addressed biotechnology, energy, vaccine production, and shale gas and fracking.[3]

This conference would not have been possible without broad support from many donors and our program committee.

Major Donors

Case Western Reserve University, MetroHealth Medical Center, Taipei Medical University, and the Global Center for Health Innovation. Cosponsors were the Cleveland Clinic, Cleveland Foundation, Cleveland State University, Kent State University, Kelvin and Eleanor Smith Foundation, and University Hospitals of Cleveland.

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Special thanks are due to Tom Budinger, guest coeditor of this issue. The program committee is indebted to Tom for his herculean efforts, along with science writer Pamela Reynolds and *Bridge* managing editor Cameron Fletcher, for assembling these monographs into a cohesive account of the national problem of concussion.

P. Hunter Peckham (NAE)
Case Western Reserve University and
MetroHealth Medical Center
Conference General Chair

[2] The complete presentations are available at the conference website (www.concussion2015.org).

[3] The latter two were featured in the fall 2006 and summer 2014 issues of the *Bridge*, available at www.nae.edu/21020.aspx.

Editor's Note

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An Overview of Concussion
History and Needed Research

This paper summarizes a symposium on concussion held at Case Western Reserve University on June 23–24, 2015, and supported in part by the National Academies of Engineering and Medicine.[1] It reviews evidence for the seriousness of the problem of concussion (also called *mild traumatic brain injury, mTBI*) and considers relevant engineering, medical, and biological aspects; provides background, including relevant experimental results, on epidemiology, diagnosis, brain tissue injury mechanisms, histopathology, noninvasive imaging detection of brain injury, blood biomarkers, and progress toward prevention and treatment; and summarizes the short papers based on the presentations.

The papers consider concussion in athletics/sports, combat, and road accidents, and address biomechanics and biomarkers, diagnosis, long-term consequences, prevention, treatments, and patient management. They convey the current state of knowledge in these areas as well as what can be learned through experiments and computer simulations and modelling. Answers to questions raised by participants at the symposium are also elaborated in the following pages.

The symposium revealed areas of great need for research, of which the need for understanding the long-term consequences of concussion stood out as the most significant.

[1] The symposium and this issue of the *Bridge* follow recent reports from the National Academies on *Sports-Related Concussions in Youth* (IOM 2014) and a *Review of Department of Defense Test Protocols for Combat Helmets* (NRC 2014).

History

Concussion is recognized as a brain injury induced by biomechanical forces, that may or may not cause loss of consciousness, and that typically causes rapid onset of short-lived impairment of neurological function with no abnormalities visible on standard structural neuroimaging studies. This definition has evolved over time, as earlier criteria required loss of consciousness and amnesia.

The relationship of brain trauma to behavioral changes became an object of great interest to neuroscientists in 1848, when the head of an affable and well-liked railroad worker, Phineas Gage, was penetrated by an iron spike. After a miraculous recovery his personality changed such that he appeared to be a different person (Harlow 1948). Some 160 years later the same personality changes were found to accompany severe brain pathology in victims of multiple episodes of brain trauma.

Four historical events brought the attention of the public, military, government, engineers, and physicians to the importance of understanding concussion and its effects. The first was the occurrence of 18 deaths and 159 serious injuries from college football within 10 years of the first game between Harvard and the University of Pennsylvania in the early 1880s (Harrison 2014).

The second group of events started with the controversial diagnoses (e.g., psychiatric disorder vs. organic brain trauma) during and after World War I, with reports of physiological consequences (short-term defects in vision, olfaction, and bowel elimination) of artillery shell blasts (Myers 1915). Before that, surgeons during the American Civil War had reported that injured soldiers manifested psychiatric behavior and muscle paralysis unrelated to a specific impact injury to the head or body (Mitchell et al. 1864).

Scientists argued for decades about the mechanisms that explain psychiatric symptoms, though even in 1916 the neuropathological evidence was compelling for veterans of explosions (Mott 1916, 1917). (Mott subsequently countered his contention that brain injury was the cause of shell shock by arguing that the principal cause was psychiatric; Mott 1919.)

The formal recognition of posttraumatic stress disorder (PTSD) by the American Psychiatric Association (APA) in 1980 was a turning point in discussions of causation and diagnosis—and about whether PTSD is

the result of psychological stress or physical injury of the central nervous system (Jones and Wessely 2014).

The third historical event was the marked increase in incidents of brain trauma caused by blasts from improvised explosive devices (IEDs) used during the conflicts in the Middle East. Survivors manifested psychological symptoms and behavior changes, and upon death showed histopathology evidence of tissue injuries similar to those of veteran boxers.

The fourth event is the recently clarified pathology of long-term and progressive dysfunction among NFL players whose behaviors changed and who became depressed and even suicidal. They had brain pathologies similar to people who suffered multiple concussions in boxing or survived blast injuries. The diagnosis of cerebral traumatic encephalopathy (CTE) was identified from postmortem studies of these players (McKee et al. 2009; Omalu et al. 2006).

Persistent Questions

What is not well known are the quantitative thresholds for forces and the number of traumatic events that lead to long-term cognitive and physical dysfunction. Data from animal experiments can produce curves defining the probability of injury vs. physical impact, but they are not yet reliable for determining thresholds for human concussion, particularly in different age groups and genders.

There has also been considerable discussion of methods to diagnose and determine whether a concussion has occurred. In athletics, current practice relies on player reports, coach or trainer observation, personal accelerometer data, and video evaluation algorithms. But more than 50 percent of sports players do not report symptoms of concussion.

There is a need to classify individuals who have had some level of brain trauma and to develop a state-level or national registry for the long-term follow-up necessary to answer the questions: What are the long-term consequences of mild brain trauma? And how efficacious are proposed treatment strategies, none of which is currently widely accepted?

Epidemiology

Military

The incidence of brain injury during military engagements has recently become a consequence of major importance because of the use of IEDs in the wars in Iraq and Afghanistan. These weapons produce a rapidly expanding high-pressure blast wave from which soldiers survive (thanks to protective armor) but not without brain injuries.

In 2000–2015 there were 270,000 concussions in the military, and from 2005 to 2011 the yearly incidence of mTBI doubled, to 24,000 cases (figure 1). Data indicate that 84 percent of IED-induced concussions occur within 10 meters of the blast, 93 percent within 30 m (cf. Perl paper, this symposium). Many who have been in close proximity to an IED-generated blast develop neurologic and behavioral systems referred to as *postconcussive syndrome* (PCS), which is closely related to PTSD.

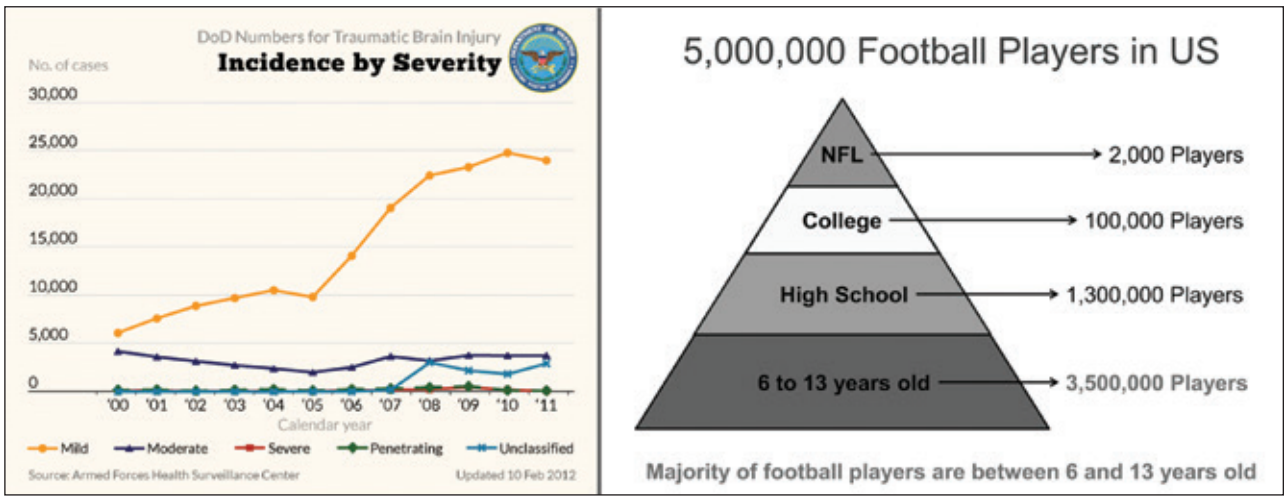

FIGURE 1 Left: Incidence of military brain injuries classified by severity, 2000–2011. Right: Population of football players from youth to professional levels. Sources: Left: http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi; right: reprinted with permission from Young et al. (2014).

Symposium papers by Hack, Kovacs, Perl, and Ruff examine the mechanisms, consequences, and treatment of blast injuries.

Sports

There are 300,000 sports-related concussions annually in the United States (Gessel et al. 2007)—more than 10 times the annual military incidence. Attention by the public and healthcare providers to sports-related TBI has focused largely on NFL players who develop serious personality changes and whose brains have shown pathologies similar to those of boxers with histories of repetitive concussions.

There is evidence that high school athletes have the greatest annual concussion incidence—more than 55,000 per year, with the expectation that a concussion will occur 4.7 times per 10,000 athletic events (AE; Gessel et al. 2007). But this statistic is known to be low: in a survey of 1,532 high school players only 47 percent reported their concussions (McCrea et al. 2004).

The National Collegiate Athletic Association (NCAA) collects standardized injury and exposure data for 15 collegiate sports through its Injury Surveillance System (cf. Hainline paper). About 1 million exposure records over a 16-year period (1988–2004) showed 182,000 injuries (Hootman et al. 2007) and a doubling in the concussion rate for all 15 sports, from 1.7 to 3.4 per 10,000 AE. But the NCAA defines an injury as requiring medical attention and at least one day of absence from play, and these criteria result in an underestimate.

Football is the collision sport with the highest incidence of injury. Of 5 million football players (figure 1), 4.8 million are 6–18 years old, and football injuries account for about 25 percent of emergency department visits in this age group. Collegiate football concussions are estimated at a rate of 6.7 per 10,000 AE (Zuckerman et al. 2015).

The seriousness of sports-related concussions is underscored by the known cumulative effects of three or more concussive episodes (Collins et al. 2002; Guskiewicz et al. 2003).

Road Collisions

Road collisions (automobile, motorcycle, pedestrian, bicycle) result in 200,000 head injuries per year in the United States (cf. Michael paper). But these statistics are based on loss of consciousness and hospital admissions, and so, again, do not accurately represent the incidence of concussive events. In addition to the lack of an effective means of diagnosis, there is no agreed definition of a concussive threshold—for example, even whiplash dynamics can cause brain injuries.

Child and Adolescent TBI from All Causes

Traumatic brain injury is the leading cause of disability and death in children and adolescents in the United States. An average of 62,000 children per year sustain brain injuries requiring hospitalization as a result of motor vehicle crashes, falls, sports injuries, physical abuse, and other causes. According to the Centers for Disease Control and Prevention (CDC), the two age groups at greatest risk for TBI are ages 0–4 and 15–19; among children ages 0–14 years, TBI results annually in an estimated in 2,685 deaths, 37,000 hospitalizations, and 435,000 emergency department visits (Langlois et al. 2004). Falls are the leading cause of TBI for children ages 0–4, but approximately 1,300 US children experience severe or fatal brain trauma from child abuse every year.[2]

Infants and toddlers are in a special class for studies of biomechanical linkages to brain tissue injury because their brain tissues appear to have an unexpected elastic modulus, leading to a critical strain 3.6 times lower in infants relative to toddlers, as inferred from animal studies (Ibrahim et al. 2010). This puts very young babies at a high risk for brain injury from rotational accelerations.

Mechanisms of Brain Trauma

Because the brain is encased in a rigid skull, the primary mode of deformation in response to a blow to the head, fall, or rapid deceleration is isochoric: a combination of shear, tension (stretch), and shape change (distortion) without volume change. If the tissue is compressed in one direction, it is stretched in other directions.

Brain trauma can result from four external processes (figure 2): direct head impact with or from an object (e.g., windshield, floor, another helmet, or projectile), whiplash with no direct head contact, vertical deceleration of the body (e.g., impact between the pelvis and ground), or stress force to the body remote from the head (e.g., high-pressure hit to the thorax).

[2] According to the Brain Injury Association of America (www.biausa.org/brain-injury-children.htm; accessed February 23, 2016).

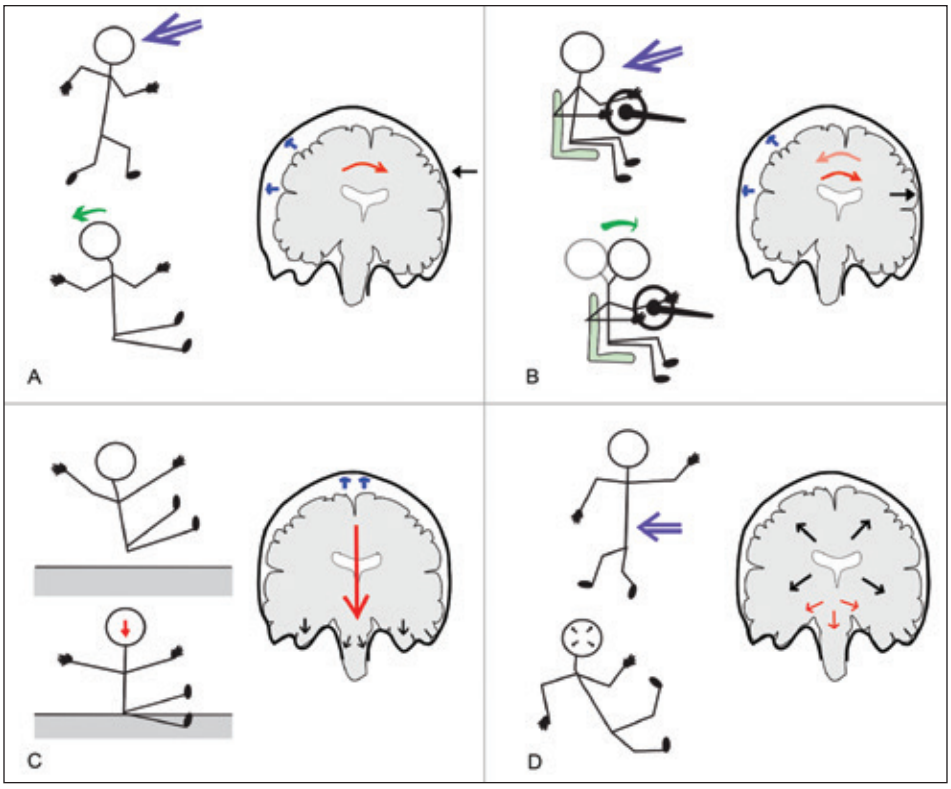

FIGURE 2 Brain motions relative to the head for (A) a left side hit to the head, (B) a left side hit to a vehicle (whiplash), (C) a fall with the impact between the pelvis bottom and a surface, and (D) a hit to the thorax. Green arrows denote head movement; red arrows denote brain movement at the moment of impact relative to the skull movement; black arrows denote the initial pressure direction; and blue arrows in the brain denote negative pressure or tension. The ubiquitous presence of negative pressure in impact and rotational accelerations has received little attention (Krave et al. 2005).

Direct Head Impacts and Whiplash

An impact to the head—whether from a nonpenetrating bullet, collision with the windshield, contact with the floor, an explosive blast overpressure, or collision between two athletes—can be considered as a force per area or pressure. When the acceleration of the skull and brain initiates at slightly different times, both positive and negative pressures occur over 10 to 50 ms intervals. These range from a fraction of an atmosphere to two atmospheres (Krave et al. 2005) and are induced by rotational accelerations associated with head or body impacts (figure 2).

The rate of change of momentum (mass × velocity) over time is the force. For most head contacts in sports, brain accelerations and decelerations are governed by the conservation of momentum. The force per area in and of itself will not injure the tissues; as explained below, injuries are from differential strains associated with brain deformation, from shears associated with the different material properties of the brain tissues. The shear or elastic modulus (Young's modulus) is 10,000 times less than the bulk modulus. Thus, for example, an 80 kg body travelling at 6 m/s that strikes a 5 kg head only loosely tethered to a 75 kg body imparts an extremely high rotational velocity over a short period of time, causing an injury that may be proportional to the change in rotational velocity. Rotation of the head accompanies almost every directional hit except to the top of the head.

Injury is also related to the rate of change in velocity—that is, acceleration and deceleration—which explains whiplash as a cause of concussion. Because the brain is not tightly connected to the skull, any rotation results in a differential movement of the brain relative to the skull. The resulting shear stresses are believed to be the basic mechanism of diffuse axonal injury (discussed below).

Vertical Deceleration of the Body and Stress Force to the Body

Concussion can result from impacts and injuries to other areas of the body. Damage from the transmission of kinetic energy from a point of impact on the torso to remote body organs has been observed in a number of cases (Cannon 2001; Krajsa 2009; Sperry 1993). For example, the finding of hemorrhages in the sclera and conjunctiva of the eye in an anterior chest gunshot–wounded subject is evidence that a ballistic impact can lead to the remote transfer of a large pressure pulse through, in this case, the vena cava and vascular circuits (Sperry 1993). More recent evidence for remote organ damage is from a histopathological analysis of 33 deaths from gunshots to the thorax in individuals not wearing

protective vests and without head wounds or a history of head trauma (Krajsa 2009). In all cases, microscopic hemorrhages were observed on histological examination of tissue slices from throughout the brain.

A second mechanism of injury to organs remote from the impact site is stroke-like ischemia caused by air embolism, whether from a blast wave or blunt trauma to the torso in a collision or a nonpenetrating bullet hit to a protective vest. Arterial air embolism has been reported to cause immediate death from blast injuries (Rossle 1950).

Factors in Assessing Links between Physical Forces and Brain Injury

A variety of factors must be considered in experiments to evaluate the links between applied forces and injury to the brain. For example, the type of injury will vary depending on the following conditions:

- magnitude of the impact
- stress rate and duration of the impact
- direction of the impact and the body part impacted (e.g., angle of attack on the head, thorax)
- protection
- neck strength (proportion of the momentum transferred to the body mass).

Tissue Injury

Tissue injury thresholds depend on the following:

- Linear acceleration/deceleration resulting in contusions and coup/countercoup trauma.
- Rotational acceleration/deceleration resulting in shear stress (the most likely cause of axonal injury from axonal strains in white matter).
- Rotational velocity, which depends on Newton's Third Law (conservation of momentum), wherein a hit to the head that is not firmly supported by the body can result in an almost instantaneous velocity higher than that of the attack. A rotational acceleration causes motion of the skull relative to the brain and the resulting strains can rupture blood vessels and render axons dysfunctional. Strain tolerance thresholds of 10–15 percent have been suggested (Maxwell et al. 1997), but this figure may vary widely as different tissues have different material properties and the amount of strain depends on both the maximum applied stress and the stress rate (Donnelly and Medige 1997).
- The material properties of brain tissue: the brain does not compress, but it does distort. Metrics for brain tissue material behavior are characterized by a bulk modulus of 2.5×10^9 Pa (similar to water) and a shear modulus less than 10^4 Pa, or a force per area difference of 100,000. An analogy is the difference in force needed to compress a deck of playing cards vs. that needed to scatter them by an impact to the side of the deck.
- Variability in shear moduli of brain tissues such as white matter, grey matter, vessels, and coverings. The membranes between the skull and brain—the dura mater, arachnoid structure, and pia mater—have different material properties and are key components involved in brain injuries because they support blood vessels that traverse the space between the skull and brain surface. A rotation of the brain relative to the skull can rupture these vessels. Pressures (positive and negative) can in principle lead to vascular leaks that have not yet been carefully investigated.

Events at the Neuron Level

Diffuse Axonal Injury

Axonal injury is believed to be a primary mechanism responsible for TBI-induced impairments (Smith et al. 1999, and Smith paper in this issue). Diffuse axonal injury (DAI) was first reported in collision-based injuries with limited periods of survival and in autopsy findings of disrupted white matter tracts and normal grey matter (Strich 1956, 1961). Nondisruptive or reactive axonal injuries manifest over long periods and are ascribed to axonal membrane damage. Morphological study of axonal injuries using nonhuman primates subjected to head acceleration has shown that shear forces create varying degrees of axonal damage including fragmentation, although animal models do not accurately reflect spatial and temporal patterns of axonal injury in the human brain (Maxwell et al. 1997).

Loss of Neuronal Functioning

Injuries to neurons are not from pressure itself but from neuronal stretches beyond the critical point (e.g., 10 percent) such that there is a loss of the electrical polarization needed for neuronal functioning and the neural membrane fails, opening channels and allowing a rush inward of sodium ions and calcium (Ommaya et al. 1994; Smith in this issue). The resulting osmotic

pressure causes swelling and a cascade leading to dysfunction of the neuron (figure 3).

The neuron functions by facilitating signals using a dynamic change in membrane potential that propagates along the neuron (to induce a nerve firing one has only to bump the elbow or be struck below the knee cap). If there is a loss of the resting membrane potential of −90 mV (established by the different concentrations of sodium, potassium, and chloride ions), the propagation fails. The failure of function after a blow to the head could be the result of a loss of the ability of neurons to maintain the membrane potential. The recovery of that potential might be one second or several days (e.g., coma). If there is an electrical discharge of all or many of the nerves in the brain, brain enzymes need to reestablish membrane potentials for the system to, in effect, reset. Thus at the time of a concussion one would expect loss of nerve reflexes, and that is exactly what was found in the first extensive animal experiments designed to determine the physiology of concussion (Denny-Brown and Russell 1941).

Methods to Study Brain Injury

Sensors to Measure Impact Forces

Understanding of concussion requires knowledge of the characteristics of the physical forces transmitted to the brain. To that end, sensors attached to a helmet, headband, skullcap, mouthguard, or athlete's head were introduced 40 years ago (Moon et al. 1971; Reid et al. 1971). Studies with instrumented helmets to determine the severity of forces involved in football impacts (Rowson et al. 2009) led to the commercial accelerometer-based Head Impact Telemetry (HIT) System (Simbex, Lebanon, NH), now mounted in football helmets and used to directly measure the head's linear and rotational acceleration and the helmet impact location without interfering with normal play. Position, magnitude, and trajectory can be calculated for an assessment of the impact history of each player (figure 4).

Studies have gathered impact data from helmet sensors used in elementary, high school, and collegiate football. At the elementary level, no concussions were detected in 3,059 recorded impacts (Young et al. 2014). At the high school and collegiate levels, a study of 289,916 hits to 449 players reported 17 diagnosed concussions and found that a concussion could be predicted with 75 percent accuracy from hits over 96 g in force (Greenwald et al. 2008). Concussion is also a concern for female collegiate ice hockey players (Wilcox et al. 2015).

The sensor technology can be used in all sports activities, and the data can inform biomechanical assessments linking head impact to clinical outcomes of concussion (Crisco et al. 2012; Greenwald et al. 2008; King et al. 2015).

Animal Models to Determine Injury Thresholds

Animal models can provide a controlled laboratory setting to investigate relationships between the risk of concussion and rapid head rotation magnitude and

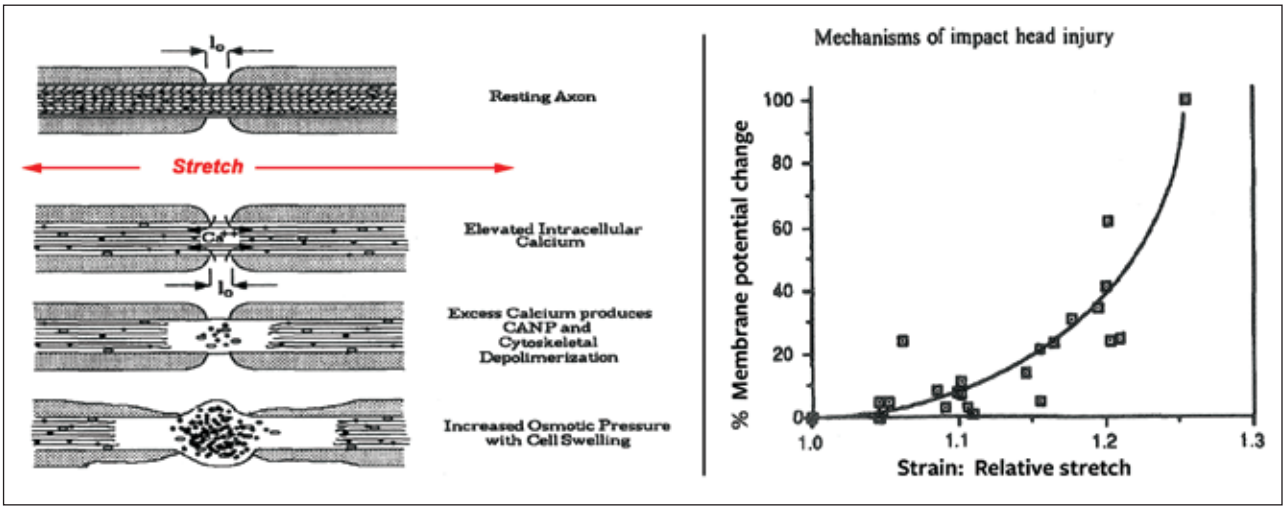

FIGURE 3 Left: Graphic depiction of events occurring in axons under shear stress. The stress disrupts membranes, resulting in ion concentration changes that lead to a loss of membrane potential and thus of nerve conduction. Right: Loss of membrane potential due to a stretch where the first decrease in membrane potential is seen at a 5% stretch and a 50% reduction at a 20% stretch. The critical strain for most tissues of the brain is 10%. CANP = calcium-activated neutral protease. Reprinted with permission from Ommaya et al. (1994).

direction, as well as the contributions of age, sex, and previous injury to the biomechanical thresholds for concussion. Animal model–derived biomechanical thresholds provide insight into how head impacts and sudden head movements produce brain deformations and how these deformations result in a spectrum of brain injuries. Methods proposed for human diagnosis are applicable to animal experiments and can enhance this direction of discovery.

The choice of the animal is important as it needs to have anatomy and tissue properties similar to those of the human brain. The rodent has relatively little grey matter; instead, swine and nonhuman primates make good models for head-hit or ballistic injuries. Pigs can be used for post-TBI behavioral, motor, memory, learning, and cognitive assessments and for determination of the importance of the direction of head rotation on head injury responses. They are a poor model for blast injury, however, as the head tissues provide much more protection than those of the human. Animal models are discussed in the papers by Margulies and Radovitzky and colleagues (see also Friess et al. 2009; Sullivan et al. 2013a,b).

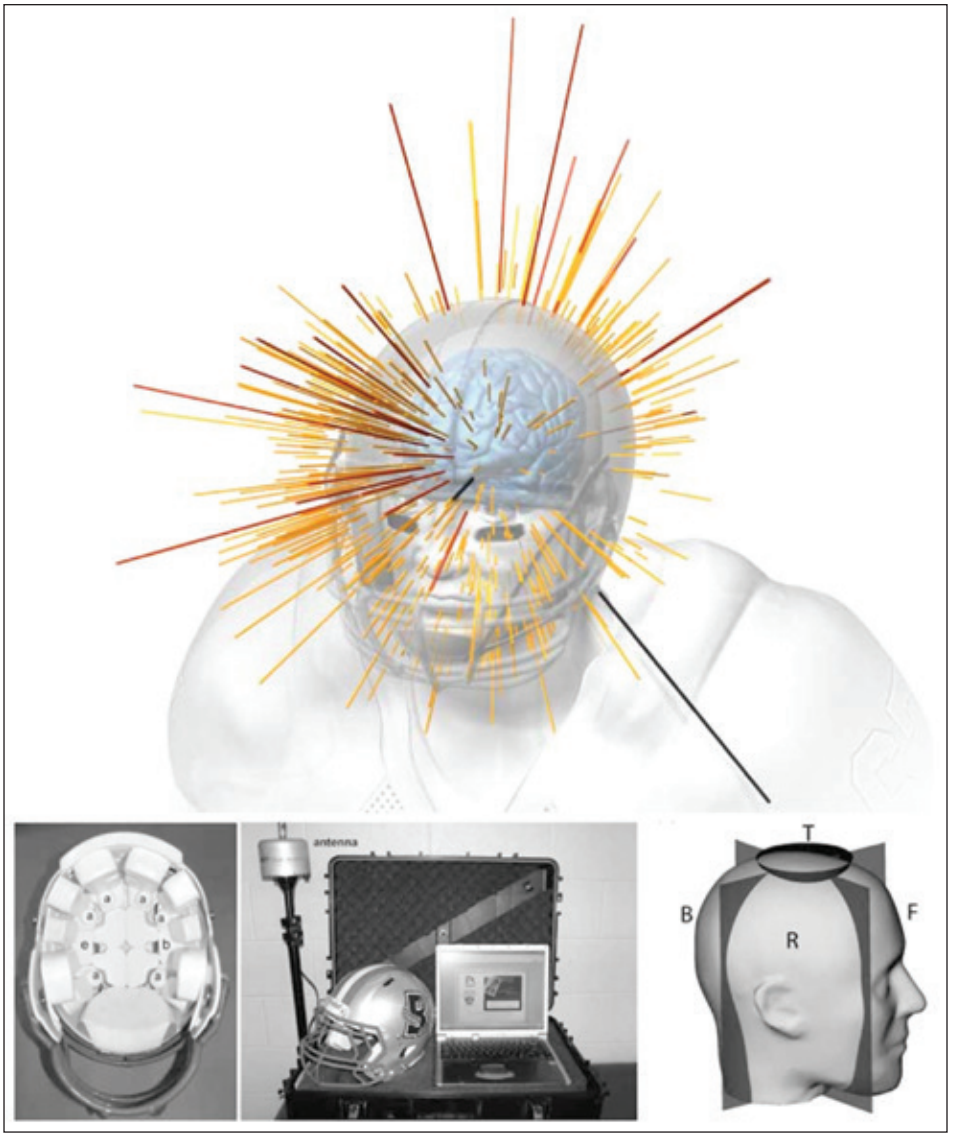

FIGURE 4 Helmets instrumented with accelerometers and wireless transmission equipment can provide information on the position, amplitude, and trajectory of each hit. Top: Graphic representation of mild (yellow), moderate (red), and two concussive (black) hits. Length indicates acceleration. Credit: Bryan Christie Design. Bottom: Instrumented football helmet with the Head Impact Telemetry System (HITS). Reprinted with permission from Crisco et al. (2011).

Extending results from animal studies to humans also requires proper scaling of the data from animals with brain masses 10 times smaller than the human brain and with head tissue that provides relatively more protection from impacts (cf. Radovitzky et al. paper). In addition, factors must be included to account for changes in brain tissue material properties with age and sex as well as differences in tissue properties between animal and human brains.

Computer Simulations and Modelling

There has been significant progress toward developing the basic science, algorithms, simulation software, and hardware infrastructure to study the complex problem of brain injury, but the full potential of computer modelling and simulation for enhancing understanding of injury biomechanics and the design of protection systems is yet to be realized.

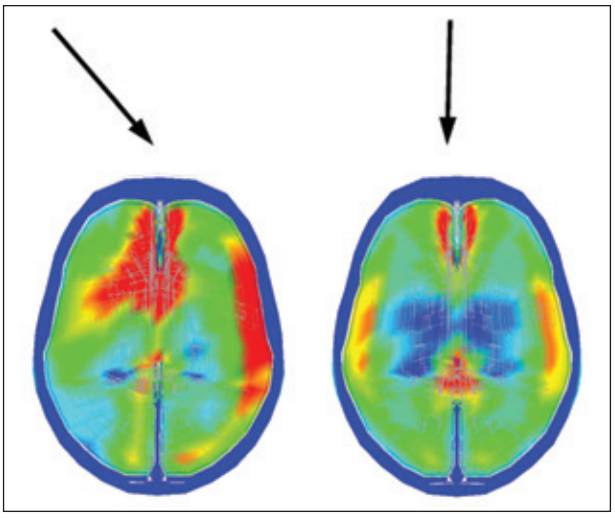

FIGURE 5 Finite element computer simulation for nonpenetrating ballistic hits to a military helmet. Principal strains in simulated brain material from projectile-induced kinetic energy striking a helmet at two angles. Blue is 0%, green is 2%, and red is >4% relative change in length or tissue stretch. Reprinted with permission from Aare and Kleiven (2008).

Modelling and simulation of human injury biomechanics are needed because tests cannot be conducted on the living human system, and cadaver studies cannot give reliable results because of postmortem changes in tissue property and brain fluid. Animal testing and physical surrogates yield useful insights in some cases, but, as explained above, they do not provide adequate answers linking the characteristics of a head impact to the tissue injury. In vitro studies use applied strains and strain rates but these do not allow links to the actual forces of the impact. A simulation must include the correct ranges (force per area), rate, and duration of stress.

An example of computer simulations to show the dependence of tissue strains on the direction of a nonpenetrating bullet impact to a helmet is shown in figure 5. These computational simulations can be used to optimize the design of protective helmets for athletes, motorcycle riders, police, and soldiers.

Computer simulations to understand highway collisions and improve protection are used by the National Highway Transportation Safety Agency (NHTSA; see Michael paper). A Simulated Injury Monitor (SIMon) finite element head model uses vehicle dummy head kinematics as an input and calculates the probability of three types of injury: DAI, contusions, and subdural hematomas (Takhounts et al. 2003). An upgraded version of that system has used data from instrumented helmets on professional football players (Takhounts et al. 2008). A more recent study using a finite element model of the human head reported the dynamic response of the brain during the first milliseconds after an impact with velocities of 10, 6, and 2 meters/second (m/s) (von Holst and Li 2013). The results show a dynamic triple maxima sequence: first, strain energy density, then intracranial pressure, followed by the first principal strain.

The main progress in computational modelling of traumatic physical effects on the central nervous system has been on blast-induced TBI. Blasts can cause significant levels of pressure, volumetric tension, and shear stress in focal areas in a short time, with stress patterns dependent on the orientation of the blast wave and the complex geometry of the skull, brain, and tissue interfaces (Moore et al. 2009; Panzer et al. 2012; Radovitzky et al., this issue). These studies showed that direct propagation of blast waves into the brain through soft tissues (eyes, sinuses) was the main mechanism of energy transfer from the shock wave and that blast stresses can cause concussion. Subsequently, a 27,971-element head model—with a brain, CSF, skull, dura mater, pia mater, and scalp, among other components (Chafi et al. 2010)—showed that blasts with overpressures of 243–881 kPa could cause concussion and DAI.

However, simulation strategies are limited by poor spatial resolution. Moreover, the relative motion of the brain and skull is not modelled correctly without a volume element resolution less than 2 mm, and inclusion of the anatomy and correct gauge of the material properties of vessels and other connective tissues between the brain surface and the skull.

Diagnosis of Concussion

Posttraumatic Stress Disorder vs. Traumatic Brain Injury

First it will be helpful to distinguish between concussion and posttraumatic stress disorder, which is not necessarily a long-term consequence of brain trauma. PTSD is the diagnostic term that evolved from abnormal psychological behavior related to battlefield stress; it also applies to the symptoms of patients who survived traumatic psychological experiences after which depression, anxiety episodes, social withdrawal, and other symptoms occurred without evidence of an organic cause. According to the APA definition, PTSD is caused by a psychologically traumatic environmental event, with the assumption that any accompanying biological abnormality must also have been traumatically induced. The development of PTSD also depends on the severity or existence of geneti-

cally based, disease-induced, or drug-related neurochemical and neuroanatomical abnormalities.

The complexities of PTSD, particularly in veterans returning from war zones, result in variable correlations between histories of battlefield stress and concussions from blasts or collisions (cf. Ruff paper). An extensive review provides evidence for the neurochemical and neuroanatomical basis of PTSD (Pitman et al. 2012).

Clinical Evaluation

At the time of a concussive event, trainers, coaches, collision witnesses, data from instrumented athletes, and the victim's reports of symptoms can lead to a diagnosis, though frequently of variable reliability, particularly from a soldier or athlete who is anxious to return to fight or play. The promise of a threshold diagnosis from an instrumented helmet requires an understanding of the links between impact metrics and brain injury as well as knowledge of the threshold for concussion without loss of consciousness (LOC).

Diagnosis of concussion without LOC and postconcussion evaluations currently rely on multiple clinical "symptoms and signs" approaches with four components:

1. Cognitive: concentration, memory, information processing, executive function
2. Motor: reaction time, coordination
3. Vestibular: balance, dizziness, vision/oculomotor function
4. Physical: headache, neck pain, sleep disturbance.

To facilitate concussion diagnosis, posttrauma assessment, and overall management of athletes the Cleveland Clinic has developed an innovative multidisciplinary program that enables quantification of signs associated with these four components using available electronics in iPhones and iPads (e.g., accelerometers, optical methods, voice-guided protocols). The innovation is available as the Cleveland Clinic Concussion (C3) App (cf. Alberts paper).

Based on studies by Robert Ruff described at this symposium, there is also the possibility of a test to assess the olfactory capabilities of a concussed person. Decreased odor detection thresholds are very common in victims of mTBI (Ruff et al. 2012).

Cognitive Testing

A number of cognitive tests are available, some of them computer based and easily performed by the soldier or athlete before and after deployment or sports activities. Two methods appropriate for impact sport evaluations are the Sport Concussion Assessment Tool 3 (SCAT3) (Guskiewicz et al. 2013) and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) (Van Kampen et al. 2006).

Noninvasive Imaging

Magnetic Resonance Imaging (MRI)

MRI techniques for imaging the brain include structural MRI, functional MRI (fMRI), diffusion-weighted MRI, and magnetic resonance spectroscopy (MRS). Structural MRI reveals anatomic detail that is useful in cases of severe brain trauma, intracranial bleeding, and edema, but it is generally not considered useful for diagnosing mTBI or as a diagnostic method immediately after a concussive event.

The use of fMRI to assess brain blood flow responses to cognitive challenges before, during, and after football play has shown remarkable changes in high school athletes (cf. Talavage paper). As an example, figure 6 shows a decline in brain responsiveness to a cognitive test or stimulation (indicated by blood flow amount and distribution) after football playing in an athlete who was not diagnosed with a concussion (Talavage et al. 2014).

MRI diffusion tensor imaging (tractography) allows calculations and image presentations of the principal directions of the major nerve tracts (oriented axons) in the brain and has shown disruption in the normal pattern of tracts. Diagnostic use with TBI patients has shown remarkable success (Tong et al. 2003; van Boven et al. 2009), but the method is expensive and resolution is limited, although it will improve when magnets with field strengths above 14 Tesla become available (Budinger et al. 2016). This method is applicable to evaluation of the long-term consequences of multiple concussions and provides a means of associating brain connectivity changes to behavior.

Functional connectivity density mapping (FCDM) uses fMRI data to calculate short- and long-range FCD (Caeyenberghs et al. 2015). This method has had success in comparing the circuit connectivity of patients with traumatic axonal injury (TAI) with controls using a stimulus protocol, the sensory organization test (SOT). There was significantly increased short-range FCD in frontal regions in the TAI group and significantly decreased long-range FCD in frontal and subcortical regions, and the latter was associated with lower balance ability. FCDM may thus be a valuable tool for selectively predicting functional motor deficits in TAI patients.

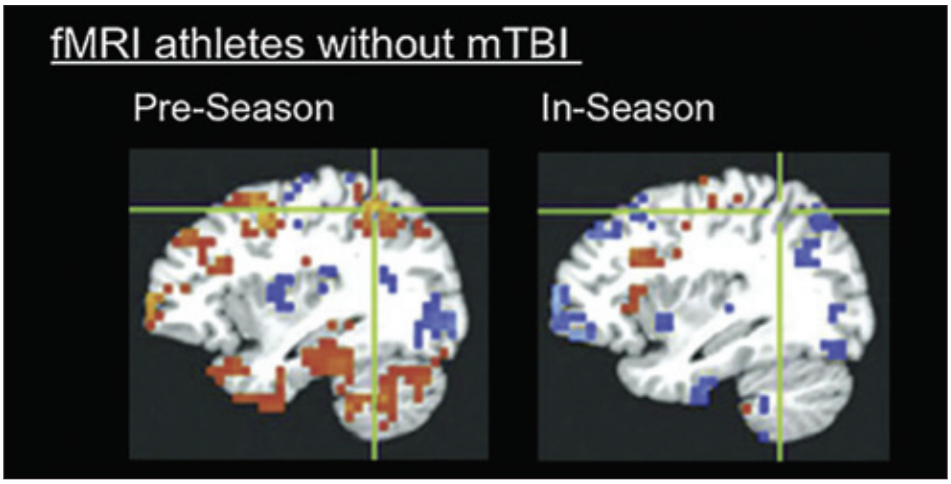

FIGURE 6 Functional magnetic resonance imaging (fMRI) study of a high school football player who did not have symptoms of a concussion, before (left) and during (right) the play season. Colored dots indicate regions of increases in the average level of blood flow during a working memory task as a function of task difficulty (red-yellow = harder, blue-cyan = easier). The in-season image shows that, after exposure to repetitive subconcussive blows, there is a marked loss of blood flow change as a function of task difficulty (cf. Talavage et al. 2014). Images provided by T. Talavage, E. Nauman, and L. Leverenz, Purdue University, with permission.

MRS has the unique ability to show the chemical content (neurometabolite) of specific regions of the brain. For example, a brain MRS study of 19 TBI vs. 28 control subjects showed significant changes in metabolites associated with neuron maintenance and energy metabolism over a 6-month period after concussion (Brooks et al. 2000).

Positron Emission Tomography (PET)

Studies of CTE using PET, with an [F-18]FDDNP tracer that accumulates at tissue sites where tau protein exists, show early involvement of the amygdala, thalamus, midbrain (figure 7), and other brain areas that participate in the processing of emotions, mood, and behavior (Barrio et al. 2015; Small et al. 2013). The PET tracer detects phosphorylated tau (p-tau) protein deposits analogous to the tau protein immunostain results from neuropathologists on brain tissue slices as shown in the McKee, Perl, and Kovacs papers. PET imaging studies in 14 CTE subjects showed intense uptake in the amygdala, several areas of the frontal cortex (the anterior cingulate gyrus, medial thalamus, hypothalamus, and dorsal midbrain), but no significant uptake in normal subjects or Alzheimer's patients (Barrio et al. 2015).

PET may prove useful for noninvasive imaging of brain inflammation (figure 7, right). Injury to any tissue in the body results in release of cytokines that signal circulating cells and the immune system to commence repair. This leads to inflammation, which is expected to occur in the brain after an injury (further evidence for inflammation after brain trauma comes from autopsy data). More than 3 months after injury, TBI cases displayed extensive, densely packed, reactive microglia, indicative of inflammation, whereas there was no inflammation in control subjects or acutely injured cases (Johnson et al. 2013). Reactive microglia and inflammation were present in 28 percent of cases with survival up to 18 years posttrauma, and accompanied with ongoing white matter degradation.

PET imaging has not yet been used to assess concussion, but a clinical trial could yield important new information about diagnostic and prognostic potentials as well as the potentials for nonsteroidal anti-inflammatory treatment of mTBI.

Electroencephalography (EEG)

Advances in the measurement of EEG signals from the brain have been incorporated by the Department of Defense (DOD) for a primary assessment of TBI as an indicator for further evaluation (cf. Hack paper). Quantitative EEG has been shown to be highly sensitive (96 percent) in identifying postconcussion symptoms (Duff et al. 2004).

X-Ray Computed Tomography (CT)

There are no reliable diagnostic patterns for CT use with an asymptomatic victim, unless skull fracture is suspected. However, in cases with progressive physiological signs and loss of consciousness after an alert period, CT can show progressive edema and even hemorrhage. But it is not the preferred brain imaging method for diagnosing brain trauma in the conscious victim.

Brain Tissue Injury Serum Biomarkers

Serum levels of most brain proteins are elevated after concussion, and several have reasonable diagnostic accuracy for distinguishing concussion from

nonconcussion (cf. paper by Bazarian). The use of brain imaging to identify levels of S100B, UCH-L1, and GFAP can also predict which concussed patients will have intracranial hemorrhage, early detection of which can be lifesaving. And levels of alpha-II spectrin and p-tau predict postconcussion outcomes such as symptom reduction and timing of return to sports. S100B is used clinically in several European and Asian countries to determine whether an X-ray CT scan should be done; its use in the United States awaits approval by the Food and Drug Administration (FDA).

Serum markers are useful for determining the prognosis and return to normal status of a known concussed individual. But they lack specificity, as aerobic exercise and injuries outside the brain can lead to elevations of these markers of tissue injury; they have not been tested in the first hour after a potentially concussive event; and normal serum levels vary widely among individuals, necessitating pre-event baseline studies.

Hypopituitarism

Chronic hypopituitarism is defined by deficient production of one or more pituitary hormones at least one year after injury. The diagnosis is made by measurement of one or more of the pituitary hormones using serum samples. The incidence of hypopituitarism related to TBI is discussed under Late Effects of Brain Trauma.

Postmortem Brain Pathology

The concussed brain exhibits global atrophy, decreases in volume of specific brain regions (e.g., hippocampus, corpus callosum), and an increase in ventricle volumes. The brain pathology of CTE (cf. McKee et al. 2010, 2013; Omalu et al. 2006) is similar in some respects to that of other forms of dementia (e.g., cerebral atrophy and enlargement of the ventricles) but is distinguished from them by the deposition of p-tau protein in a unique pattern in the brain by immune staining on tissue sections (cf. McKee paper; figure 7).

PET imaging may be useful for in vivo imaging and diagnosis of CTE, but, as a method to monitor progression and evaluate proposed therapies, it must be used well before behavioral symptoms and balance deteriorations are observed.

Late Effects of Brain Trauma

CTE and Other Neurodegeneration

Chronic traumatic encephalopathy develops insidiously many years after exposure to repetitive brain trauma. It is characterized by one or more of the following symptoms: depression, paranoia, impulsivity, rage, headaches, coordination problems, dysarthria, gait changes, and defects in memory (Stern et al. 2013).

Second impact syndrome (SIS) occurs when a person who has sustained an initial head injury, usually a

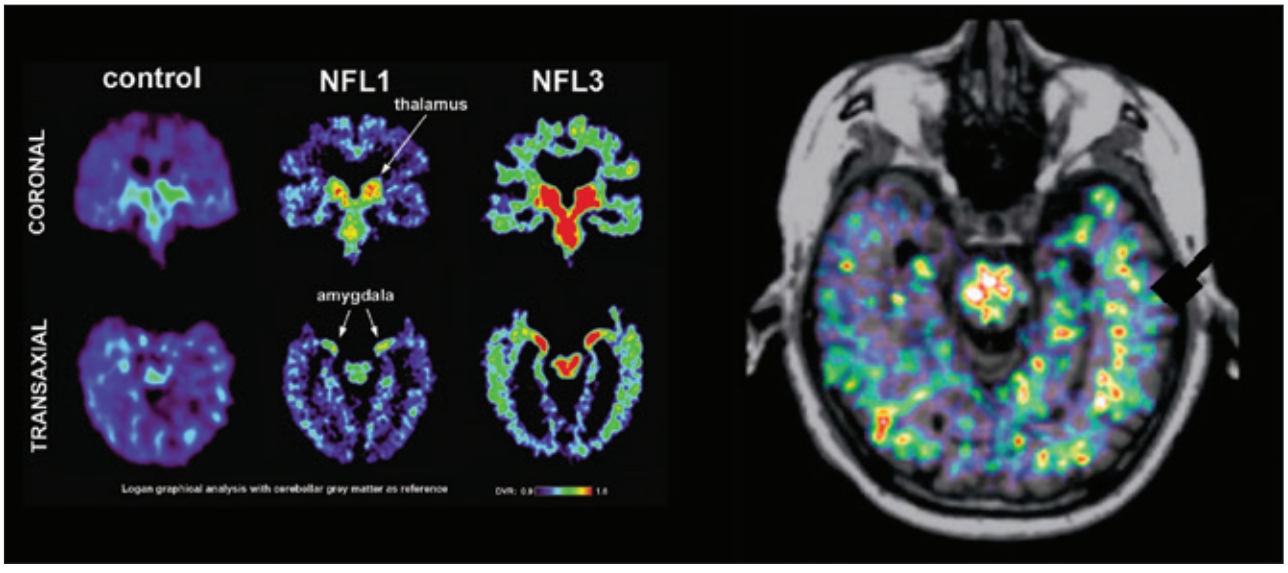

FIGURE 7 Positron emission tomographs (PET). Left: A tracer shows phosphorylated tau protein deposits in the thalamus and amygdala of two living NFL players. These are the same areas where deposits are seen at autopsy. Right: Brain inflammation shown through the use of a tracer for the peripheral benzodiazepine receptor complex of activated microglial cells of an Alzheimer's disease patient. Red = high, yellow = intermediate, and green = low uptake; blue = normal background. Left image set reprinted with permission from Small et al. (2013); right image reprinted with permission from Cagnin et al. (2007).

concussion, sustains a second head injury before symptoms associated with the first have fully cleared (e.g., Cantu and Hyman 2012; Guskiewicz et al. 2003; Young et al. 2014). Since the late 1990s it has been recognized as an eventual cause of death in 50 percent of cases. Most commonly reported in football, SIS can occur during any sport that can produce head blows; in the 1920s brain degeneration from repeated blows to the head was noted in boxers (*dementia pugilistica*).

The phenomenon of SIS has called attention to the consequences of multiple minor head trauma events in youth sports and the possibility that repetitive minor hits *without symptoms of concussion* can result in the neurodegeneration of CTE decades later. All youths involved in impact sports are at risk.

Basal Brain Structures

There are a number of structures in the base of the brain whose functions are involved in cognitive, psychological, and behavioral changes related to impact head trauma, blast trauma, and PTSD. The anatomy of most of these components is shown in a sagittal section drawing of the brain along with an inset picture of the skull base (figure 8). The amygdala, cingulate gyrus, corpus callosum, hippocampus, hypothalamus and pituitary, olfactory bulb, prefrontal cortex, and putamen show evidence, both at autopsy and by in vivo MRI and PET, of anatomical and functional defects. A few examples illustrate the involvement of these areas in brain trauma and its long-term consequences.

Amygdala–Medial Prefrontal Cortex

The amygdala plays a critical role in processing emotion and mediating fear. Imaging studies in PTSD patients have revealed decreased neural activity in the medial prefrontal cortex (mPFC), which modulates the amygdala, and simultaneously increased amygdala activation (Francati et al. 2007; Shin et al. 2005). An uninhibited or overactive amygdala results in an excessive state of fear and anticipation of fear (Pitman et al. 2012; Whalen 1998).

Hippocampus

Hippocampal volume measurements using MRI can aid in evaluating the progression of previous traumatic brain tissue injuries. Anatomic MRI and quantitative volumetric analysis reveal diminished hippocampal size in patients with mild cognitive impairment (MCI) relative to controls (Jack et al. 1999; Seab et al. 1988). The diminished size was not correlated with overall brain atrophy due, for example, to aging. Stress-induced damage to the hippocampus has been shown in persons with PTSD (Bremner 2001), as has post-TBI loss of neuronal layers in the hippocampal pyramidal layer (Maxwell et al. 2003).

Hypothalamus and Pituitary

The hypothalamus is a major site of deposition of p-tau protein detected via PET imaging in NFL football players and at autopsy in football players, war veterans, and boxers. An essential function of the hypothalamus is the production or stimulation of eight hormones from the pituitary. These hormones are essential for the functions of other organs (e.g., thyroid, adrenal glands, breasts, uterus, gonads) as well as growth, lipid metabolism, and some aspects of behavior.

As many as 40 percent of subjects who have sustained blunt brain trauma have some symptoms and signs of compromised pituitary function (Bondanelli et al. 2005). In contrast, the prevalence of hypopituitarism in the general population is estimated at 0.03 percent. A major symptom of hypopituitarism in 15–20 percent of patients is a decrease in growth hormone (GH), frequently associated with PTSD symptoms (Kelly et al. 2006; Powner et al. 2006). TBI patients also develop gonadal hormone deficiencies, 10–30 percent develop hypothyroidism, and many experience chronic adrenal failure because of low adrenocorticotropic hormone (ACTH) secretion from the pituitary. Adolescent and pediatric patients with TBI have a high incidence of GH deficiency and hypogonadism (Aimaretti et al. 2005).

Incidence and hormonal deficiency patterns differ between victims of blast injury and blunt trauma, with a prevalence of 32 percent vs. only 3 percent, respectively, but the numbers studied were only 13 and 38, respectively (Baxter et al. 2013). In another study 42 percent of veterans with blast injuries showed abnormally low levels of at least one pituitary hormone (Wilkinson et al. 2012). The dysfunction might not be from injury to the pituitary itself; its function is dependent on the health of the hypothalamus, a region known to exhibit pathological changes from brain trauma. (Links between brain trauma and pituitary pathology have not been reported, probably because neuropathologists do not receive the pituitary with the brain; Ann McKee, personal communication, 2015.)

Research on the functioning of the human hypothalamus-pituitary system is important because hormones

play a vital role in everyday functioning, from social behavior to neuronal dendritic growth (Cheng et al. 2003). Hormonal deficiencies can be treated.

Putamen

The putamen is involved in executive function, motor control, learning, and, of relevance to mTBI late symptoms, the "hate circuit"—it plays a role in brain activity associated with contempt and disgust (Zeki and Romaya 2008). It is important in the study of TBI because abnormalities have been found in psychopathic individuals (at autopsy as well as through in vivo PET imaging of asymmetric metabolic function; Budinger patient archives, figure 8).

Treatment

There are no FDA-approved diagnostics or therapies for TBI, and more than 30 clinical trials of pharmaceutical products to treat it have failed. There are no agreed protocols other than rest and progressive return to work or

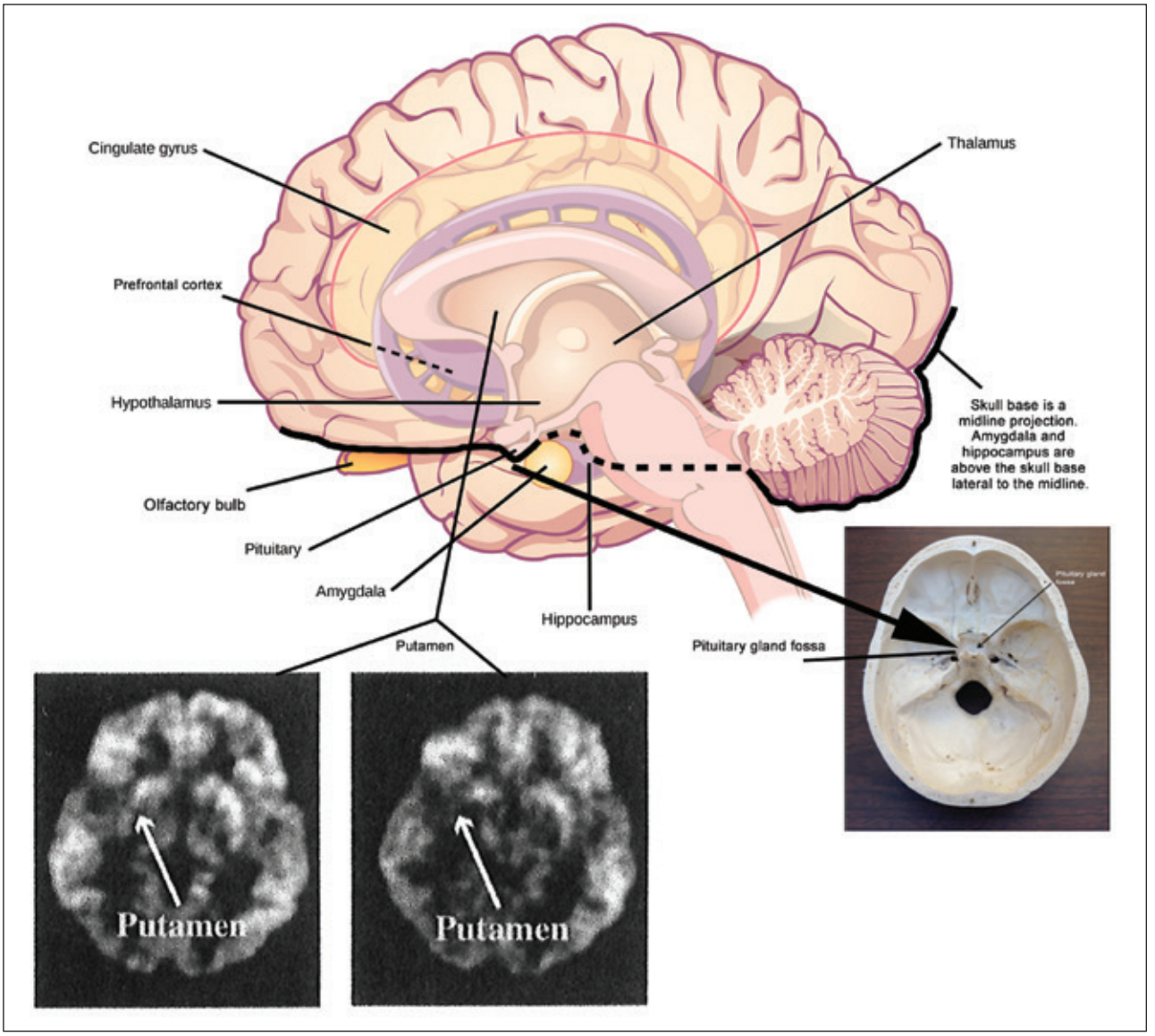

FIGURE 8 Top: Drawing of a sagittal section of the human brain showing many of the brain regions with long-term pathological consequences years after mild brain trauma. Right inset: The bony structure supporting the base of the brain. Left lower images show metabolic deficiency in the right putamen of a violent criminal using fluorodeoxyglucose positron tomography. The putamen is a region of known pathology in brain trauma. Sources: Biology, OpenStax CNX (February 20, 2014), available at http://cnx.org/contents/185cbf87-c72e-48f5-b51e-f14f21b5eabd@9.20; and Budinger patient files.

play depending on symptoms and signs. Even the determination of the level of rest is controversial.

Causes of the failed clinical trials seem now to have been recognized and there has been progress toward consensus on protocols and measurement methods through cooperation between the DOD, CDC, and FDA (cf. Hack paper). A major disappointment was the failure of progesterone as an efficacious drug in the final analysis, although some trials were successful. Diagnostic scoring sensitivity for the different grades of TBI and the associated heterogeneity of treated and controlled subjects are believed to be important issues for the cooperative group to resolve, as detailed in the Hack paper.

Anti-inflammatory drugs. There is evidence of brain inflammation based on PET imaging and elevated serum proteins as well as autopsy studies of patients who died as a result of blunt trauma to the head. If inflammation is involved (with or without headaches), an early treatment might be nonsteroidal anti-inflammatory drugs. More research is required.

Folic acid. Experimental trials have shown promising results using folic acid to enhance functional recovery in a piglet animal model of recovery after concussion from rotational accelerations (Naim et al. 2010).

Pituitary hormones. Hypopituitarism is easily treated using hormonal replacement regimes (e.g., growth hormone, ACTH, thyroid, oxytocin). But detection methods can be cumbersome. Detection of growth hormone deficits requires infusion of a stimulant such as insulin. Alternatively, a short period of interval exercise will cause an increase in growth hormone (Karagiorgos et al. 1979) that can be detected by a simple blood test before and after exercise.

Hypothermia. Hypothermia has not been successful in clinical trials as a treatment for severe TBI (Kramer et al. 2012), but this may be because the treatment was initiated several hours after brain trauma, whereas in successful animal trials it was initiated much earlier (Smith et al. 2013).

Conclusion

The causes, detection, prevention, and treatment of concussion are persistent challenges. The engineering disciplines of materials, mechanics, modelling, and simulation are needed in the work of physiologists, cell biologists, and clinicians dealing with concussion.

Government agencies (e.g., DOD, VA, NHTSA, DOT, NIH) and the NCAA are increasingly aware of the serious problem of head injuries from football, combat blasts, and vehicle collisions. However, there has been less emphasis on head injuries in pre–high school youths, although this is the largest population engaged in impact sports. The importance of long-term consequences of head injuries has become the focus of attention only in the last few years. The papers in this issue outline the myriad dimensions of concussion that require concentrated research to enhance understanding, prevention, and treatment.

Acknowledgments

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Effective care of concussion requires the coordination of both clinical resources and handoffs between providers.

A Multidisciplinary Approach to Concussion Management

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Jay L. Alberts

A significant challenge in the diagnosis and management of athletes and military personnel with concussion is the diverse background, training, clinical management approach and outcomes used by the multidisciplinary team of clinicians involved. Further challenging the continuity of care is the disparity of resources and access to technology and electronic health records available in the various settings in which concussion care and management occur—from the field to the emergency department and, finally, the clinical setting.

Effective care of concussion requires the coordination of both clinical resources and handoffs between providers (Broglio et al. 2014). A fundamental difficulty in this coordination is the use of discipline-specific measures of motor and cognitive function. In our research we used motor-control principles in the design of motor and cognitive assessments, and quantified the tests using objective biomechanical measures.

A Concussion App

Many mobile devices come equipped with a suite of inertial sensors (e.g., a linear accelerometer and gyroscope) as well as a capacitive touch screen, and so are ideally suited to transition from expensive electronic notebooks to handheld data collection systems. Using these capacities, we developed the Cleveland Clinic Concussion (C3) app to document injury in the field, facil-

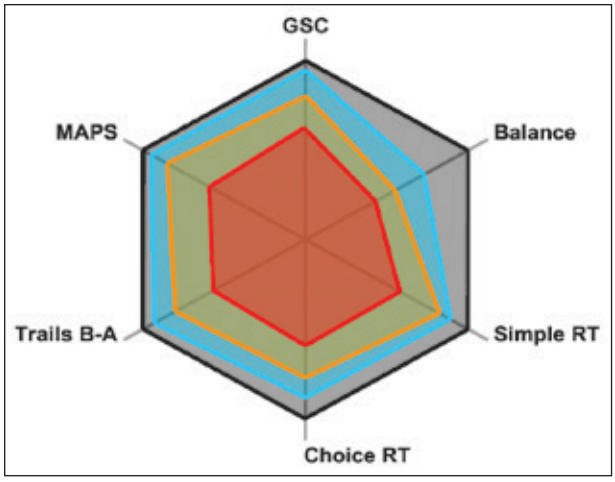

FIGURE 1 A representative performance polygon for an athlete before and after concussion. The perimeter represents this athlete's individual performance on each of the assessment modules as well as a graded symptom checklist. The red polygon represents the level of function 48 hours after injury. The yellow and blue outlines represent postinjury assessments at day 10 (yellow) and day 16 (blue). For this patient, they are nearly identical to the baseline measures, with the exception of balance. Assessments are based on the following tests: Trails B − A = time to complete trail making B test less completion time of test A; simple RT = one-choice simple reaction time; choice RT = two-choice reaction time; balance = composite biomechanical score from iPad measures during performance of all 6 BESS (Balance Error Scoring System) stances; GSC = performance on the Graded Symptom Checklist; MAPS = assessment of memory and processing speed.

itate the objective evaluation of the multiple domains of neurologic function affected by concussion, and document the return to play rehabilitation process. The C3 app contains an incident report module, five assessment modules for evaluating various aspects of neurologic function, and a return to play module (Alberts and Linder 2015; Alberts et al. 2015).

Operationally, athletes or military personnel complete a baseline evaluation at the beginning of a season or as part of their medical intake. The baseline data are used as a comparison for subsequent data collection sessions to guide treatment and return to play decisions by a multidisciplinary treatment team. If participants do not have a baseline, their information is expressed against age- and gender-based normative values. The assessments measure performance on the following tasks:

- a comparison of times to complete two trail making tests,
- one- and two-choice simple reaction times,
- the six Balance Error Scoring System (BESS) stances (Guskiewicz et al. 2001),
- the Graded Symptom Checklist,[1] and
- memory and processing speed.

Collectively, these modules allow for the systematic documentation of the injury and an objective measurement of the signs and symptoms associated with the injury over time. All of these data are then linked to a return to play module in which the athletic trainer or other member of the provider team systematically increases the aerobic demands of activity while monitoring symptoms and eventually creates simulated practice and game activities to aid in determining whether the athlete is ready to return to play. The ability to document and share the documentation related to the progression is critical from a patient management perspective as well as a medical-legal perspective.

The radar plot in figure 1 illustrates assessment based on these modules for a concussion patient in the days and weeks after injury. The perimeter of the polygon represents the baseline level on each of the domains evaluated. The red polygon represents the level of function in these domains approximately 48 hours after injury, the yellow polygon 10 days after, and blue 16 days postinjury.

In this case, the athlete has recovered in terms of symptoms and performance on tests evaluating neurocognitive functioning, but his balance, based on objective biomechanical data, is not back to normal. Because the patient is more than 14 days postinjury and has lingering postural instability, he would be considered a candidate for vestibular therapy. The vestibular therapist has access to the technology and the previous postural stability assessments, facilitating both the handoff between providers and the development of an effective rehabilitation plan of care.

To date, we have baseline tested more than 30,000 athletes and characterized more than 6,000 athletes with concussion using the C3 technology and concussion care path (Alberts and Linder 2015).

Beyond the App: Care Coordination

Technology is great, but its use requires people. We have been fortunate to have clinical buy-in and acceptance.

[1] This checklist is modelled after the Sport Concussion Assessment Tool, 3rd edition (SCAT3), available at http://bjsm.bmj.com/content/47/5/259.full.pdf+html.

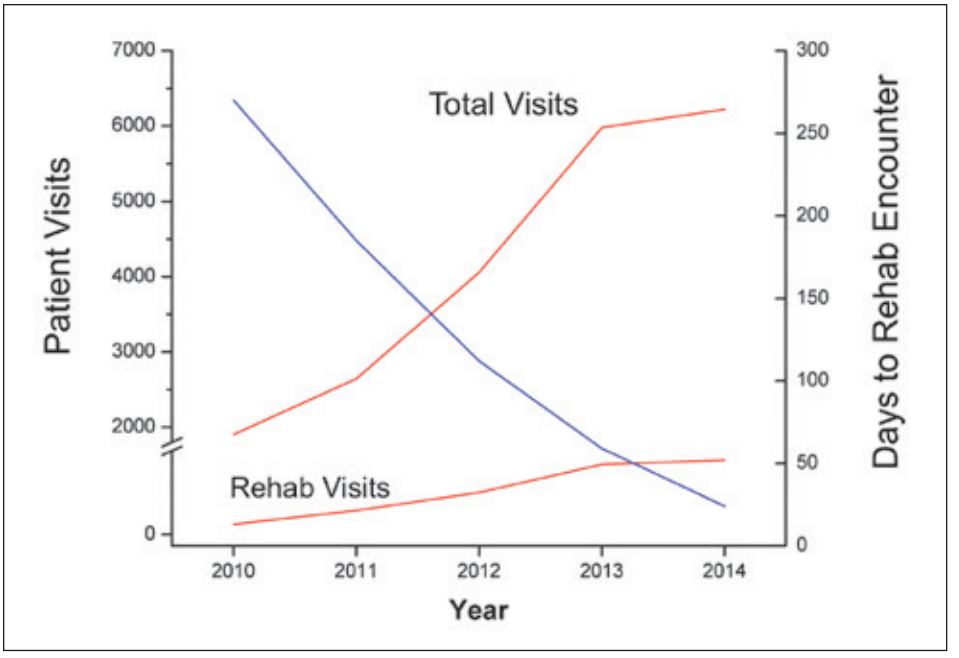

FIGURE 2 Number of total and rehab concussion patient visits, 2010–2014 (red lines, left y-axis), and number of days to first rehabilitation encounter (blue line, right y-axis).

An important tenet of clinical care is to get the patient to the right provider at the right time. Figure 2 shows the number of concussion patient visits and rehabilitation sessions (encounters) from 2010 to 2014 (red lines, left axis). Rehab encounters initially were very low in 2010, but there was a significant increase in 2013 and 2014, when the care path and C3 technology were released.

Importantly, as shown in figure 2 (blue line, right axis), the number of days to the first rehabilitation visit after seeing a physician decreased from more than 250 in 2010 to approximately 23 in 2014. Thus technology is helping to get the patient to the right provider at the right time.

Health care is undergoing a transition from volume to value; typically value is the quotient of outcomes over cost. Significant effort has gone into evaluating and attempting to reduce cost as a method of improving value. Enabling providers with affordable technology not only decreases cost but also, importantly, improves patient outcomes through a more efficient path of return to play or referral to specialty care. Both outcome and cost data are being evaluated in this model. It is hypothesized that the cost of care will decrease as unnecessary visits to other providers are reduced, unnecessary imaging is eliminated, and outcomes improve.

Conclusion

From a best practices perspective, a multifactorial assessment that includes a baseline helps to facilitate the return to play and the all-important return to learn process. Our approach combines immediate evaluation to discern any suspected concussion with postinjury serial assessments, and uses those assessments to assist in both clinical pattern recognition and treatment. Moreover, the mobile aspect of the system facilitates the engagement of the parent, coach, and school administrators that is critical for the safety and care of athletes.

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In the near future it may be possible to diagnose concussion with a simple blood test.

Can Serum Brain Proteins Aid in Concussion Identification?

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Jeffrey J. Bazarian

The current method of diagnosing a concussion on the athletic field, battlefield, or even in the emergency department is unreliable and likely inaccurate: It relies on self-report of symptoms from the person who is injured or from a witness, if there is one. The symptoms that indicate concussion are a brief loss of consciousness, period of amnesia, or confusion. There is no x-ray, blood test, or scan to help make the diagnosis.

Concussion Diagnosis: Shortcomings

The current method of concussion diagnosis has several obvious drawbacks. Someone hit on the head may not be able to recall the details of the injury precisely because the part of the brain that controls short-term memory is affected. Yet the patient's recollection of events is usually required to make the diagnosis. The conversation in an emergency department goes something like this:

Doctor: "Tell me what happened, Mr. Smith."
Mr. Smith: "I dunno, Doc. I have no idea."
Doctor: "All right. You clearly have a concussion. You can go home now."

It's hard for anyone to have confidence in a diagnosis of brain injury when this is how it is established.

Recollection of the events associated with an injury may also be altered by drug or alcohol use, or preexisting dementia, both common among patients

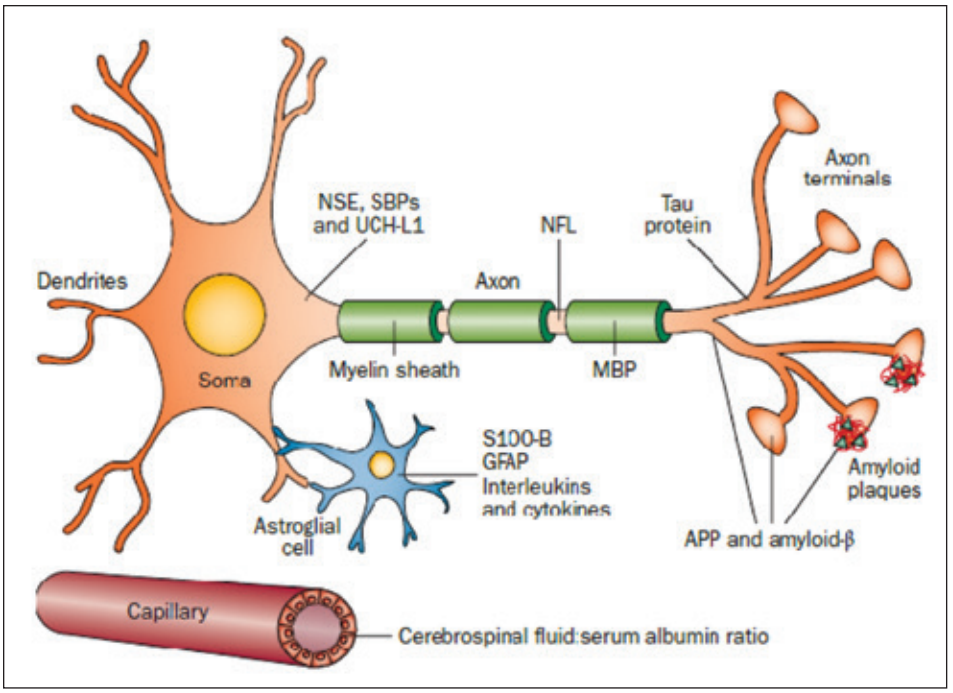

FIGURE 1 Concussion results in the release of proteins—from neurons (orange), astrocytes (blue), and oligodendrocytes (green)—that may be detected in the blood. APP = amyloid precursor protein; GFAP = glial fibrillary acidic protein; MBP = myelin basic protein; NFL = neurofilament light chain; NSE = neuron-specific enolase; S100B = S100 calcium-binding protein B; SBP = spectrin breakdown products; UCH-L1 = ubiquitin carboxyl-terminal hydrolase L1. Reprinted with permission from Zetterberg et al. (2013).

presenting to emergency departments. And how does one make this diagnosis in preverbal children? Finally, two patient groups, warfighters and athletes, may well remember injury events but not want to tell a healthcare provider because they want to be back with their unit or team.

Not surprisingly, given the current state of diagnosis, concussions are often overlooked. A recent study showed that a third of athletes did not realize they had a concussion (Meehan et al. 2013). This might be understandable given that most athletes don't have a medical degree. However, hospital-based healthcare providers don't fare much better: Three studies of head-injured patients presenting to emergency departments found that concussions were missed in 56–89 percent of cases (Delaney et al. 2005; De Maio et al. 2014; Powell et al. 2008)!

A Diagnostic Blood Test

Fortunately, help is on the way. In the near future it may be possible to diagnose concussion, also known as *mild traumatic brain injury (mTBI)*, with a simple blood test. Although still in the research stage, such a blood test could remove much of the doubt associated with trying to determine if a concussion has occurred.

After a concussion, proteins are released from the breakdown of the brain's primary cell type, neurons, as well as from supporting cells such as astrocytes and oligodendrocytes (figure 1). This process of axonal injury provides an opportunity to detect these proteins in the blood (Zetterberg et al. 2013).

The traditional thinking has been that proteins released during axonal injury diffuse into the space between brain cells (interstitial space), then into the fluid surrounding the brain (cerebrospinal fluid), and finally across the normally closed blood-brain barrier to reach the peripheral circulation, where they can be detected in a blood sample. Traditional thinking also held that a head blow hard enough to cause concussion also transiently opened the blood-brain barrier, allowing brain proteins to pass.

As it turns out, how proteins get from the brain into the blood may be a bit more complicated, which has implications for interpreting the results of a blood test in the context of a head injury.

It now appears that there is an alternative route for brain proteins to gain access to the blood, and it may sometimes be blocked during a concussion, preventing markers of brain damage from reaching the peripheral circulation. In this route, called the *glymphatic pathway*, brain proteins diffuse into the interstitial space and then into the brain's lymphatic system, which empties into the blood (Brinker et al. 2014; Plog et al. 2015).

Brain researcher Maiken Nedergaard of the University of Rochester determined that flow along the glymphatic pathway was reduced in mice that were sleep deprived and in mice subjected to repeated subconcussive head hits (Plog et al. 2015). These findings have important implications if they are confirmed in

TABLE 1 Status of research and development on key brain proteins as biomarkers of concussion

Marker	Brain cell of origin	Elevated after mTBI	Diagnostic accuracy	Predicts abn head CT	Predicts outcome	In clinical use +
S100B	Astrocyte	yes	yes	yes	no	yes
UCH-L1	Neuron	yes	yes	yes	equivocal	no
GFAP	Astrocyte	yes	yes	yes	equivocal	no
α-II-spectrin	Neuron	yes	yes		yes	no
Tau	Neuron	yes	yes		yes	no
NSE	Neuron	no			no	no
CKBB	Neuron	yes	no	no		no
MBP	Oligodendrocyte	yes	no			no
Aβ42	Neuron	no				no

Aβ42 = amyloid-beta protein 42; abn = abnormal; CKBB = creatine kinase isoenzyme BB; CT = computed tomography; GFAP = glial fibrillary acidic protein; MBP = myelin basic protein; mTBI = mild traumatic brain injury (concussion); NSE = neuron-specific enolase; S100B = S100 calcium-binding protein B; UCH-L1 = ubiquitin carboxyl-terminal hydrolase L1; + = in Europe, but not in the United States or Canada.

humans: Serum brain protein levels could be falsely negative among patients chronically sleep deprived or subject to repeated head hits—such as student athletes and warfighters.

Detecting Brain Proteins in the Blood

It has taken many years for scientists to develop techniques to detect the very low concentrations of brain proteins in the blood. Table 1 depicts the status of research and development on the key brain proteins currently under investigation. Several proteins, such as amyloid-beta protein 42 (Aβ42) and neuron-specific enolase (NSE), were found to be poor diagnostics of concussion and have not been studied further (Zetterberg et al. 2013).

The table shows that serum levels of most brain proteins are elevated after mTBI, and several of them—S100B, UCH-L1, GFAP,[1] alpha-II spectrin, and tau—provide reasonable diagnostic accuracy for distinguishing concussion from nonconcussion (Zetterberg et al. 2013). Only S100B is in use clinically, but not in North America. It is used clinically in several European and Asian countries, not for diagnosis but to determine who should undergo a computed tomography (CT) scan of the head.

Levels of S100B, UCH-L1, and GFAP can also predict which concussed patients will have intracranial hemorrhage on a head CT scan (Papa et al. 2012; Welch et al. 2016). Intracranial hemorrhage occurs in about 5–10 percent of mTBI patients, and early detection and neurosurgery can be lifesaving. So it is important for a putative marker of brain injury to be able to detect not only concussion but also the subset of concussed patients with intracranial hemorrhages.

Levels of alpha-II spectrin and tau appear to predict postconcussion outcomes such as symptom reduction and timing of return to sports.

Limitations of Brain Injury Markers

There are several limitations to the use of these proteins as brain injury markers. First, they are much more sensitive than they are specific, and their negative predictive value is higher than their positive predictive value. This may be because these proteins exist in small amounts in tissues outside the brain; for example, S100B is found in cartilage and fat cells, and tau in peripheral nerves. Thus, these markers are better at ruling out concussion (or intracranial hemorrhage) than ruling it in.

[1] S100B is S100 calcium-binding protein B, UCH-L1 is ubiquitin carboxyl-terminal hydrolase L1, and GFAP is glial fibrillary acidic protein.

Second, these markers have not been tested in the first hour after injury, which would be important for applying them in nonhospital settings such as the athletic field, battlefield, or scene of a mass casualty. Data on marker accuracy come from studies of marker levels in the 3- to 12-hour postinjury window, with a minority examining levels at 1 hour (Rothoerl et al. 2000; Shahim et al. 2014; Townend et al. 2006).

Third, the serum levels of brain markers tend to go up with physical exertion. The reasons for this are not clear, but this effect complicates interpretation of an increased level after an injury incurred during a sporting event or combat operation (Shahim et al. 2015; Stålnacke et al. 2003, 2006).

Finally, there is large interindividual variation in the serum levels of these proteins in normal, uninjured persons (Kiechle et al. 2014; Shahim et al. 2014). This fact complicates efforts to find a single cutoff value separating concussed from nonconcussed individuals.

Research Needs

These limitations need to be addressed if brain markers are to provide clinical value to the management of patients with head injuries.

The low specificity problem could be addressed by combining results from two or more proteins rather than a single marker.

The lack of information on marker accuracy within the first hour of injury requires research on blood samples obtained immediately after injury, which may be most practical in athletic settings.

Determining the effects of physical exertion on marker levels would be a simple matter of serum sampling at various time points after aerobic activity.

Finally, the difficulty in defining a single postinjury cutoff might be addressed by obtaining preinjury marker levels and then examining changes from baseline, rather than a single postinjury value. Of course, this solution will help address the problem only in patient cohorts where a baseline is obtainable, such as athletes and perhaps warfighters.

In terms of actual implementation, moving brain markers into clinical use in the United States would require approval by the Food and Drug Administration. And the development of point-of-care devices would be necessary for these tests to become part of return to play decision making on athletic fields across the country.

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Rule changes, neck strengthening, and education can all help reduce the risk of concussion on the playing field.

Opportunities for Prevention of Athletic Concussion on the Playing Field

Robert C. Cantu is medical director of both the Cantu Concussion Center at Emerson Hospital and the National Center for Catastrophic Sports Injury Research.

Robert C. Cantu

A person can have functional abnormalities of the brain in the absence of symptoms and a diagnosis of concussion. This creates particular risks for athletes, as injury may go undetected during and even after a drill or game.

What can be done to reduce the risk of concussion and subconcussive head trauma among athletes? There are four main areas to consider in such efforts: protective equipment, increasing the neck strength of athletes, changes to game and practice rules, and education to modify behavior and exposure.

Helmets and other protective headgear can attenuate the highly focal, linear impacts that lead to skull fracture, concussions, and intracranial bleeding, but they are not very effective in reducing rotational accelerations. The human brain is highly sensitive to injury from rotational impacts, but no helmet has been designed that can dampen shear stresses from such impacts. For this reason helmets will likely never be the major way to reduce concussions.

Neck Strength

Can increased neck strength and bracing for impact reduce the likelihood of concussion? At the most basic level, collisions are governed by Newton's second law: force = mass × acceleration. If a small mass is hit with a given force, a significant acceleration will occur, compared to a large mass hit with the same force. Hits of over 20 g in acceleration of the head can occur in

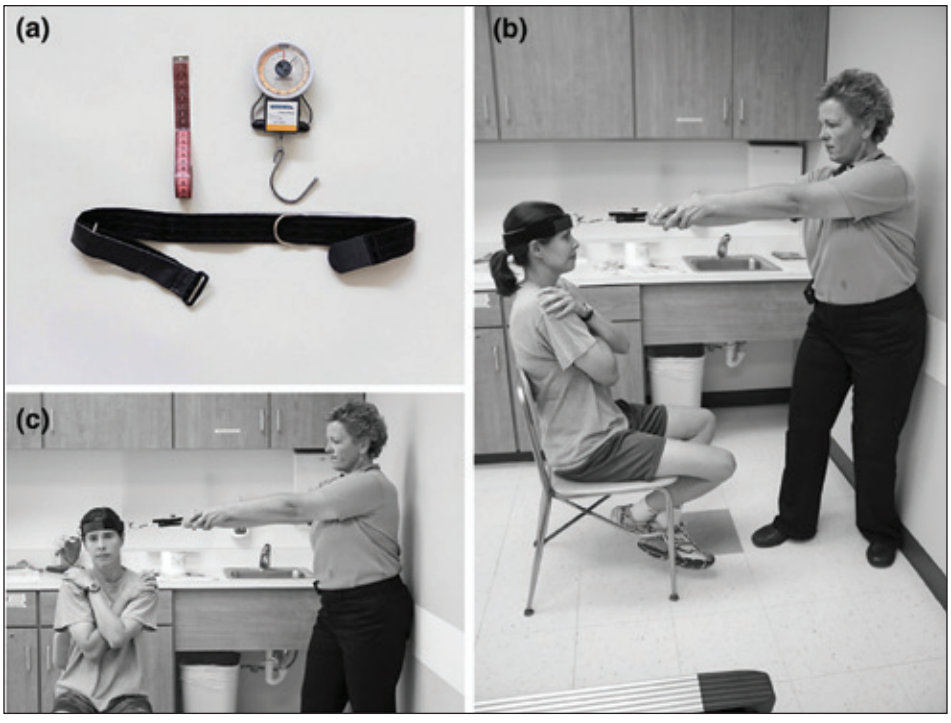

FIGURE 1 (a) Hand-held tension scale and Velcro adjustable head strap with a D ring. (b) Demonstration of proper measurement of neck extension with the developed neck strength measurement tool. (c) Demonstration of proper measurement of right lateral flexion. Reprinted with permission from Collins et al. (2014).

the act of tackling or being tackled. Increasing the mass can decrease the acceleration that causes concussion.

Two populations at increased risk for concussion are women, who have roughly two to three times the incidence of concussion in the same sports men play, and youth. Both tend to have weaker necks than adult men.

Strengthening the neck—by increasing its girth and stiffness—and bracing for impact protect the head by connecting it more solidly to the rest of the body. The acceleration of the head upon impact is reduced as the incoming force meets a resistance more comparable to the mass of the body rather than the small mass of the head (i.e., conservation of momentum).

We recently conducted a study that showed that athletes with the greatest neck strength had the fewest concussions, and those with the least had the highest number of concussions (Collins et al. 2014). We found that, adjusted for gender and sport, essentially one pound of increased neck strength decreased the odds for a concussion by 5 percent.

Neck strength can be reliably measured with a very inexpensive device and minimal training (figure 1). Adding neck strengthening exercises to training regimens could be a viable and attainable part of a concussion reduction plan for athletes.

Game and Practice Rules

The incidence of concussion can be reduced by rule changes, especially those that reduce hits to the head. Such rule changes are being adopted or considered for both professional and youth athletes.

Changes in the NFL

Concussions and subconcussive blows can be dramatically reduced in helmet-to-helmet collisions by limiting full contact in practice. The NFL allows 14 full contact practices during the 18 weeks of the season—less than one a week—and none in the off-season.

Another significant new NFL rule prohibits above-the-shoulder hits to a "defenseless player," defined as a player who cannot see the approach of the impact. Penalties range from 15 yards to fines and removal from the game, depending on the circumstances. The ability of a player to brace for impact, for example by engaging neck strength, is crucial to prevent brain injury.

A further factor in reducing the incidence of concussion is moving the kickoff up to the 35-yard line. The kickoff runback is recognized as the most dangerous play in football (per seconds of play). As a result of this change the ball is run back less than 50 percent of the time, eliminating half of these risky episodes.

During practice, tackling drills in which the player is not taken to the ground or a robot is used also reduce concussion risk.

Thanks to these changes, a comparison of annual data from the National Football League (NFL)[1] shows a 25 percent reduction in concussion incidence from 2013 to 2014 (the concussion rate per game in the NFL was 0.43 in 2014). And concussions from helmet-to-

[1] I serve as a senior advisor to the NFL's Head, Neck, and Spine Committee.

helmet hits, the most common cause of concussion, declined 28 percent from 2013 to 2014. From 2012 to 2014 season concussions went down 43 percent.

Changes for Youth Athletes

A program called "Practice Like the Pros" can decrease the risk of brain trauma for young athletes by bringing some of the improved professional football conventions to youth and college athletes. The program minimizes the risk of injury in practice by tackling without bringing the opponent to the ground.

Education can reduce the incidence of subconcussive and concussive trauma by teaching athletes to develop an awareness of their own concussion risk and alter their behavior accordingly. They may choose to play fewer or different sports, modify their hours of practice, or change their style of play.

Rules that limit the number of hits to an athlete's head in a week, month, or season can also reduce the incidence of head trauma. It is ironic that there are pitch counts in youth baseball to prevent ulnar collateral ligament injuries, which are reparable, but not hit counts to the head (in football or any other sport) to lower the risk of traumatic brain injury. Hit counts have been shown to work.

In one study of three youth football teams (ages 9 to 12), one team had an average of 145 hits during the season, while another was as low as 61 (Cobb et al. 2013). The difference between the teams was the way the coach ran the practices and taught tackling techniques.

Summary

Protective equipment has not been proven to significantly reduce overall concussion risk. Instead, a number of behavioral and rule changes can improve protection from head injury. Neck strengthening and bracing for impact can protect against brain trauma. Changes in the NFL's competition play rules can reduce injuries substantially. And athletes can modify their exposure and behavior through education. As with any change, each risk strategy must be carefully examined to prevent unintended consequences that result in other types of injury.

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Regulatory science is inadequate, but is a reflection of the state of the more general science in the field of TBI.

TBI Clinical Trials

Past, Present, and Future

Dallas C. Hack is former director, Combat Casualty Care Research Program, US Army Medical Research and Materiel Command.

Dallas C. Hack

More than 30 clinical trials of pharmaceutical products to treat traumatic brain injury (TBI) have failed and the US Food and Drug Administration (FDA) has not approved any diagnostics or therapies for TBI.

Since 2007 the Department of Defense (DOD) has been the largest funder of TBI research. However, any policy recommending use of unapproved regulated medical products can be approved only by the president. The repeated trial failure has had a direct impact on the DOD's ability to field regulated products for the care of servicemembers who suffer a TBI, whether in combat or in training.

Background

Traumatic brain injury is a continuum of heterogenic insults to the subcellular and cellular structure. The current approach using the Glasgow Coma Scale (GCS) to categorize TBI is the equivalent of describing cancer as mild, moderate, and severe and then expecting that one treatment will cure all cancer.

The use of progesterone to treat TBI has been researched extensively, with more than 200 preclinical studies as well as successful phase I and phase II trials. Yet two high-profile clinical trials to validate the use of progesterone as a treatment for TBI were terminated for futility in 2014 (Manley 2015; Skolnick et al. 2012; Wright et al. 2014).

Analysis showed that the participants, enrolled based on the GCS, were heterogeneous—multiple causes may contribute to the same GCS score, including diffuse axonal injury, diffuse swelling, contusion, and hematoma. In addition, the measure of effect, the Glasgow Outcome Scale Extended (GOSE), was too insensitive to show a significant difference between treatment and control groups. The GOSE is essentially a disability score rather than a strict measure of brain function.[1]

Another challenge in treating TBI is to understand which cases will have lingering or delayed effects from a blow to the head. Frequently, TBI patients can pass a neurocognitive test within days after the injury, but when challenged more significantly—such as with multitasking or with low levels of hypoxia as experienced at 7,500 feet—they show deficits on the same neurocognitive tests. Functional magnetic resonance imaging (fMRI) and high-density electroencephalography (EEG) show that the brains of these individuals have not returned to normal months later even when the patients appear normal based on the single neurocognitive test administered.

Recent Clinical Trials: Challenges and Analysis

Difficulties experienced in moving TBI-related products through the clinical trial and regulatory process in two diagnostic efforts prompted the DOD to reevaluate the entire paradigm of TBI clinical trials.

Two Challenging Experiences

The first effort, involving a quantitative EEG (QEEG) system (figure 1) with machine learning to screen for changes in brain function after an impact to the head (Ayaz et al. 2015), entailed more than 18 months of discussions with the FDA before arriving at agreement to use the comparison measure of a positive computed tomography (CT) scan and a mutually agreed indication for use. The pivotal trial was successful and the device received clearance from the FDA as an indicator of whether a CT scan was indicated by the New Orleans Criteria. In other words, the QEEG is being compared to a test for brain bleeding, not a test of brain dysfunction. A brain injury involving bleeding is likely more serious than a concussion not involving bleeding.

[1] Of note, the participants in both trials had improved outcomes from a traditional standard of care, based on adherence to care protocols.

FIGURE 1 The BrainScope quantitative EEG system, AHEAD-200, which analyzes the brain waves of an individual suspected to have suffered a brain injury. Reprinted with permission from BrainScope.

The second effort, which included a blood test for proteins usually not present without a brain injury (Papa et al. 2012a,b), had a similar course before being cleared to perform the pivotal trial. The 2,000-patient multicenter international clinical trial has now been completed and, if the analysis is successful, an application should be filed, again as a comparison with a CT scan. Previous trials with these biomarkers have shown virtually complete sensitivity but less than 25 percent specificity in mild TBI (GCS 13–15[2]): the blood test simply detected brain injuries that did not have associated bleeding.

Truly a better comparison measure than the CT scan is needed. The difficulty in arriving at agreed measures was judged to be due to the lack of validation trials of other measures according to regulatory standards. The regulatory science is inadequate, but is a reflection of the state of the more general science in the field of TBI.

Analysis

The TBI field has been very introspective, with numerous analyses of the causes of failed clinical trials (Bullock et al. 2002; Burke et al. 2015; Dickinson et al. 2000; Farin and Marshall 2004; Kabadi and Faden 2014; Li et al. 2014; Loane and Faden 2010; Maas et al. 1999, 2010; Narayan et al. 2002; Tolias and Bullock 2004)—a much higher ratio of review than other fields, such as Alzheimer's disease or stroke, which each have in excess

[2] A GCS score of 3–8 denotes a severe brain injury and 9–12 moderate injury.

of 300 failed clinical trials. The results of the analyses have recurring themes; in summary, the main recommendations are to

(1) ensure that an appropriate study population has been selected to minimize heterogeneity,
(2) identify appropriate primary and secondary endpoints,
(3) conduct careful statistical analysis, and
(4) improve the translation of experimental results to the bedside.

DOD Efforts to Improve TBI Clinical Trials

The DOD initiated two foundational efforts to solve the fundamental difficulties with past clinical trials. In 2011 the DOD and the Centers for Disease Control and Prevention (CDC) funded a cooperative effort to review the total English language scientific literature with the goal of developing an evidence-based definition of concussion. The review determined that the literature did not provide enough granularity for a definitive definition but served as a first step for a systematic review of "prevalent and consistent indicators," identified as

> (1) observed and documented disorientation or confusion immediately after the event, (2) impaired balance within 1 day after injury, (3) slower reaction time within 2 days after injury, and/or (4) impaired verbal learning and memory within 2 days after injury. [Carney et al. 2014, p. S3]

This is insufficient to define the enrollment criteria for an enriched study cohort. The DOD therefore initiated, in collaboration with the Brain Trauma Foundation, the Brain Trauma Evidence Consortium with the following four mission areas:

1. Dynamic Model Initiative. Produce a paradigm shift in brain trauma classification and treatment. The goal of this first-priority area is to improve the study enrollment criteria process to reduce the heterogeneity challenges of the current, GCS-based criteria.
2. Investigator Collaboration. Coordinate, harmonize, pool, and analyze existing and ongoing research efforts to maximize efficiency and accelerate the acquisition of urgently needed information, technology, and protocols.
3. Living Guidelines System. Produce evidence-based guidelines for the treatment of the full spectrum of brain trauma, developed in the context of the dynamic model.
4. Research, Education, Dissemination, and Implementation. Develop a comprehensive program for guideline dissemination and implementation.

The DOD's second major initiative, the TBI Endpoints Development (TED) consortium, commenced in September 2014 (figure 2). Formulated to address the inadequate endpoints (CT scan and/or GOSE) currently validated for clinical studies of regulated products, this two-phase effort will first evaluate the multitude of existing assessments and select the measures with the highest amount of evidence supporting their use in the regulatory process. Phase two will validate the selected measures with processes that meet the FDA's qualification process for drug development tools.

Key to this effort is the substantial involvement of the FDA in shaping, selecting, managing, and executing the TED initiative. It is anticipated that TED will lead to an expanded pathway for product approval and enable successful clinical trials that validate products to diagnose and treat TBI.

Other Major Initiatives

The current research landscape includes a wide range of studies—ranging from preclinical to clinical, acute to postmortem, premorbid to long-range effects, and from pilot to large multinational—with funding by government, academic, industry, and nonprofit entities. Following are examples of large studies currently under way:

- TRACK-TBI (Transforming Research and Clinical Knowledge in TBI; https://tracktbi.ucsf.edu),
- the Army Study to Assess Risk and Resilience in Servicemembers (STARRS; http://armystarrs.org),
- the NCAA-DOD Grand Alliance Concussion, Assessment, Research, and Education (CARE) Consortium (www.careconsortium.net), and
- the Chronic Effects of Neurotrauma Consortium (https://cenc.rti.org).

In addition, as outlined in the National Research Action Plan (DOD/VA/DHHS/DOEd 2013), the principal investigators of larger government studies have coordinated numerous study protocol elements, case report forms, biomarkers, imaging studies, and biospecimens, for the most part contributing all the collected data to the Federal Interagency Traumatic Brain Injury Research (FITBIR; https://fitbir.nih.gov/) data repository. FITBIR is a joint effort of the DOD and NIH that

will make federally funded research data available to other researchers through a governance process. This level of coordination and data transparency will allow much more information to be gained from the data collected than the isolated studies of the past.

Conclusion

Two main corrections are needed for future TBI trials: enrichment of the study population and validation of multiple, meaningful primary, coprimary, and secondary endpoints to assess efficacy. These changes, together with diagnostic or therapeutic products developed to address the pathophysiology of the disease process, will lead to approved products and techniques that will improve outcome for the millions who suffer a traumatic brain injury each year.

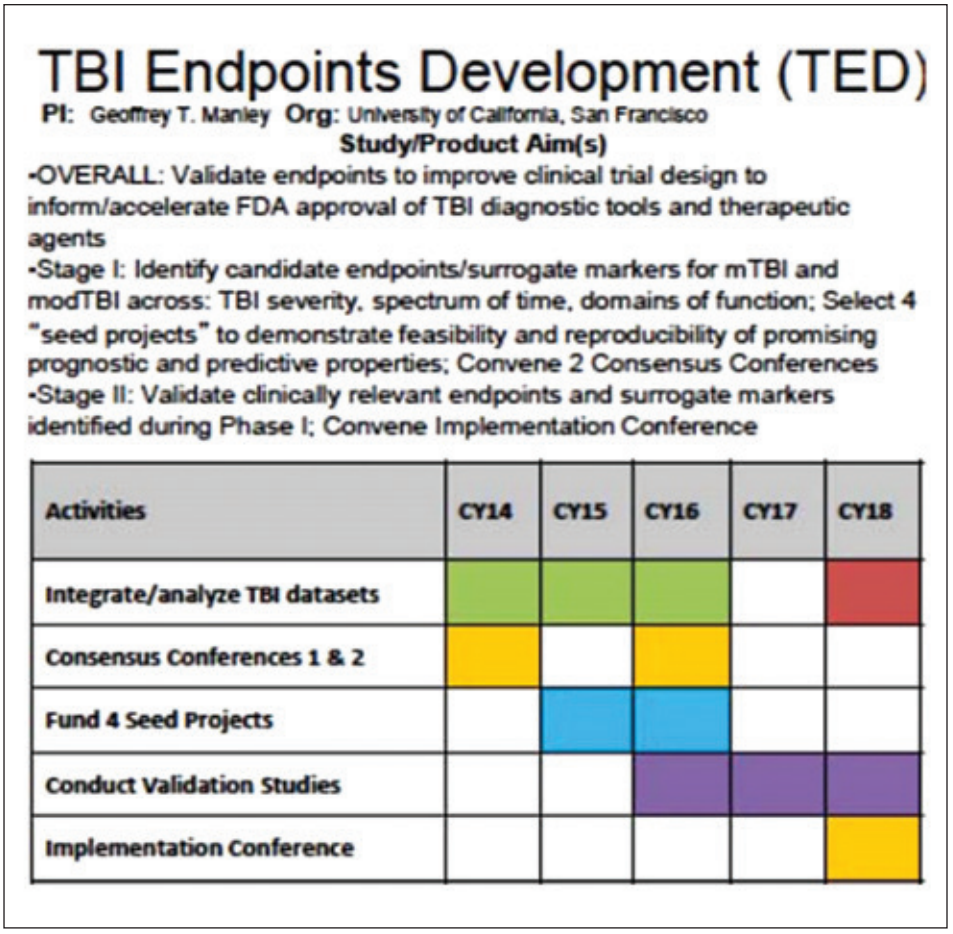

FIGURE 2 TBI Endpoints Development (TED) study activities. Reprinted with permission from G.T. Manley.

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Risk of concussion cannot be eliminated from sports. But safety can be improved through increasingly better informed decisions.

Concussion and the NCAA

Report from the Chief Medical Officer

Brian W. Hainline is chief medical officer, National Collegiate Athletic Association.

Brian W. Hainline

The National Collegiate Athletic Association (NCAA) is the national governing body of intercollegiate varsity athletics. About 460,000 student-athletes from 1,100 schools are involved in the organization, which represents 23 sports and 90 national championships. The NCAA has taken a leadership role to enhance understanding and mitigation of concussion.

Background

Concussion is one of nine strategic priorities for the NCAA Sport Science Institute, which I oversee as the NCAA's first chief medical officer (appointed in 2013). The other strategic priorities are mental health; cardiac health; overuse injuries and periodization; doping and substance abuse; nutrition, sleep, and performance; sexual assault and interpersonal violence; athletics healthcare administration; and data-driven decisions. All of these areas represent important public health concerns in sports, yet understanding of causes, effective strategies for mitigation, and methods to acquire knowledge are limited.

For example, there is no adequate definition of concussion reflecting the injury mechanism or localization in the brain. The accepted definition is limited to an imprecise description of the symptoms of concussion: a change in brain function, following a force to the head, that may be accompanied by temporary loss of consciousness but is also identified in awake individuals,

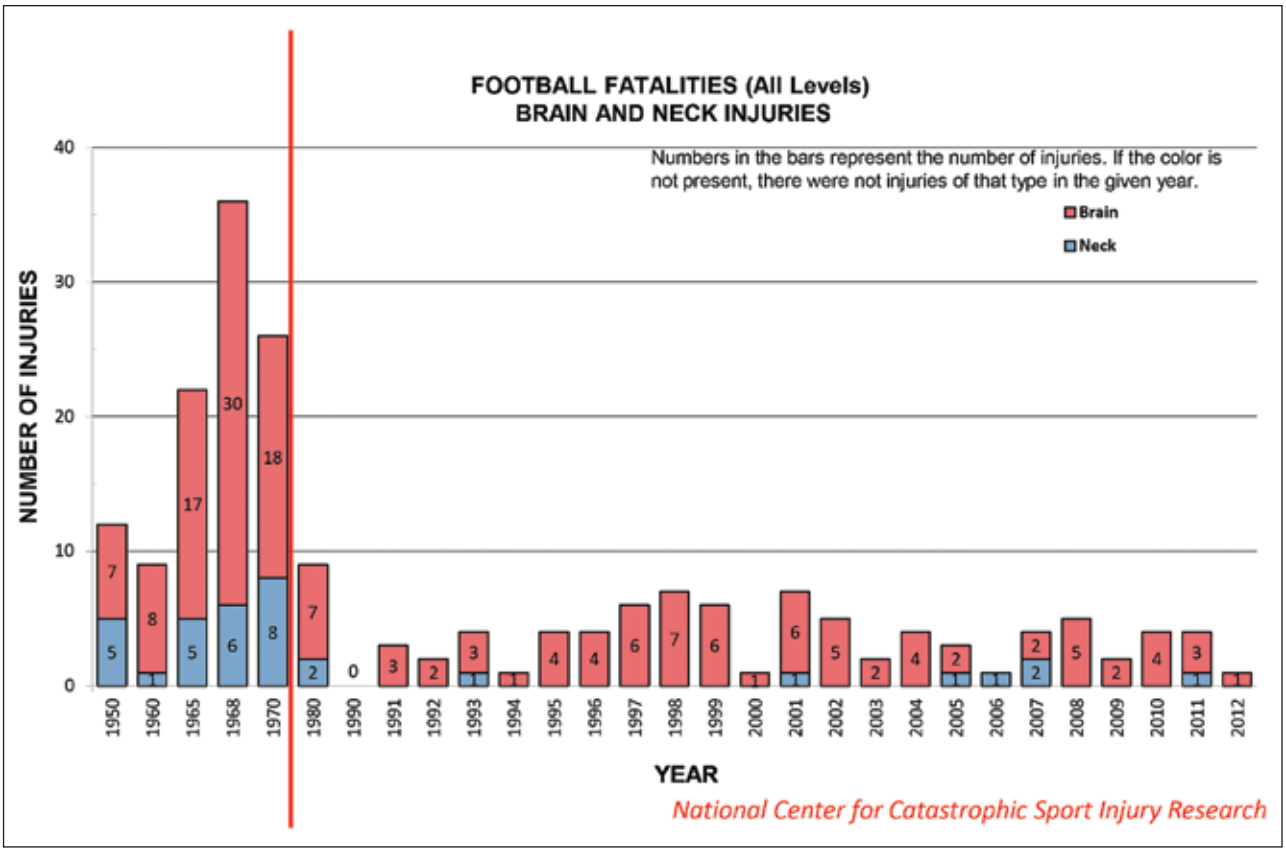

FIGURE 1 Fatalities in football, 1950–2012. Note the marked decrease in injuries after the prohibition on spearing in the 1970s. Reprinted with permission from the National Center for Catastrophic Sport Injury Research.

and that has measures of neurologic and cognitive dysfunction (Carney et al. 2014). From a data-driven decision-making perspective, information is lacking about the range of consequences of concussions, the preferred treatment, and when to allow a concussed athlete to return to play.

Athletic and Military Concussion

Concussion incidence in the United States is estimated at 3.8 million per year (Iverson et al. 2004), over 300,000 of which result from sports collisions (Gessel et al. 2007). As shown in figure 1, however, football fatalities associated with concussion and other head and neck injuries have been declining.

The rate of concussion for intercollegiate sports overall is shown in figure 2 (Zuckerman et al. 2015). The highest-rate sport is men's wrestling, a contact sport. Note, however, the high level of risk in many women's sports—soccer, ice hockey, basketball, and lacrosse. Women's lacrosse is a noncontact sport, while men's lacrosse is not, yet the concussion rate for women's lacrosse is higher. Understanding of the reasons for differences in concussion between the sexes is poor, although it goes beyond differences in neck strength and includes mechanisms of contact and differing neurophysiological responses.

There are many similarities in the NCAA and Department of Defense (DOD) missions to mitigate injury and in the events that lead to traumatic brain injury in sports and military activity. For example, most NCAA head injuries are classified as mild (i.e., concussion), and 97 percent of the traumatic brain injuries in US veterans of the wars in Iraq and Afghanistan are mild; of those, about 85 percent happened in a way that is biomechanically similar to a sport concussion, while only 15 percent resulted from blast injuries (Cameron et al. 2012), which are biomechanically distinct from direct physical trauma.

Moreover, NCAA student-athletes and military servicemembers share many demographics: they are similar in age, athleticism, risk taking, and the practice of pushing themselves to the edge of excellence. One crucial difference is that there is more control in the college athletic environment than in the military theater.

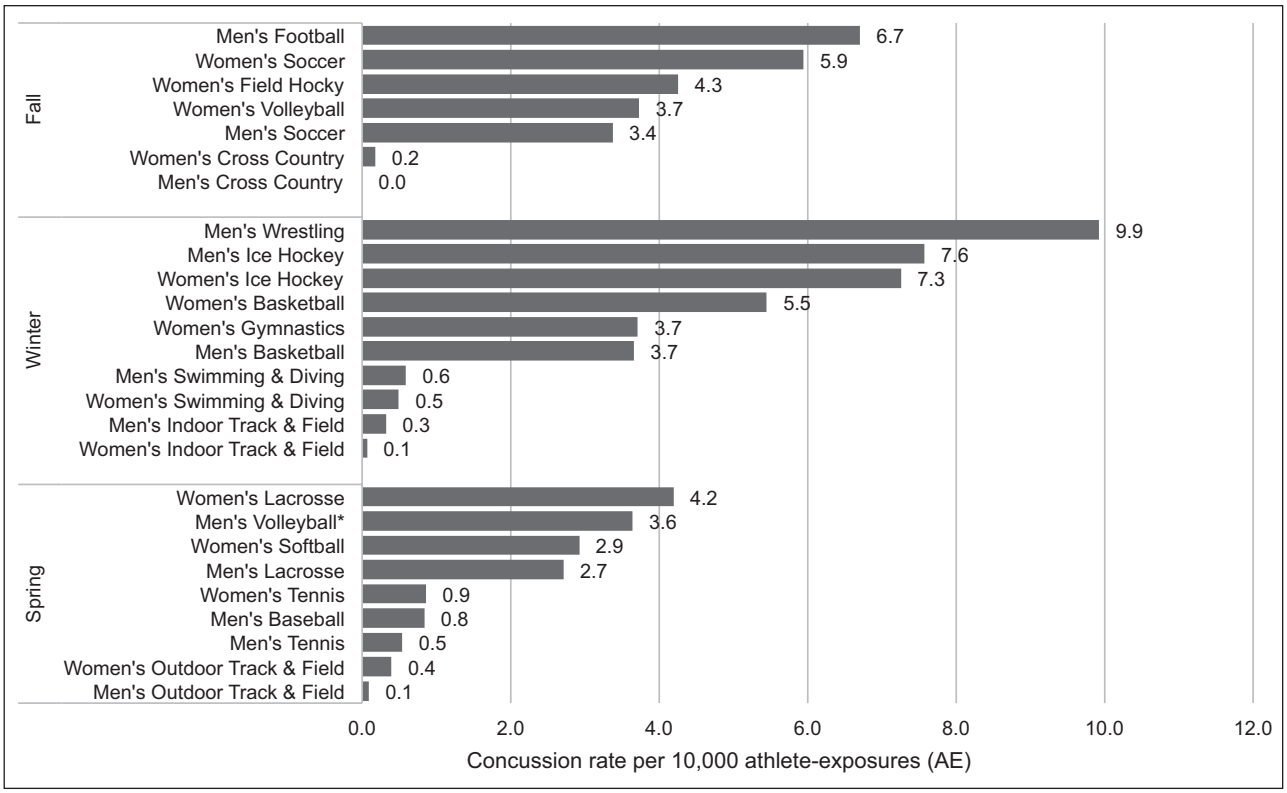

FIGURE 2 Concussion rates in 26 college sports, 2009/10–2014/15 academic years: National Collegiate Athletic Association Injury Surveillance Program (NCAA-ISP). * Men's volleyball data were collected during the 2013/14 and 2014/15 academic years only. An athlete-exposure is defined as one student-athlete's participation in one NCAA-sanctioned competition or practice. Data updated from Kerr et al. (2014) and Zuckerman et al. (2015).

NCAA-DOD Grand Alliance Study

Because of these similarities and the need to close the concussion knowledge gap, the NCAA and DOD are collaborating in a landmark study titled NCAA-DOD Grand Alliance, which consists of the CARE Consortium and the Mind Matters Challenge (NCAA 2014).

Concussion Assessment, Research, and Education (CARE) Consortium

This initiative is the largest prospective, clinical, longitudinal study of concussion in history. The two primary aims of the study are to determine the natural history of concussion and to define neurobiological recovery after concussion. The three primary study centers are the Medical College of Wisconsin (Michael McCrea, principal investigator), Indiana University (Tom McAllister, PI), and the University of Michigan (Steven Broglio, PI). The 3-year study is being conducted at 30 NCAA member schools, including the four service academies. At every site each student-athlete in every sport undergoes an exceptionally rigorous baseline exam and serial exams after concussion.

In addition, the advanced research component of the CARE Consortium is evaluating neurobiological recovery in seven sports: men's football, men's and women's lacrosse, men's and women's ice hockey, and men's and women's soccer. This research is taking place at four schools, where student-athletes in the seven sports wear a head sensor during competition and practice, and undergo baseline genetic testing, assessment of blood biomarkers, and postconcussive brain imaging studies that are synced with the TRACK-TBI methodology[1] (NINDS 2012). After an injury or suspected injury, baseline measurements are repeated as shown in figure 3.

It is anticipated that in 3 years, 35,000 student-athletes will be enrolled in the clinical study and about 1,600 student athletes will be enrolled in the advanced research core. The conservative estimate, based on a 2 percent concussion rate, is that there will

[1] The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study is funded by the National Institute of Neurological Disorders and Stroke (NINDS) and housed at the University of California, San Francisco.

	Pre-Season	Acute Concussion		Sub-Acute Concussion			Post-Concussion
	Baseline	<6hrs Post-Injury	24-48hrs Post-Injury	Asymptomatic / Cleared for Return to Play Progression	Unrestricted Return to Play	7 days following Return to Play	6 Months Post-Injury
Neurocognitive and Behavioral Testing (CSC)	X	X	X	X	X	X	X
Blood Biomarker & DNA Collection	X	X	X	X		X	X
Multi-modal MRI Studies	O		X	X		X	X

Head Impact Measurement: HITS (FB) and non-helmeted sensors (FB, SCR, LAX, IH)

FIGURE 3 Assessment protocol for baseline testing and assessment of student athletes in selected sports for the longitudinal clinical study core (CSC) and advanced research core (ARC) of the NCAA-DOD Grand Alliance Concussion Assessment, Research, and Education (CARE) Consortium. FB = football; HITS = Head Impact Telemetry System; IH = ice hockey; LAX = lacrosse; MRI = magnetic resonance imaging; SCR = soccer.

be 750 concussions in the clinical study and 75 in the advanced research core.

There are active discussions to extend this study in a Framingham model to over 35 years, and to expand enrollment to precollege-level sports.

Mind Matters Challenge

The NCAA-DOD Mind Matters Challenge is an education and research challenge open to all NCAA schools and the public at large (NCAA 2014). The education component of the challenge calls on participants to develop, within one year, compelling educational content and delivery that will help change the culture of concussion in young adults. For the research challenge, applicants must describe a 3-year study to provide methods to change the culture of concussion and perceived norms for coaches, student-athletes, parents, administrators, and the public at large. Six winners have been chosen for the educational challenge, and eight for the research challenge.

New NCAA Guidelines

In January 2014 NCAA and medical organization colleagues met to develop interassociation guidelines—for concussion, football practice, and independent medical care—aimed at helping to mitigate and manage sport-related concussion.[2] The guidelines have been endorsed by eleven prominent medical organizations.

The medical care guidelines state that coaches *do not* make medical decisions. Athletic trainers and team physicians (primary athletics healthcare providers) must make all medical decisions with unchallengeable autonomous authority.

The year-round football practice live contact guidelines are based on best available evidence. They are an important start, but we ultimately hope to individualize guidelines based on emerging head sensor data.

The concussion diagnosis and management guidelines may not seem particularly revolutionary, but in some ways they are. Developed by clinical experts who pioneered the field, one accepted method for assessing concussion and guiding decisions for return to play is known as ImPACT (Immediate Post-Concussion

[2] The Safety in College Football Summit was held January 22–23, 2014, in Atlanta. The three sets of guidelines are available at www.ncaa.org/health-and-safety/; the list of summit participants is available at www.ncaa.org/health-and-safety/appendix.

Assessment and Cognitive Testing). ImPACT provides trained clinicians with neurocognitive assessment tools, and is the most widely used and most scientifically validated computerized concussion evaluation system.

But ImPACT alone is insufficient. Rather, a multimodal method of preparticipation assessment is needed, and the postconcussion phase must emphasize return to learn as much as return to play.

Conclusion

Some of these changes can help, but they must also be updated with emerging data and consensus, including changes in the rules of sport. For example, when the rules of football prevented spearing in the 1970s, the incidence of cervical spine injuries decreased dramatically (Bailes et al. 2007). More recently, when the kickoff in football was moved five yards closer to the end zone, and the ball placement from a touchback moved five yards the other way, the concussion rate fell 50 percent relative to all other injuries.[3]

But no matter how safe the rules for all contact, collision, or even noncontact sports, the risk of concussion cannot be eliminated. Sport brings exceptional benefits that must be weighed against the risks. Our goal is to continually improve safety in sport through data-driven decisions and consensus. At the NCAA, we believe that progress is well under way.

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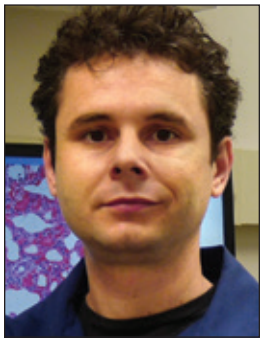
[3] Personal communication with Tom Dompier, Datalys Center, January 2015.

Controlled, reproducible interdisciplinary research is critical to improve understanding of traumatic brain injury.

Research to Understand Explosion-Related Injuries in Military Personnel



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S. Krisztian Kovacs

Explosive blast–related traumatic brain injury (TBI), specifically primary blast- or shockwave-related TBI, is highly prevalent among military personnel. The majority of battlefield wounds in 21st century military conflicts are due to explosive devices—in the recent wars in Iraq and Afghanistan, almost 80 percent of injury was due to explosion. It is estimated that 20 percent of US military personnel had TBI between 2001 and 2008; and in just the first quarter of 2015, according to the Department of Defense, almost 6,000 US military servicemembers suffered some degree of TBI (83 percent being mild TBI, which may elude diagnosis and thus go untreated) (DOD 2015).

One of the distinct features of recent military conflicts is the high survival rate of victims of TBI. This is a result of improved body armor, which has decreased the rate of fatal chest and lung injury, and advanced medical care, both of which have contributed to a killed-to-wounded ratio of 1:10, the lowest in modern history. As a result, however, doctors see more brain trauma in surviving soldiers (Bandak et al. 2015).

This paper reviews the basic biomechanics of blast injuries, experimental animal blast models, and some relevant pathology discovered through our research group's blast experiments conducted on rats (other animal models are mice, swine, and monkeys).

What Happens During a Blast?

Traumatic brain injury occurs in multiple ways: it can be caused by nonpenetrating projectile hits, indirect acceleration/deceleration forces, blasts, or penetrating trauma to the head. Primary, nonpenetrating blast injury is the effect of the shockwave propagating through the body and the head, and is the focus of the research in my laboratory. Other explosion-induced injuries can be caused by being struck by material propelled by the explosive blast, by the body's being thrown by the blast, and by radiation, toxic fumes, or burns.

Primary and Secondary Effects

In terms of tissue response, injury may be primary and secondary. Acute (primary) injury may directly damage the structural elements of the brain and trigger secondary pathophysiological processes such as inflammation, ischemic and hypoxic damage due to diminished blood flow or lack of oxygen, reactive oxygen species formation, or excitatory amino acid release and iron-mediated cell death. These secondary injuries involve biochemical and cellular changes that occur days and even years after the traumatic event and result in symptoms such as cognitive and personality changes as well as modulated gene expression and/or protein regulation (CDC, NIH, DOD, VA Leadership Panel 2013).

Specific Effects of Shockwaves

Our studies are designed to examine damage due to shockwaves, the leading elements of pressure disturbance in a blast. The compressibility of air causes the front of this pressure disturbance to steepen, reaching and surpassing the speed of sound.

Shockwaves can injure the brain both directly and indirectly. Direct mechanisms include spallation, which occurs between tissues with different densities and different acoustic impedance and may result in direct tissue disruption. Rapid rise in intracranial pressure after a blast can lead to bubble formation at the boundary of the cerebrospinal fluid and brain tissue, and may cause cavitation with axonal stretching and blood vessel disruption. Direct mechanisms also include skull deformation with elastic rebound, intracranial wave reflection off the inner surface of the skull, and acceleration/deceleration forces resulting in axonal injury from shear stress and strains (Rosenfeld et al. 2013).

One of the most important indirect mechanisms is kinetic energy transfer through large blood vessels from the abdomen and chest. Hypothetically, waves oscillating through large blood vessels after the blast can cause brain damage. Air embolism from lung injury is another indirect mechanism (Bandak et al. 2015; Cernak and Noble-Haeusslein 2009; Rosenfeld et al. 2013).

Another consideration is the effect of multiple blast events. Ongoing studies suggest that chronic traumatic encephalopathy may occur in soldiers exposed to multiple blast events, with neuropathological changes similar to those with previous sport concussion, but more research is needed (Goldstein et al. 2012; McKee et al. 2009).

Biochemical and cellular changes occur days and even years after a traumatic event and result in symptoms such as cognitive and personality changes.

How Do We Study Blast Injuries?

The limited availability of human tissues and lack of specific clinical signs, especially at the beginning of the disease, make clinical blast TBI research challenging. Animal models of blast TBI are therefore essential to characterize injuries and disorders, and should imitate real-life human blast conditions.

The most frequently used animal models are tube and open-field models. The former may be blast or shock tube experiments with explosives or with compressed air and gas explosions. Open-field experiments and blast tubes ("blast wave generators") closely mimic real-life blast events.

Irrespective of the species and method used, the neuropathological changes are very similar and axonal injury/degeneration is the principal outcome. Microglia activation, astrocyte activation, and occasional cell death have also been reported in the central nervous system. Numerous blast models describe injuries to the optic pathways, the auditory system, and long white matter fiber tracts of the brain. Reports of intracranial hemorrhages or petechial bleedings are less common in blast models, but are a prevalent finding in human injuries from blunt trauma caused by vehicle, projectile,

FIGURE 1 Blast wave generator. Photo credit: USUHS Neurotrauma Laboratory.

and sports collisions. The evidence of blast brain injury is usually best seen microscopically 7–14 days after the event (de Lanerolle et al. 2015; Kovacs et al. 2014; Needham et al. 2015).

Method

Blast experiments on rats conducted by our research group were carried out using a 6-foot diameter, 70-foot long blast tube (or blast wave generator, BWG) (figure 1). We studied only primary blasts, using uncased explosives, with the body protected by an insulated aluminum holder that left only the animal's head and neck exposed. To ensure that there was no movement of the head during the blast, we restrained it using a rigid sling support.

Pressure changes in several locations near the animal were measured during the blast (figure 2). According to our data the BWG was able to produce an almost ideal Friedlander wave that is typical of free-field blasts.

In animals that died during or shortly after the blast, with peak overpressures beyond 45–50 psi, we detected brain edema, subarachnoid hemorrhage, and frank tissue disruption with parenchymal microhemorrhages. We assessed effects in the animals 24 hours, 7 days, and 28 days after the blast. In animals that survived the blast, exposed to approximately 30 psi overpressure or less, we observed limited evidence of gross abnormalities in the brain; for example, subdural hemorrhages and microhemorrhages were seen after 24 hours.

The most significant pathology, as in other blast models (e.g., Bauman et al. 2009), was multifocal axonal injury (detected by FD Neurotech silver stain kit; figure 3). Axonal damage more frequently involved the optic pathway, but cerebellar structures and brainstem areas also showed axonal pathology, mostly after 7 and 28 days. Astrocyte activation was present in the optic pathways after 7 and 28 days. Activated microglial cells appeared as early as 24 hours after the blast and remained visible after 28 days in brain areas that showed signs of axonal injury.

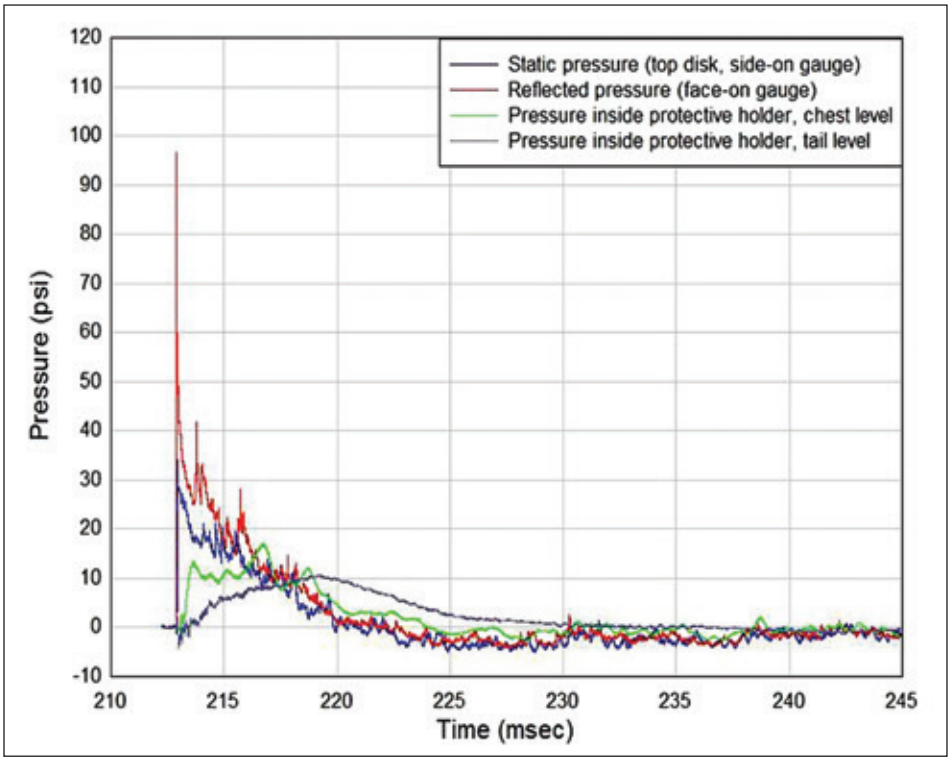

FIGURE 2 Blast pressure-time profile. Positive phase duration (7.1–10.4 ms) was a little longer than in other blast models (by 5–7 ms) to account for the increased distance between the charge and target. We measured peak pressures of 15–50 psi.

Observations

In our blast tube animal model we observed axonal injury that showed blast-intensity- and time-dependent changes. With increased intervals between blast exposure and pathological examinations, there was an increase in the number of brain regions with evidence of axonal injury. Axons were the most vulnerable structures to primary explosive blast, and direct forces from the shockwave

may have been transmitted through weak areas (e.g., eyes) on the skull.

We also compared the results of our blast model to another nonpenetrating blunt head trauma model (fluid percussion injury; Dixon et al. 1987) and a penetrating ballistic brain injury model (Williams et al. 2005). In identifying axonal injuries using common procedures—hematoxylin and eosin (H&E)–stained standard slides, amyloid precursor protein (APP) immunohistochemistry, FD Neurotech silver staining, and Fluoro-Jade B (FJB) staining—we noted that silver staining and FJB clearly showed evidence of axonal injury in some cases where APP showed little or none. We conclude that H&E and APP staining underestimated the extent of injury caused by the shockwave, and that blasts may have a different and unique biomechanical effect on axonal fibers.

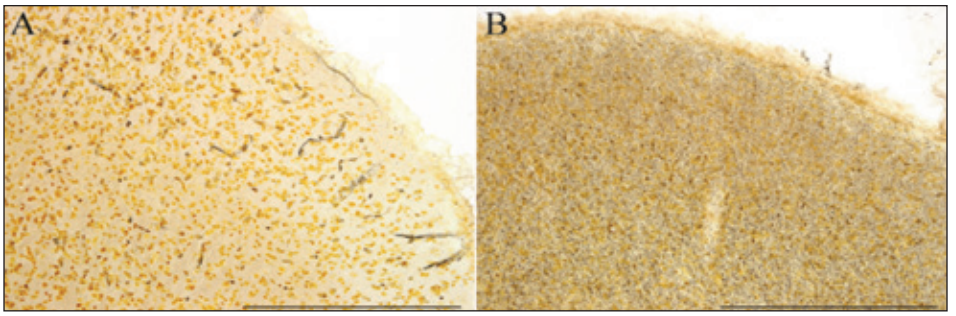

FIGURE 3 FD Neurotech silver staining shows strong (B) axonal degeneration mostly in the optic nerve layer of the superior colliculus (midbrain) with the characteristic fine granular black staining pattern. There is no evidence of the same pattern in control animals (A). Photo credit: USUHS Neurotrauma Laboratory.

Conclusion

Animal models are excellent research tools to study blasts, but because of the variety of methods used and the lack of basic data reporting, such as pressure changes and physical properties of the blasts, results have been controversial. Moreover, rodent brains are different from those with grey-to-white-matter ratios and architectures closer to those of primates, and this is an important factor to consider as the biomechanical parameters of brain tissues are significant in injury models. Scaling animal models to humans is a key consideration, as discussed by Radovitzky and colleagues (2015) in this issue.

Research suggests that axons are the brain structure most vulnerable to explosive blast. Controlled, reproducible interdisciplinary research is critical to improved understanding of the mechanics of blast injuries and the identification of neuropathological structural changes.

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Research is needed to better understand the biomechanics of concussion and enhance injury prevention, safety equipment design, rules of play, treatments, and interventions.

Emerging Insight from Human and Animal Studies about the Biomechanics of Concussion

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Susan S. Margulies

Biomechanics can provide insight into the mechanisms of concussion, including the interrelationships among the forces experienced during impact, head and neck movements, tissue stiffness of the materials that compose the head/neck complex, deformation of structures at the macroscopic and microscopic level, and biological responses to the various forces imposed on the head.

Biological responses in traumatic brain injuries (TBIs) may be immediate or delayed, be structural (torn vessels and axons) or functional (changes in blood flow or neurological status), and differ with maturation. Biomechanical investigations typically include a variety of approaches:

- direct measurements of loading conditions and responses in humans, animals, and anthropomorphic surrogates (i.e., crash test dummies);
- visualization of tissue responses to prescribed loads to characterize the responses of complex geometries or composite structures;
- mechanical property testing of individual components to identify changes with age;
- computational models to predict how tissues will deform during impact or rapid head rotation; and

- identification of the timecourse of cell or tissue responses to specified deformations in order to define thresholds associated with various types of injuries.

Sources of Concussion Data for Research

Biomechanics investigators can use human data obtained prospectively (via sensors; Camarillo et al. 2013; Crisco et al. 2010; Daniel et al. 2012; Rowson et al. 2009, 2012) or retrospectively (via crash reconstructions) to help understand what scenarios cause TBIs. Concussions are diagnosed based on symptoms, and most assessments are influenced by the patients' awareness of or willingness to report their symptoms. But this less reliable form of data gathering skews the dataset and undermines the process of identifying objective biomechanical thresholds associated with concussion using instrumented volunteers. Biomechanical data are occasionally captured by sensors in helmets, patches, and mouthguards but they often report limited information about the rotational head movements associated with concussion.

To obtain kinematic information in more controlled settings, anthropomorphic surrogates (crash test dummies) and laboratory-based studies are used to reenact film and witness accounts of sports-related events in order to estimate the forces of impact and head movements (kinematics). But surrogates cannot be used to predict or measure brain injuries or tissue distortions.

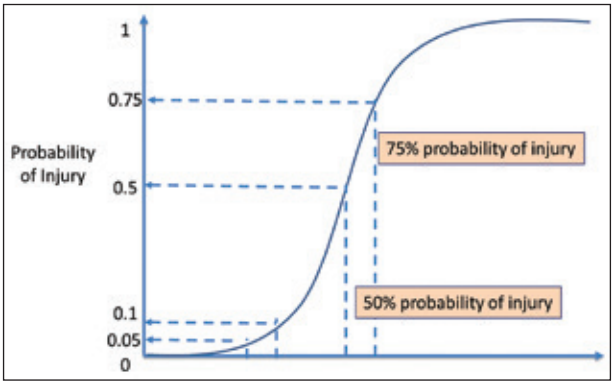

FIGURE 1 Injury risk curve relating a mechanical parameter (head acceleration, shown on the x-axis) to the probability of injury (y-axis). A given reduction in the mechanical parameter does not correspond to an equivalent reduction in injury risk, as shown by the sigmoidal shape of the curve. If the reduction in the mechanical parameter is on the left side of the curve, the corresponding reduction in injury risk is rather small (e.g., 10 percent to 5 percent). In contrast, if the reduction in the mechanical parameter is in the steep portion of the curve, the actual injury risk reduction could be rather large (e.g., 75 percent to 50 percent). Adapted from IOM (2014).

Instead, results obtained using surrogates must be correlated with animal studies, autopsy reports, and patient records to infer biological responses to kinematic loading conditions, or with computational models to infer tissue deformations resulting from a head rotation or impact.

Computational models are used to estimate the tissue distortions and stresses that may result from a rapid head motion or head impact, using lifelike tissue stiffness values for children and adults (Cheng et al. 2008). Like surrogates, computational models cannot predict concussion; predicted tissue distortions in response to lifelike loading conditions must be correlated with animal or human data.

Animal models can provide a controlled laboratory setting to investigate the relationships between the risk of concussion and rapid head rotation magnitude and direction, as well as the contributions of age, sex, and previous concussions to biomechanical thresholds for concussion. Animal model–derived biomechanical thresholds are typically for more severe brain injuries than concussion, but animal models do provide insight into how head impacts and sudden head movements produce brain deformations and how such deformations result in a spectrum of brain injuries, from mild to severe TBI.

Human Studies of Concussion Biomechanics

Quantifying the relationship between biomechanical input and clinical outcome is critical to the advancement of concussion prevention principles, including the assessment of injury risk, the design of protective equipment such as helmets, and the development of training and policies intended to limit exposure to head impacts and injury risk.

Measuring Injury Risk and Impact

The most common approach to quantifying the link between biomechanical input and concussion is through injury risk curves (figure 1), which describe injury probability given a specific mechanical input—for example, concussion risk given a particular head acceleration. Pellman, Rowson, Duma, and colleagues (Pellman et al. 2003; Rowson and Duma 2011) have used football head impact data to describe the relationship between linear acceleration and concussion risk (Rowson and Duma 2013) and between rotational acceleration and concussion risk (Rowson et al. 2012).

Head impact sensors have been widely used to understand the link between the biomechanics of head

impact and clinical outcomes of concussion in humans (Brainard et al. 2012; Crisco et al. 2010; Mihalik et al. 2007; Rowson et al. 2009; Wilcox et al. 2015). These sensors—attached to a helmet, headband, skullcap, or mouthguard, or directly attached to the athlete's head (Bartsch et al. 2014; Hernandez et al. 2015; King et al. 2015)—consist of accelerometers, and in some cases gyroscopes, to estimate the magnitude of linear and rotational acceleration experienced by the athlete during head impact.

Recent studies, however, have quantified errors in risk curves associated with significant sensor inaccuracy (Allison et al. 2014, 2015; Funk et al. 2012; Jadischke et al. 2013), underreporting of concussion (estimated at 53 percent; McCrea et al. 2004), and incorrect clinical diagnosis (Elliott et al. 2015). Decreasing sources of error will be important for improving the accuracy of injury risk estimates.

Challenges in Diagnosis and Assessment

Improvements in concussion reporting and diagnosis are essential to define injury risk curves for concussion. Concussion diagnosis remains largely an inexact clinical determination, using subjective assessments and symptom self-reports (IOM 2014; Master et al. 2014) of neurocognitive effects (van Kampen et al. 2006), vestibular balance (Corwin et al. 2015; Guskiewicz 2011), oculomotor/visual systems (Master et al. 2015), and sleep (Towns et al. 2015).

Current clinical assessments—the Sport Concussion Assessment Tool 3 (SCAT3) (Guskiewicz et al. 2013), Vestibulo-Oculomotor Screen (Mucha et al. 2014), King-Devick Test (Galetta et al. 2013), computerized neurocognitive testing such as the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) (van Kampen et al. 2006), and self-report of symptoms like the Post-Concussion Symptom Scale (Chen et al. 2007)—have components that are subjective and dependent on the effort of the injured individual or influenced by repeated testing effects (Resch et al. 2013). Moreover, because concussion may be diagnosed by a variety of individuals—parents, coaches, trainers, primary care, emergency medicine, or urgent care clinicians (Leong et al. 2014; Taylor et al. 2015)—it is important to develop robust, accessible, and validated metrics for use.

Future research should target the validation of objective, graded, effort-independent neurologic system assessments (such as vestibular balance, eye tracking, visual function, and sleep) for concussion to enable timely and accurate diagnosis across a wide age spectrum. These quantitative involuntary metrics can also be used to guide clinical diagnosis and management of concussion and inform evidence-based decisions about athletes' return to sport.

Animal models are useful for measuring physiological responses, neuropathology, and neurofunctional changes at prescribed time-points after injury.

Animal Studies of Concussion Biomechanics

Because human data and computational models have limitations, researchers use experimental substitutes such as animals, tissues, and isolated cells to create controllable settings with similar predisposing conditions and reproducible mechanical loads.

Extensive Utility of Animal Studies

Animal models are useful for measuring physiological responses, neuropathology, and neurofunctional changes at prescribed time-points after injury. As a surrogate for humans, the animal models most commonly used to study brain injury are mice and rats, but ovine, porcine, and nonhuman primate models have also been used (Browne et al. 2011; Durham et al. 2000; Finnie et al. 2012; Gennarelli et al. 1981, 1982; Viano et al. 2012). Because reports indicate that rodents have limited similarity to human genomic and proteomic responses, injury timecourses, and grey and white brain matter distribution (Duhaime 2006; Seok et al. 2013), there may be challenges in applying what is learned about injury in the rodent brain to humans (Wall and Shani 2008). Animal models are nonetheless a valuable tool for understanding how head impacts and sudden head movements translate to short- and long-term biological responses, and how environment and agents can exacerbate or mitigate these responses.

Pigs are a popular large animal model used for assessing motor, cognitive, and behavioral responses after

traumatic brain injury, stroke, and cardiac arrest (Gieling et al. 2011; Jiwa et al. 2010; Lind et al. 2007; Sullivan et al. 2013a,b; Wang et al. 2012). A sensitive and specific battery of behavioral, motor, memory, learning, and cognitive assessments developed for piglets have revealed the timecourse after traumatic brain injury and the importance of the direction of head rotation for head injury responses (Friess et al. 2007, 2009; Naim et al. 2010; Sullivan et al. 2013a,b). And recently developed objective assessments in the piglet show the feasibility of translating nonverbal assessments used in human studies, including balance, activity/rest, and serum biomarkers, to piglets (Costine et al. 2012; Diaz-Arrastia et al. 2013; Egea-Guerrero et al. 2012; Kilbaugh et al. 2015; Kochanek et al. 2013; Okonkwo et al. 2013).

When the head contacts a stationary or moving object there is a rapid change in velocity and a possible deformation of the skull.

Effects of Velocity Change and Rotation

Researchers have determined that, with or without a helmet, when the head contacts a stationary or moving object there is a rapid change in velocity and a possible deformation of the skull. Skull deformation may produce a local contusion or hemorrhage if the deformations of the tissues exceed their injury thresholds. When the properties of the contact surfaces are softer or allow sliding or deformation, the rate of velocity change is lower. Similarly, if there is no head contact but only body contact, the deceleration of the moving head is usually lower than when the head is contacted directly.

After the initial rapid change in velocity caused by impact to the head or body, the motion of the head is influenced by the location of the initial point of contact and the interaction between the head, neck, and body. There are three possible types of responses to head contact. First, if the contact is directed through the center of mass of the brain (centroid), there may be linear motion and no rotation of the head. Animal studies have shown that these purely linear motions produce little brain motion or distortion and no concussion (Hardy et al. 2001; Ommaya and Gennarelli 1974; Ommaya and Hirsch 1971; Ommaya et al. 1966).

However, most often the contact force is not directed through the centroid of the brain, and in the second type of response to contact the head may rotate without a linear motion (e.g., shaking the head "no"). The rotational motion produces a distortion of the brain's neural and vascular structures in the skull because the brain is softer than and loosely coupled to the skull.

Third, and more commonly, a head impact produces both linear acceleration and rotation of the head. Internal structures of the head, such as the falx cerebri and tentorium, influence how the brain moves in the skull and may cause local brain regions to have very high deformations only in certain directions of head rotation. For example, sagittal and coronal rotations may produce more severe injuries in primates at lower accelerations and velocities (Gennarelli et al. 1982).

Moreover, animal and human studies have shown a general trend that higher rotational velocities and accelerations—rather than linear accelerations—can cause larger diffuse brain deformations and worse diffuse brain injuries (Gennarelli et al. 2003; Kimpara and Iwamoto 2012; Ommaya and Hirsch 1971), and that head injuries depend on the direction of head motion as well as on the magnitude of rotational kinematics (Eucker et al. 2011; Gennarelli et al. 1981; Ommaya and Gennarelli 1974; Sullivan et al. 2013a, 2015). Animal studies have indicated that it is important to limit the duration of exposure to acceleration, as concussions occur when that duration is increased (Ommaya 1966; Ommaya et al. 1966).

Research in New Tools and Technologies to Increase Understanding

Ongoing studies are identifying the causal relationship between head rotational acceleration magnitude and direction and head injury outcomes, and the influence of age, sex, and previous exposures to head injury. But further research is needed to understand the biomechanics of concussion and define thresholds for rotational accelerations associated with concussion across the age spectrum.

Emerging research in objective, involuntary neurofunctional metrics and biomarkers can bridge the gap between human and animal research, and provide

important insight into the biomechanics of concussion, to provide a rational foundation for injury prevention, safety equipment design, rules of play, treatments and interventions.

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Intense research efforts are under way to identify biomarkers to detect and monitor chronic traumatic encephalopathy during life.

Association between Repetitive Head Impacts and Development of Chronic Traumatic Encephalopathy

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The variety of clinical symptoms associated with boxing was first described in 1928 by Harrison Martland, who found abnormalities in "nearly one half of the fighters who have stayed in the game long enough." The general public referred to the condition as "punch drunk," "goofy," and "slug-nutty" (Critchley 1957; Parker 1934), and the scientific terms were *dementia pugilistica* (Millspaugh 1937) and *chronic traumatic encephalopathy* (CTE) (Critchley 1949).

The clinical symptoms of CTE typically develop insidiously, years to decades after exposure to repetitive brain trauma (Corsellis et al. 1973; McKee et al. 2013; Stern et al. 2013), although occasionally they develop while an individual is still active in a sport and may be difficult to distinguish from prolonged postconcussive syndrome. A distinguishing feature between postconcussive syndrome and CTE is that symptoms of the former do not progress to become more debilitating (Mez et al. 2016b).

The age at onset of CTE symptoms is often midlife (mean = 44.3 years, standard error of the mean [SEM] = 1.5, range 16–83 years), decades after retirement from the sport (mean = 14.5 years, SEM = 1.6, n = 104). Nearly a quarter of individuals later diagnosed with CTE were symptomatic at the time of their retirement from sports. The clinical course is often protracted (mean duration = 15.0 years, SEM = 1.2, n = 125) (McKee et al. 2013; Stein et al. 2014, 2015).

Clinical Features of CTE

Presentation

The clinical presentation of CTE characteristically begins in one or more of four distinct domains: mood, behavior, cognitive, and motor. The mood disorder is most commonly depression. Behavioral symptoms include explosivity, verbal and physical violence, loss of control, impulsivity, paranoia, and rage behaviors (Montenigro et al. 2014; Stern et al. 2013). Cognitively, the most prominent deficits are in memory, executive functioning, and attention. Approximately 45 percent of subjects with CTE develop dementia, and in individuals over the age of 60 years at the time of death, dementia was found in 66 percent. Motor symptoms such as dysarthria (unclear articulation), dysphagia (difficulty swallowing), coordination problems, and Parkinsonism (tremor, decreased facial expression, rigidity, and gait instability) may also develop (Mez et al. 2013). Chronic headaches also occur in 30 percent (Stern et al. 2013).

Stern and colleagues (2013) distinguish two courses of clinical presentation. The first presents with mood and behavioral symptoms early in life (mean age = 35 years) and progresses in severity to include cognitive symptoms later in the disease course. The second presents with cognitive symptoms later in life (mean age = 60 years) and often progresses to include mood and behavioral symptoms.

Diagnosis

Preliminary criteria for the clinical diagnosis of CTE have been proposed by three groups (reported in Jordan 2013; Montenigro et al. 2014; Victoroff 2013). The criteria differentiate between possible and probable CTE based on various clinical symptomology and follow a structure similar to the National Institute on Aging–Alzheimer's Association clinical diagnostic criteria for other neurodegenerative diseases (McKhann et al. 2011). The Montenigro criteria distinguish between the clinical syndrome of CTE, referred to as *traumatic encephalopathy syndrome* (TES), and the pathological diagnosis of CTE, which is based on postmortem evaluation. TES is further characterized in subtypes—behavioral/mood variant, cognitive variant, mixed variant, and TES dementia—based on the presence or absence of various groups of symptoms (Montenigro et al. 2014).

To date, nearly all information collected regarding the clinical presentation of CTE has come from retrospective analysis of subjects analyzed after death (McKee et al. 2013; Stern et al. 2013). Ongoing large-scale retrospective studies, such as the recently funded Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) UO1 project funded by the National Institute of Neurological Disease and Stroke (NINDS) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB), examine the clinical presentation of brain donors designated as "at risk" for the development of CTE, develop a blinded consensus clinical diagnosis, and compare that diagnosis to equally blinded postmortem neuropathological assessment (Mez et al. 2015).

Preliminary indications are that the clinical criteria for CTE are highly sensitive but lack specificity (Mez et al. 2016a). Additional analyses using data from the UNITE study will provide detailed information on the specificity of item-level symptoms to allow further refinements in the clinical criteria. Recent funding of large-scale longitudinal prospective studies will also help clarify the precise clinical distinctions between CTE and other neurodegenerative and neuropsychiatric disorders.

The most prominent cognitive deficits are in memory, executive functioning, and attention, and about 45 percent of subjects with CTE develop dementia.

In Vivo Biomarkers

The use of in vivo biomarkers could greatly improve the accurate diagnosis of CTE during life, as well as facilitate the monitoring of disease progression and the efficacy of disease-modifying therapies. While no diagnostic biomarkers are currently available, several promising techniques are being developed.

Tau-specific ligands used in positron emission tomography have demonstrated encouraging results in Alzheimer's disease (Chien et al. 2013; Xia et al. 2013) and mild cognitive impairment (Johnson et al. 2015). Studies using diffusion tensor imaging have detected changes in white matter integrity after head trauma (Koerte et al. 2012). Other studies have examined functional connectivity through the use of functional magnetic resonance

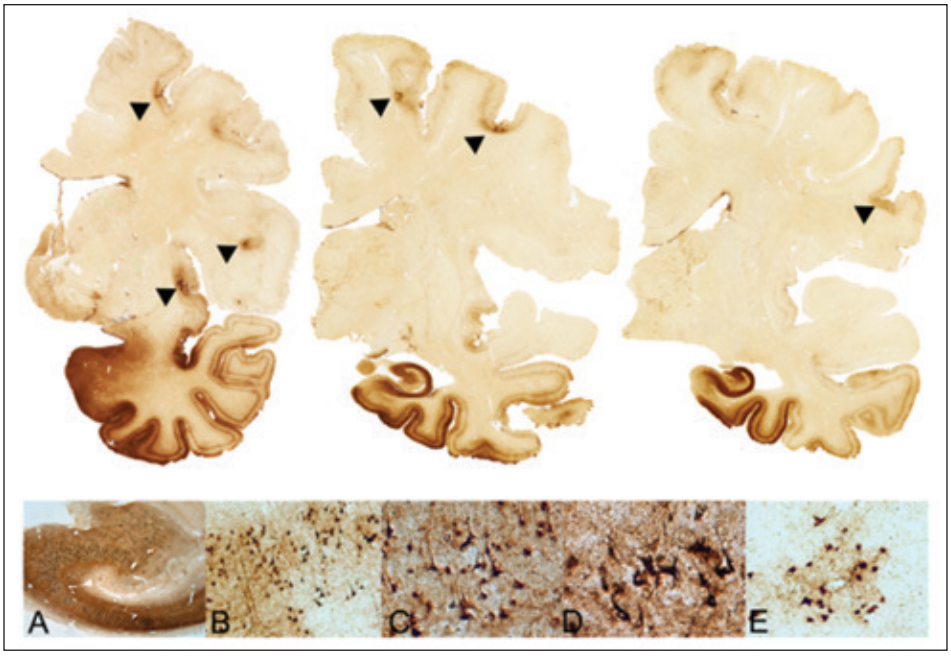

FIGURE 1 Neuropathological changes in advanced (stage IV) chronic traumatic encephalopathy (CTE). Whole mount coronal sections (top row) show widespread phosphorylated tau pathology, most severe at the depths of the cortical sulci in the frontal and insular cortices (arrowheads). Microscopically there are dense neurofibrillary tangles and thorned astrocytes (dark spots in the bottom row of images) in all regions of the hippocampus (A), superficial layers of cortex (B,C,D), and perivascular regions (E). All images: 50 μ tissue sections, CP-13 immunostain.

imaging, magnetic resonance spectroscopy, and cerebrospinal fluid and plasma protein markers (including phosphorylated [p-tau] and total tau) (Buerger et al. 2006; Lin et al. 2012; McKhann et al. 2011) as potential in vivo diagnostic tools.

Neuropathology of CTE

Gross Pathology

The neuropathology of CTE is distinctive. Although grossly identifiable changes are minimal in early stages of CTE, in advanced disease there may be macroscopic changes such as reduced brain weight, cerebral atrophy (most severe in the frontal, anterior temporal, and medial temporal lobes), fenestrations in the cavum septum pellucidum, enlargement of the lateral and third ventricles, thinning of the corpus callosum, atrophy of the diencephalon and mammillary bodies, and depigmentation of the locus coeruleus and substantia nigra.

Microscopic Pathology

Microscopically, CTE is characterized by the deposition of hyperphosphorylated tau protein as neurofibrillary tangles (NFTs), thorned astrocytes (TAs), and neurites in a unique pattern in the brain. The tau pathology is characteristically a perivascular distribution and shows a predilection for the depths of the cerebral sulci.

In 2013 my colleagues and I described a spectrum of p-tau pathology in 68 male subjects, ranging in age from 17 to 98 years (mean 59.5 years), with a history of exposure to repetitive brain trauma and neuropathological evidence of CTE. Based on our findings we proposed provisional criteria for neuropathological diagnosis and a 4-tiered staging scheme of pathological severity (McKee et al. 2013).

Stage I CTE is characterized by isolated perivascular foci of p-tau as NFTs and TAs present at the sulcal depths of the cerebral cortex. In stage II multiple foci of p-tau are found in the cerebral cortices, and in stage III NFTs appear in the superficial cortices adjacent to the focal epicenters, with involvement of the medial temporal lobe structures (hippocampus, amygdala, and entorhinal cortex). In Stage IV CTE there is severe widespread p-tau pathology in the cortices, diencephalon, brainstem, and cerebellum (figure 1) (McKee et al. 2013).

Other abnormalities encountered in severe CTE include abnormal deposits of the phosphorylated transactive response DNA-binding protein (TDP-43) that occasionally colocalizes with p-tau, and varying degrees of beta-amyloid (Aβ) pathology, axonal dystrophy, and neuroinflammation (McKee et al. 2010, 2013).

It is worth noting that, among former American football players, we found that the stages of CTE severity correlated significantly with the duration of exposure to football, age at death, and years since retirement from the game (McKee et al. 2013).

Beta-Amyloid Plaques

Beta-amyloid plaques are present in 52 percent of individuals with CTE (Stein et al. 2015). In contrast to the extensive Aβ plaques that characterize nearly all cases

of Alzheimer's disease, Aβ plaques in CTE, when they occur, are less dense and predominantly diffuse (McKee et al. 2009). They are also significantly associated with accelerated tauopathy, Lewy body formation, dementia, Parkinsonism, and inheritance of the ApoE4 allele (Stein et al. 2015).

Neuropathological Diagnosis

As the first part of a series of consensus panels funded by the NINDS/NIBIB to define neuropathological criteria for CTE, the criteria set forth in McKee et al. (2013) were used by seven neuropathologists to evaluate 25 cases of various tauopathies: CTE, Alzheimer's disease, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, primary age-related tauopathy, and Parkinsonism-dementia complex of Guam. The researchers evaluated the cases blinded to all information on age, gender, clinical symptoms, diagnosis, athletic exposure, and gross neuropathological findings and determined that there was good agreement between reviewers and the diagnosis of CTE and excellent identification of the cases of CTE.

Based on these results, the panel refined the diagnostic pathological criteria for CTE and defined a pathognomonic lesion for CTE, an accumulation of abnormal tau in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci and in an irregular pattern. The panel also defined supportive but nonspecific features of CTE (NINDS 2015).

Recently, two large neurodegenerative disease brain banks have reported comorbid CTE in their series (Bieniek et al. 2015; Ling et al. 2015). Bieniek and colleagues reported that 21 of 66 (31.8 percent) former athletes had cortical tau pathology consistent with CTE on postmortem neuropathological examination, whereas no CTE pathology was detected in 198 individuals who had no exposure to contact sports, including 33 individuals with documented single-incident traumatic brain injury (TBI) (Bieniek et al. 2015). Ling and colleagues found the occurrence of CTE in 11.9 percent of 268 screened cases of neurodegenerative diseases, associated with a history of TBI in 94 percent of those who exhibited CTE.

Conclusion

CTE is a neurodegenerative disease that occurs after exposure to repetitive head trauma. Cumulative exposure to trauma, not the number of concussions, is associated with the severity of p-tau pathology, suggesting that subconcussive impacts are important for disease development.

CTE most commonly manifests in midlife and produces clinical symptoms of disordered cognition, memory loss, executive dysfunction, depression, apathy, disinhibition, and irritability as well as Parkinsonism. The neuropathology of CTE is increasingly well defined; a NINDS/NIBIB panel of expert neuropathologists has identified preliminary criteria and a pathognomonic lesion for the neuropathological diagnosis of CTE. Currently, neuropathologic examination of postmortem brain tissue is the only way to diagnose CTE, although intense research efforts are under way to identify biomarkers to detect and monitor the disease during life and to develop therapies to slow or reverse its course.

Newly funded longitudinal, prospective research efforts will shed additional light on critical variables related to head trauma exposure, genetics, and lifestyle factors that influence the development of CTE.

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Federal safety standards and technological advances are helping to reduce concussion and other injuries associated with motor vehicle crashes.

Preventing Concussions in Motor Vehicle Crashes

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In the past 10 years, traffic deaths have dropped by about 25 percent (NHTSA 2015b), which is a remarkable public health improvement in a short period of time. Even so, nearly 90 people die and 2.3 million are injured every day in motor vehicle crashes in the United States (NHTSA 2015c). The Centers for Disease Control and Prevention estimates that motor vehicle crashes are the country's third leading cause of traumatic brain injury (TBI) and the leading cause of death from TBI (Faul et al. 2010).

The mission of the National Highway Traffic Safety Administration (NHTSA) is to save lives, prevent injuries, and reduce the economic burden associated with motor vehicle crashes. To that end, the agency tracks data, conducts research, administers safety grants to states, and proposes federal standards to enhance traffic safety.

The Work of NHTSA

The two primary areas of concern for NHTSA are the safety of vehicles and the behavior of drivers and road users. Our work in these areas is based on data derived from crashes—behavioral and vehicle factors leading up to the crash, how the vehicle behaves in the crash, how the occupant interacts with the inside of the vehicle during the crash, and the injury consequences.

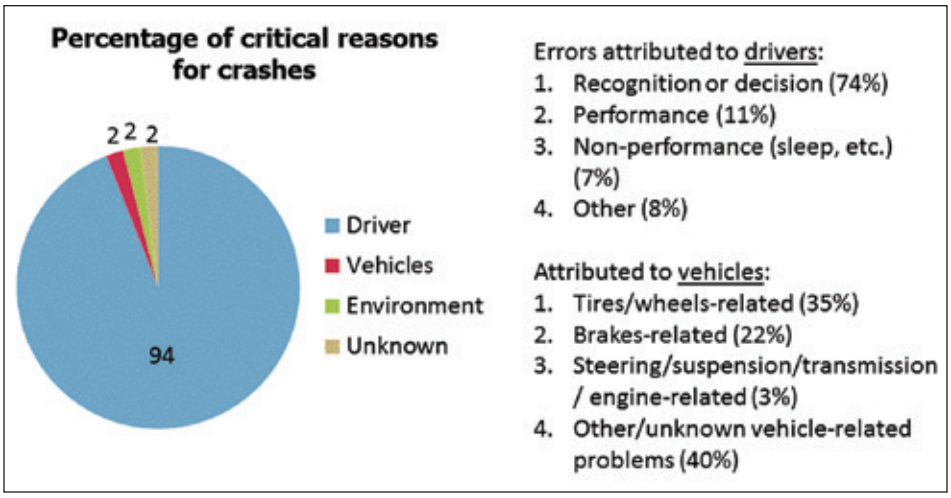

FIGURE 1 Critical reasons for motor vehicle crashes. Source: Singh (2015).

Federal Safety Standards

NHTSA sets federal motor vehicle safety standards for vehicles sold in the United States. One of the measures used to assess the performance of vehicles in crashes is the head injury criterion (HIC), a measure of linear acceleration that we use for research and regulatory purposes.

A number of NHTSA standards are based on the HIC, and they have been quite successful in reducing concussion and other serious injury as well as fatalities. For example, the addition of interior padding in vehicles has saved about 35,000 lives since it was introduced in the late 1960s, and seat belts have saved about 330,000 lives over the same time period—really remarkable for a relatively simple device. Child restraint systems have saved about 10,000 lives (Kahane 2015), and side impact protection has saved about 35,000 lives. Ejection mitigation technologies, which include curtain airbags, were recently introduced and have already saved hundreds of lives (Kahane 2014).

It is difficult to calculate cumulative numbers for motorcycle helmets, but we estimate that in 2014 they saved about 1,600 lives (NHTSA 2015a).

Crash Data Collection

Since the 1970s NHTSA has collected detailed information on every traffic fatality in the United States. The Fatality Analysis Reporting System (FARS) includes several hundred data elements on each crash. Complementing this census of roadway fatalities is a crash sampling system that can provide detailed information on injuries associated with vehicular crashes.

NHTSA has also established six crash research centers around the country as part of a Crash Injury Research and Engineering Network (CIREN). Each CIREN center typically involves a medical school and an engineering school working together to research about 50 crashes per year and publish their data and analysis.

Based on its extensive injury research, NHTSA is developing a brain injury criterion, which includes a rotational element that will complement the linear HIC measurements. Researchers hope that these measures and criteria will make it possible to better design the interior of vehicles—and reduce the number of fatal car crashes, which currently account for more than 32,000 deaths per year (NHTSA 2015c).

The Role of Behavior

Human behavior is by far the weakest link in motor vehicle safety. Our research indicates that 94 percent of all crashes are caused by driver factors; the vehicle is a factor in only about 2 percent of crashes, the roadway in about 2 percent, and other factors, including weather, account for the remaining 2 percent (Singh 2015) (figure 1). NHTSA therefore examines opportunities to change behavior to prevent crashes.

Seat Belt and Helmet Use

The reluctance of many vehicle occupants to use seat belts and of motorcycle riders to wear compliant helmets costs lives. Seat belt use rates are now at 87 percent; 100 percent use would save 2,800 more lives annually. Universal use of motorcycle helmets could save more than 700 additional lives per year. These are very low cost interventions that have high-value potential returns.

A further important objective is to increase use of motorcycle helmets that meet the Federal Motor Vehicle Safety Standards. A significant portion of motorcycle riders choose not to wear helmets certified to meet the safety standard, instead wearing noncompliant helmets that are fashionable but provide very little protection in a crash (figure 2). NHTSA recently issued

a Notice of Proposed Rulemaking (NHTSA 2015a) that aims to prevent manufacturers from selling helmets that do not meet the safety standards.

FIGURE 2 Motorcycle helmets. Only the two at the far right are certified by the US Department of Transportation. Source: NHTSA.

Technology to Address Behavioral Challenges

NHTSA and other researchers are identifying ways to address risky behaviors through technology.

Alcohol-impaired driving accounted for 31 percent (9,967) of all traffic fatalities in 2014 (NHTSA 2015c). The ignition interlock is a technology that prevents repeat offenses of driving while impaired. It requires a driver to breathe into the device before starting the vehicle; if the driver's blood alcohol concentration is above a preset limit the ignition interlock will not allow the vehicle to start. Research has shown that, while installed on an offender's vehicle, interlocks reduce repeat offenses among both first-time and repeat offenders, and even predict the risk of repeat offenses after removal (Mayer 2014).

By 2014 all states had enacted legislation requiring or permitting the use of interlocks to prevent alcohol-impaired driving. Laws and procedures vary by state, but interlocks are generally required after arrest, may be removed after a certain period of time, and may be a condition of reinstatement of a suspended license (Mayer 2014).

The Role of Emerging Technologies

The long-term solution to motor vehicle crashes may eventually be automated and driverless vehicles. Experimental vehicles now show great promise, but much research and development are needed to ensure their safe and reliable operation on a widespread basis on the roads.

NHTSA and other organizations are pilot testing vehicle-to-vehicle (V2V) and vehicle-to-infrastructure communication systems that use crash avoidance technology to warn drivers about dangerous situations that could lead to a collision. For example, V2V could warn that a vehicle up ahead is braking and the driver needs to slow down, or that it is not safe to proceed through an intersection because another car, unseen by the driver, is quickly approaching (NHTSA 2014).

In the meantime, a number of currently available driver warning systems can compensate for lack of attention and driving-skill problems. For example, some vehicles are now equipped with lane departure warning systems, and many cars have brake-assist systems and even automatic emergency braking systems. Increasingly, there will be opportunities for technologies to assist drivers in other safety-sensitive tasks.

These and other safety systems will be highlighted in NHTSA's New Car Assessment Program to educate consumers and increase demand for these important features. Driver assistance and automation systems are very promising, but the judgment, vigilance, and skill of drivers and other users remain crucial to improve road safety for the foreseeable future.

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An IED blast wave would seem to cause a unique form of TBI, but the data needed to make such a determination are scarce.

Military TBI
Is It the Same as Civilian TBI?

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Traumatic brain injury (TBI) represents a major public health issue in the United States: it is estimated that 5.3 million Americans have long-term disabilities related to a TBI (Thurman et al. 1999), equivalent to the number of patients with Alzheimer's disease (Alzheimer's Association 2015).

According to the Centers for Disease Control and Prevention, each year patients suffering a TBI cause at least 2.2 million visits to an emergency room in the United States (Faul et al. 2010). The more severe forms of TBI lead to 280,000 hospitalizations and are responsible for 52,000 deaths annually. In fact, TBI is the leading cause of death of individuals between the ages of 1 and 44 years. The annual number of deaths associated with TBI exceeds those associated with more widely acknowledged health problems, such as breast cancer (40,000 deaths/year) and influenza (50,000 deaths/year) (Faul et al. 2010).

Among the more common events leading to TBI are falls, motor vehicle accidents, assaults, and participation in contact sports. But a significant number of US citizens who suffer from the long-term effects of a TBI are current or retired servicemembers, especially those who served in Iraq and

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The opinions expressed herein are those of the author and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

FIGURE 1 Improvised explosive devices (IEDs) are the major threats in current warfare. They are the leading cause of casualties, estimated at approx. 30,000 in 2000–2015. Source: "FPCougar" by US Department of Defense, available at www.marcorsyscom.usmc.mil/ (licensed under public domain via Commons, https://commons.wikimedia.org/wiki/File:FPCougar.jpg#/media/File:FPCougar.jpg).

Afghanistan. Yet it is not known whether or how their symptoms differ from those of nonbattlefield TBI.

Given the sizable number of those affected, it is unclear why TBI remains underrecognized as a major public health problem by the lay public and those who establish policies for research funding.

Defining TBI and Concussion

Most TBIs—civilian and military—are classified as mild, commonly referred to as *concussion*. Concussion is generally defined as a transient loss of neurologic function following a blow to the head. This alteration of neurologic function may be a loss of consciousness (being "knocked out"), and many people mistakenly assume that loss of consciousness is required for a diagnosis of concussion. But symptoms may include an episode of temporary disorientation or a brief loss of memory of events without any loss of consciousness.

Concussion represents a clinical phenomenon and is not necessarily associated with any specific morphologic alterations in brain tissue integrity. Indeed, by definition, cases of concussion may not show any morphologic abnormalities on routine brain imaging by either computed tomography (CT) scanning or magnetic resonance imaging (MRI) studies.

More serious forms of TBI are characterized by the presence of a variety of abnormalities in and around the brain, including focal damage to brain tissue and the accumulation of blood in the brain itself or adjacent to it.

TBI in Military Servicemembers

Mild TBIs are common occurrences among people who serve in the military, and most are identical in nature to those seen in civilians. In fact, approximately 50 percent of new enrollees in the military indicate that they have already had at least one TBI.

On the battlefield, however, most brain injuries that military servicemembers experience are of a very different nature and represent some unique challenges.

Causes

During the past 14 years of US engagement in the wars in Iraq and Afghanistan the enemy has made use of a particularly potent weapon, the improvised explosive device (IED). IEDs are constructed using high explosive charges and metallic fragments (e.g., ball bearings) placed in a container that is hidden from sight, typically buried under a roadway. The device is detonated remotely when the target is in the vicinity (figure 1).

IEDs can have devastating effects on vehicles and personnel. They produce a rapidly expanding high-pressure blast wave that may be powerful enough to throw a vehicle roughly the size and weight of a city garbage truck more than 30 feet into the air.

In previous wars, when servicemembers lacked modern protection, exposure to an IED would have been fatal. Improvements in the design of body armor and modern helmets have saved the lives of countless servicemembers involved in combat. Those in the vicinity of an IED explosion commonly survive and *appear* to be

relatively unharmed. However, initial data indicate that 84 percent of all IED-related concussions occur within 10 meters of the blast, and 93 percent within 30 meters (IOM 2014).

Symptoms and Diagnosis

A significant percentage of servicemembers who have been in close proximity to detonated high explosives such as IEDs subsequently develop persistent neurologic and behavioral symptoms. These may include headaches, sleep disorders, memory problems, difficulty concentrating, depression, anxiety, and a tendency toward suicide. Most of these symptoms are referred to under the term *postconcussive syndrome* (PCS), but there is a significant overlap between this relatively nonspecific entity and the closely related mental health problem referred to as *posttraumatic stress disorder* (PTSD). Sorting out the differences between these two conditions, PCS and PTSD, has been a significant challenge for clinical evaluators of both active duty servicemembers and veterans.

Animal experiments have shown that the blast wave produced by a high explosive can pass through the skull as a pressure pulse and exert a force on brain tissues, but the specific effects on human brain tissue remain unclear (Rosenfeld et al. 2013). The study of such effects is complicated by the fact that there are very few real-life examples of pure blast injury. Almost invariably, with blast exposure come additional injuries (e.g., from flying fragments of shrapnel and other debris) as well as impact trauma (e.g., from the individual's body being propelled at high speed into a solid object from the blast wind that accompanies the explosion). Better understanding of the variety of effects requires examination of many brain specimens from individuals who have suffered blast explosive TBI, with both short-term and prolonged survival after the event.

Adding to the difficulty of diagnosis and treatment, many servicemembers have suffered multiple episodes of blast-related TBI during their repeated deployments to Iraq and Afghanistan. These servicemembers may be at risk for chronic traumatic encephalopathy (CTE), a progressive neurodegenerative disorder that has been seen almost exclusively among athletes who engage in contact sports (e.g., boxing, football, and hockey) and are exposed to repeated impact TBIs (as discussed in other papers from this symposium). CTE is defined by the presence of focal accumulations of the tau protein in the brain in a unique and characteristic distribution pattern, primarily within neurons, astrocytes, and neuronal processes. But only a small number of cases of CTE in servicemembers exposed to IEDs during deployment have been reported in the medical literature (Goldstein et al. 2012; McKee and Robinson 2014; Omalu et al. 2011).

Further complicating the picture is the fact that some servicemembers shown to have CTE at autopsy had participated in contact sports or experienced other types of TBI-inducing incidents such as falls or motor vehicle accidents. Therefore, whether repeated blast TBI alone leads to CTE remains unclear, and how frequent this consequence might be among military personnel is also unknown. The answers to such questions can help determine appropriate diagnosis and treatment for active servicemembers and veterans.

A significant percentage of servicemembers who have been in close proximity to a detonated IED develop persistent neurologic and behavioral symptoms.

Research Opportunities

Although high explosives were introduced into warfare in World War I, there has been very little study over the past 100 years of the pathology of blast TBI in the human brain and it is still not known whether military TBI is different from civilian TBI.

Exposure to a blast wave related to an IED or similar explosive would appear to cause a unique form of traumatic injury, especially when such exposures are multiple. But the data needed to make such a determination are scarce. Clearly, there will be some overlap between what is seen in TBI among civilians and the TBI experienced by military personnel. Much more study is needed to sort out the differences between the two.

At the Uniformed Services University of the Health Sciences (USUHS), the congressionally mandated Center for Neuroscience and Regenerative Medicine (CNRM) has established a repository of brain tissue donated for use in research. This unique facility collects

specimens from either active duty or former servicemembers, both with and without a history of TBI in their military careers. The tissue specimens are made available to researchers for the study of TBI, especially as it is encountered among military personnel.

It is through the study of donated brain specimens that many important questions can be answered. For more information on the CNRM-USUHS Brain Tissue Repository or to arrange for brain donation, please visit our website (www.researchbraininjury.org) or call 855-366-8824.

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Simulations can be used to translate the results of animal studies to human injury risk curves and guide the design of protective gear.

Computational Models of Impact and Blast Force Effects on the Brain

Scaling of Animal Injury Models and Prediction of Human TBI

Raúl A. Radovitzky, James Q. Zheng, and Thomas F. Budinger

Raúl A. Radovitzky

James Q. Zheng

Thomas F. Budinger

The goal of our research is to determine the forces transmitted to the brain resulting from the stress field of a military blast, fall, or sport or vehicle collision involving the head. This information is essential to link the external insult to the mechanism of brain tissue injury.

Epidemiological and experimental animal data relate the injury pathology to the physical parameters of the external impact, but there are several limitations. Biofidelic physical models do not include the necessary distribution of tissue stimulants with accurate tissue material properties of the human head

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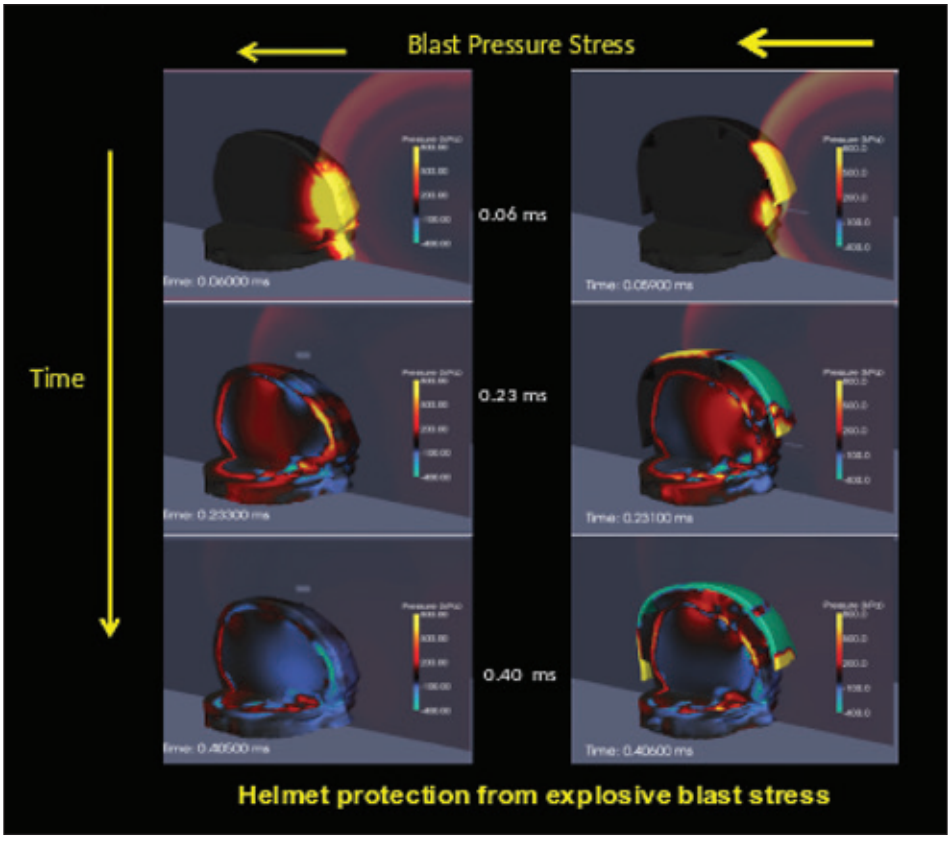

FIGURE 1 Pressure contours in simulations of the unprotected head (left) and helmeted head (right). The scale is from −400 to 800 kPa (kilopascals). Reprinted from Nyein et al. (2010).

and brain, nor the required spatial distribution of pressure sensors, to allow stress field measurements with the needed temporal and spatial fidelity. Human cadaver studies are limited by postmortem changes in material properties as well as the logistics of performing them in realistic blast and projectile impact situations. Sensors in helmets that relate acceleration and deceleration levels to a victim's behavior reveal no information about the internal mechanisms of tissue injury or even reliable thresholds for concussions.

Computer simulations can provide the high spatial and temporal resolutions needed to evaluate three-dimensional stress fields as a function of time. And the material properties corresponding to tissues of the head, skull, and brain can be assigned to human head models using magnetic resonance imaging (MRI) data and archival tissue property measurements.

Need for Animal Models

Animal models are needed to relate external forces to internal stress fields, but are useful only if the tissue injury probability functions can be translated to expectations for the human head and brain. In this paper we describe a scaling law that allows this vital transformation from animal experiments on many species to the human situation.

Knowledge of the internal force fields generated by the external impact of a broad range of physical threats will enable understanding of the mechanisms of injury. This knowledge is basic to the determination of the tolerances of the brain to external trauma and to the development of improved protection systems. Linkages between the transfer of momentum or rate of change of momentum (force) and types of tissue injury cannot be determined from current experimental data without a validated scaling law from an animal species to the human head and brain. Nor can the distribution of tissue injury and long-term effects be understood without knowledge of the stress fields and accompanying strains for specific physical impacts to the head.

Human Head and Brain Blast Simulation Studies

We performed a critical set of experiments to answer the question, Do the helmet and face mask afford important protection to the soldier exposed to a blast? The two major components of the experiments were a detailed model of the human head and a detailed description of the temporal stress field for blasts up to 800 kilopascals (kPa) arriving at the head.

Simulation of the Human Head and Brain

The design of a simulation model of the human head and brain started with an anatomical description of the position and type of all the tissues. For each tissue we assigned material parameters including elastic properties such as Young's modulus, the shear modulus, and viscoelastic properties, as well as anisotropy

tensors obtained by detailed diffusion tensor imaging using magnetic resonance. We developed this model with the Defense and Veterans Brain Injury Center (Moore et al. 2009); it was the most comprehensive model of human head material properties, with the highest spatial resolution that was practical given the computing power available.

To evaluate the protection afforded by the advanced combat helmet (ACH) we added its material properties (e.g., poroelasticity), including padding and air spacing, as these are critical to the proper description of reflections and transmission at acoustic impedance–mismatched surfaces. We added the ACH face shield position and properties as well.

Simulation of the Blast

The next major component of the experiment was a physically accurate description of the blast itself. This was a three-dimensional hydrodynamic model. The mathematical tools and related algorithms for executing the time-dependent changes of a blast involved extensive calculations that the MIT group has been perfecting for many years.

In our first experiments we showed that a blast wave has a direct transmission of stress waves into the brain through regions of the skull with soft tissue (e.g., ear canals, sinuses, nasal orifices) (Moore et al. 2009). The direction of the blast is an important determinant of the resulting stress fields in the brain, which is also the case for hits to a helmet. Figure 1 shows simulations to quantitatively evaluate the effectiveness of the helmet and shield (Nyein et al. 2010). We found that both the helmet and face shield provided significant protection, an important finding as there had been a major controversy about the possibility that the helmet increased the risk of brain injury. The results made a major impact on military protection science.

Validation of these findings using a skull and tissue stimulants in which pressure sensors were embedded is shown in figure 2. These experiments relate to protective systems for reducing stress fields. The major goal, however, is to determine the relationships between stress fields and resulting brain tissue injuries. For this goal we rely on animal models and some method to translate the data from animal models to the human head and brain.

Animal Models

The experimental arrangements for studying the effects of a range of mechanical events leading to brain tissue injuries differ depending on whether the study is for nonpenetrating low stress-rate collisions (e.g., sports

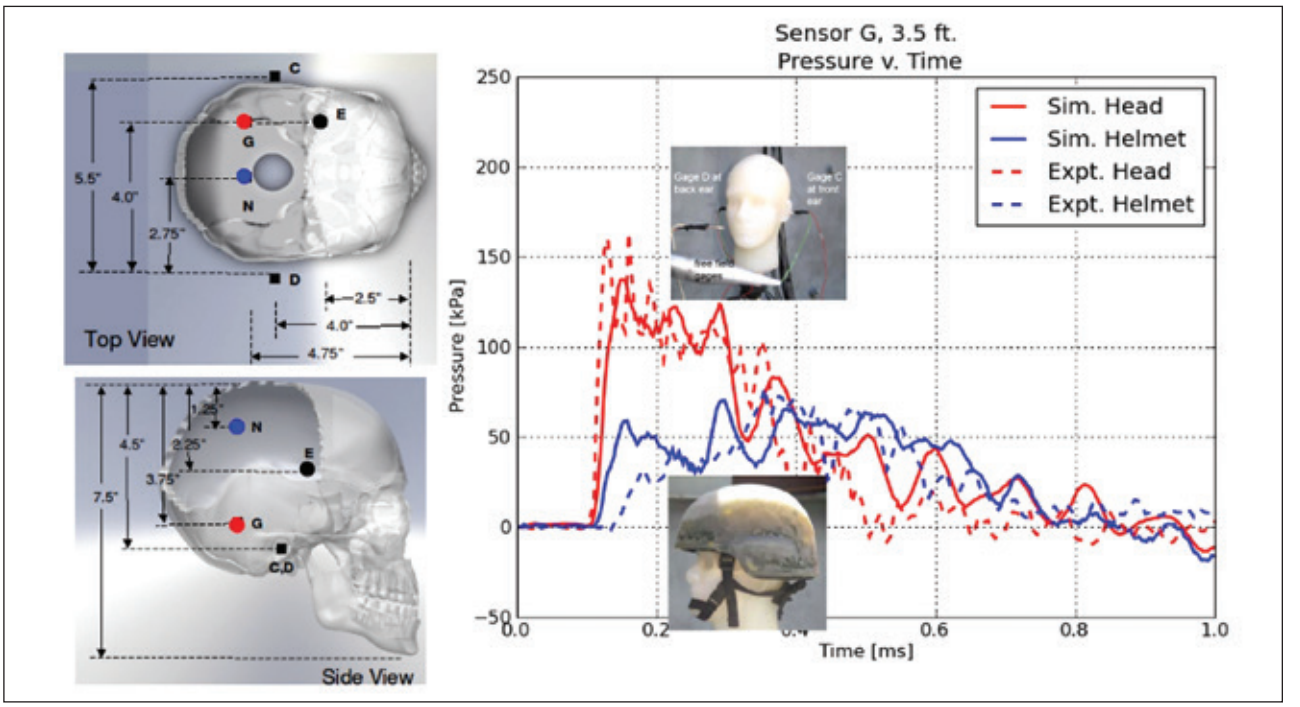

FIGURE 2 Validation against biofidelic surrogate models using tissue simulants and embedded pressure sensors. Both experiments (expt.) and simulations (sim.) consistently show that the Advanced Combat Helmet helps mitigate blast effects on the brain tissue.

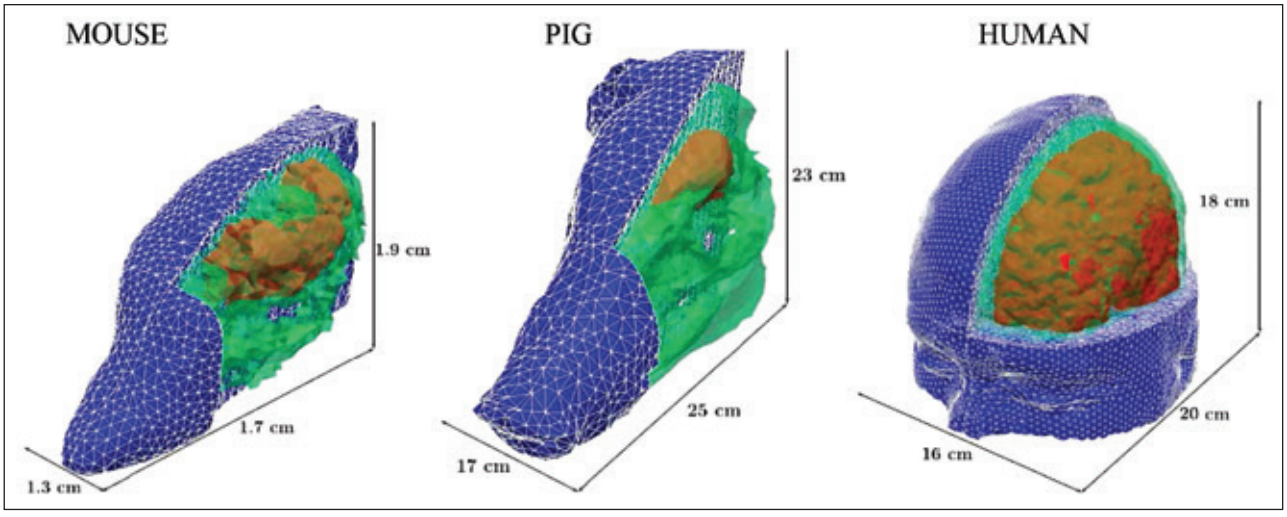

FIGURE 3 Image-based finite element models of the heads of a mouse, pig, and human (not to scale) used in simulations, depicting the relevant tissue structures: skull (green), brain (brown/red), and flesh (blue). Reprinted from Jean et al. (2014).

and vehicle collisions), high stress-rate impacts (e.g., projectiles impacting helmets), or much higher stress-rate events from explosive blasts.

Numerous methods are used to create the accelerations and physical stresses involved, but unfortunately many experiments fall short of the actual conditions experienced on the battlefield. Also problematic is the use of fixed animals that do not undergo the rotational accelerations experienced by human subjects because of the differences between a head mass that is loosely tethered to the body and the total head-body mass. Examples of animal experiments used to evaluate battlefield blast effects are reported in this issue (Kovacs, Margulies) and elsewhere (e.g., Bauman et al. 2009). The results from these experiments show either the probability of a specific injury versus the physical insult or the characteristics of tissue injury from different intensity levels or numbers of hits.

Of key importance to understanding the tolerance of the human brain to exposure to blast and other stress fields is a reliable method for relating the results of animal experiments to the human brain. We present such a method below.

Translation of Animal Experiments to Human Injury Predictions

Motivated by crash injury reduction research in the automotive industry as well as efforts to mitigate battlefield injuries using protective gear, animal experiments have been conducted in this area since World War II. They are usually guided by mechanical and physiological principles, but brain size, head tissue architecture, brain to body mass ratio, skull thickness, and other factors vary widely from species to species. Thus some scaling model is needed to relate the animal experimental data to what would be expected in the human head and brain.

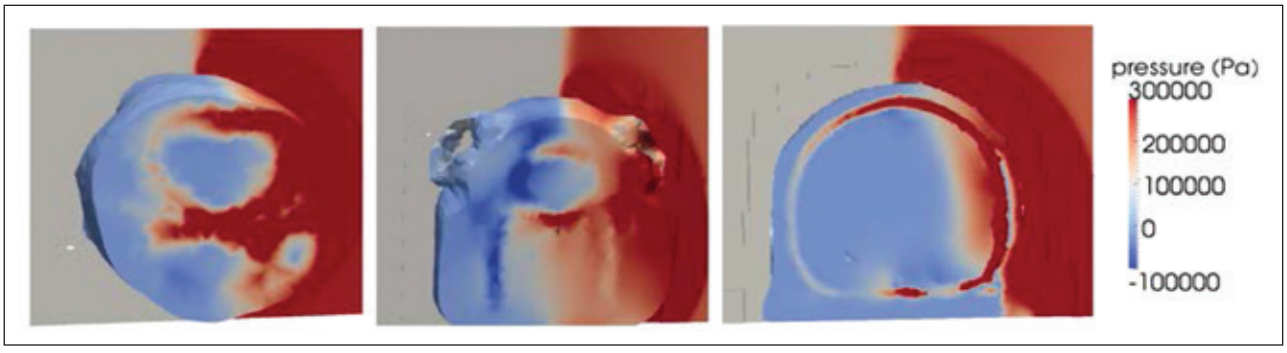

FIGURE 4 Snapshot (from the back of the head) of pressure field in the head tissues of a mouse (left), pig (center), and human (right) at t = 0.34 ms for a blast of 2 ms with an incident overpressure of 200 kPa (kilopascals), illustrating the differences in stress wave transmission across species resulting from the influence of head protective structures (e.g., the skull, skin, flesh). Reprinted from Jean et al. (2014).

Simulations are essential for developing a scaling law. The experiments described here involve simulations with three species—mice, pigs, and humans—that differ greatly in size and head architecture (figure 3). Simulations were performed with these species using three different incident blast pressures. An example is shown in figure 4. The models were based on the anatomy collected by MRI studies and tissue types using parameters similar to those used for human tissue. Once the tissue properties are assigned to volume elements and the physics of a blast is defined in space and time, the simulations give internal pressures relative to exposed stresses.

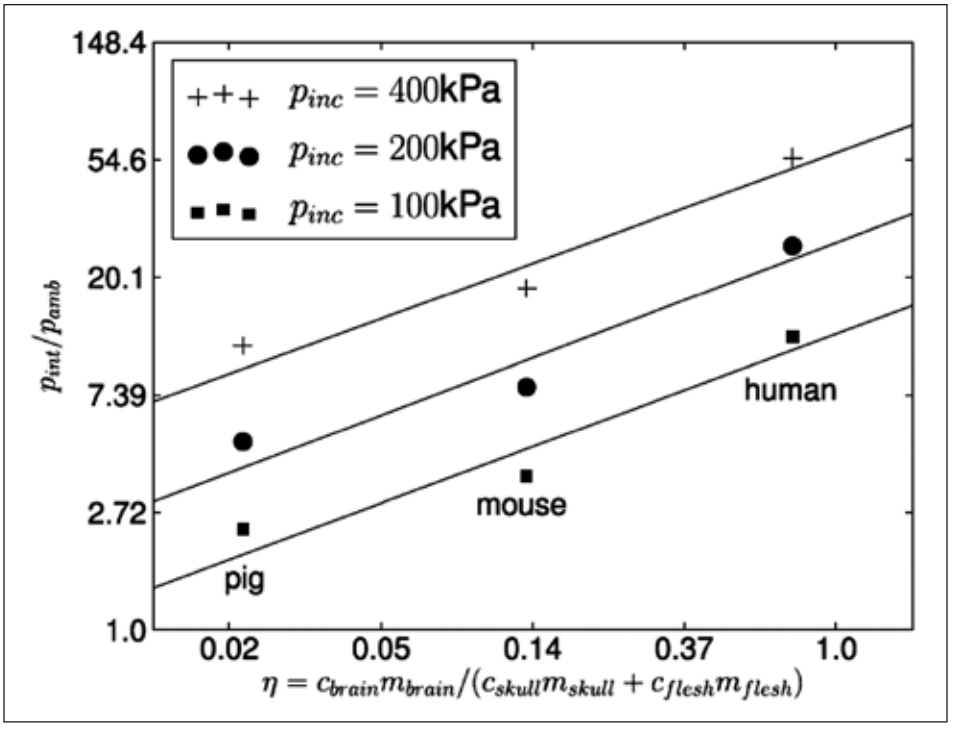

FIGURE 5 Log-log plots of normalized computed peak overpressure vs. η, where C and M denote speed of sound and the mass of the respective tissues. The normalized overpressures are calculated for three different incident blast overpressures and corresponding linear regressions. kPa = kilopascals; P_{amb} = ambient pressure; P_{inc} = incident pressure; P_{int} = intracranial pressure. Reprinted from Jean et al. (2014).

The human brain receives the highest maximum intracranial pressure from a blast, as observed for three different blast intensities in the transmitted stress range associated with concussion. The pig experiences the lowest intensities, due to the ratio of brain to skull and soft tissues. The comparison of human to swine brain mass is even more extreme (figure 3).

A proper parameter for scaling blast effects is a brain vulnerability parameter, η (the horizontal coordinate in figure 5). This is a ratio of (acoustic impedance × the mass of the brain) ÷ the sum of (acoustic impedance × the mass of the skull) + (acoustic impedance × the mass of the head tissues external to the skull). This factor results from considering this as a stress wave propagation problem. The eta parameters are 0.02, 0.13, and 0.75 for the mouse, pig, and human, respectively. The result of this work is summarized in figure 5.

The major conclusion is that humans are the most vulnerable among all mammal species, mostly because of their large brain and the relatively sparse tissue and bone protection of the head. This model enables conversion of an injury threshold S-curve for a particular type of brain injury as determined for one species to the S-curve for the human brain. An example of the major difference in predicted human survivability scaling from rabbit blast survival experiments is shown in figure 6.

Scaling based on mass differences among species (Rafaels et al. 2011) leads to the prediction that the human brain can sustain a higher threshold than the species tested. Our new scaling law actually predicts a much lower threshold for brain injury in humans.

This is of major importance as it allows a much broader use of animal experiments wherein survivability would not be the experimental parameter, using instead other measurements that cannot be performed on human subjects (e.g., axonal injury, accumulation of protein aggregates, micropetechiae).

Complementary studies that compare the histopathology, three-dimensional neuronal architecture, and injury endpoints to information that characterizes the mechanics of the impact cannot reveal mechanisms for the observed injuries without knowledge of the force fields in the brain tissue resulting from the impact. This is the principal value and need for computer simulations with high spatial and temporal fidelity.

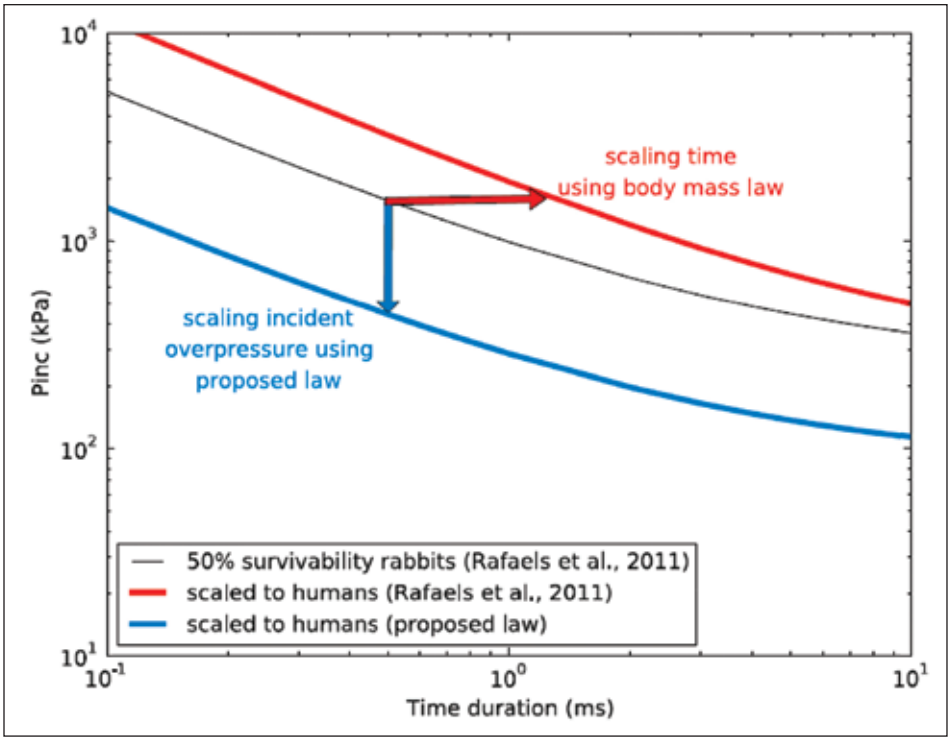

FIGURE 6 Brain injury risk criteria for human derived from rabbit test data using previous body mass scaling and our proposed scaling law accounting for tissue properties and basic animal morphological features. The figure shows plots of incident overpressure vs. time duration in log-log scale. The horizontal red arrow emphasizes the fact that in the case of mass scaling, the scaling variable is the abscissa (time duration), whereas in the new approach (vertical blue arrow) the scaling variable is the ordinate (blast incident overpressure). The black line shows 50 percent survival curve for rabbits: the incident blast overpressure plotted against the time duration, which is a typical plot for a blast injury. kPa = kilopascals; P_{inc} = incident pressure. Reprinted from Jean et al. (2014).

Proposed Studies

Two activities under way are collaborations with the Boston Marathon blast investigation, where our simulations can provide the exposure levels the victims suffered, and with the Lawrence Berkeley National Laboratory and Boston University on the investigation of stress fields in the basal-midbrain regions (including the hypothalamus, pituitary, and amygdale tissues). The long-term effects of head injuries on pituitary function are not understood, though the prevalence of pituitary dysfunction is known in NFL players, survivors of unconsciousness episodes from collisions, and war veterans.

An illustration of the importance of careful simulations with the material properties of each volume element can be appreciated from considering the complex pressure field when the variation of the pressure wave speed can be a factor of 3. The simulation will require 2 mm voxels to compute the strain map for a range of incident stresses and stress rates.

Summary

Computer simulation provides detailed estimates of the forces transmitted to the brain from an impact or blast event that may cause concussion. Animal models are not adequate for determination of the relationship between a collision or blast event and tissue damage in the human subject without a method to translate the risk threshold curves between species as shown in this paper. Simulations can be used to translate the results of animal studies to human injury risk curves and to guide the design of protective gear.

Acknowledgments

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Olfaction deficits and PTSD severity are correlated with both concussion and loss of consciousness.

Impaired Olfaction and Other Indicators of Neurological Damage Due to Mild TBI Associated with Combat

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Robert L. Ruff

Mild traumatic brain injury (mTBI), with or without loss of consciousness, is the most frequent form of TBI in US troops serving in Iraq and Afghanistan (Warden 2006). In 2006, as the director of neurology for the Department of Veterans Affairs, I was involved in setting up TBI care networks in Ohio and in mTBI screening for veterans returning from these two wars. The results described here are from a case-controlled study of Afghanistan/Iraq veterans with mTBI treated at the VA Medical Center in Cleveland.

VA Study of mTBI Effects in Veterans

Studies of combat-related mTBI have revealed a high frequency of posttraumatic stress disorder (PTSD), although the diagnosis of PTSD in veterans has not always been causally related to combat mTBI (Hoge et al. 2008). To investigate possible links between the two, we studied the presence of mTBI (revealed by physical examination) and of neurological deficits (revealed by a structured neurological examination) in US veterans of the wars in Iraq and Afghanistan. We also examined the relationship between the number of episodes of combat mTBI and the presence of neurological deficits and PTSD.

One of the challenges at the time was to evaluate people quickly. To achieve this we assembled a protocol consisting of a 50-element neurological examination, a battery of neuropsychological tests (Ruff et al. 2008), a cognition test (the Montreal Cognitive Assessment, MoCA), a

quantitative olfaction test, and a PTSD symptom severity index (PTSD Checklist–Military Version) (Ruff et al. 2008, 2012a).

There were six study groups of veterans, both military and civilian, based on type of injury: combat-acquired mTBI with loss of consciousness (LOC) (126 subjects); combat mTBI without LOC (52 subjects); combat without TBI (21 subjects); civilian mTBI with LOC (21 subjects); civilian mTBI without LOC (21 subjects); and civilian veterans without TBI (21 subjects).

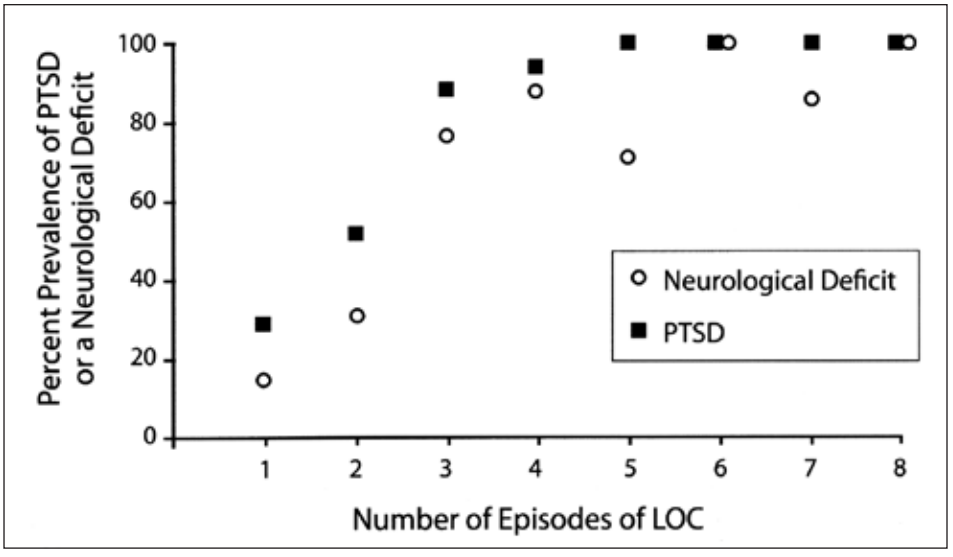

FIGURE 1 Association between number of episodes of mild traumatic brain injury (mTBI) with loss of consciousness (LOC) and prevalence of neurological deficits or posttraumatic stress disorder (PTSD). Modified from figure 2 in Ruff et al. (2012a).

Link between mTBI and PTSD

We observed the following correlations:

- Veterans with combat-acquired mTBI with LOC had a higher frequency of PTSD and lower scores on the cognition test, indicating moderate cognitive impairment.
- Veterans with PTSD and a neurological deficit had cognition scores that were below normal (24.0 ± 0.26; normal is considered 27 or greater).
- PTSD was seen almost exclusively in veterans with combat mTBI with LOC and a neurological deficit.
- Veterans with combat mTBI with LOC were more likely to have migraines and had more frequent migraines than subjects without neurological deficits or low MoCA scores.
- Neurological deficits and PTSD correlated with the number of LOC episodes (figure 1): veterans with three or more LOC episodes had a high likelihood for a neurological deficit and PTSD.

In addition, impaired sleep in servicemembers who have experienced combat mTBI is associated with PTSD, and heightens the likelihood and frequency of both headaches and behavioral and cognitive problems (Ruff et al. 2009, 2012b). Insomnia in persons with mTBI is associated with disruption of hypothalamic-pituitary-adrenal function (Theeler et al. 2013); specifically, pituitary adenylate cyclase-activating peptide (PACAP) and the PACAP receptor may prove to be a link between PTSD and migraine, as PACAP is upregulated by stress and triggers the vasodilation associated with migraine (Theeler et al. 2013).

We continued to study these subjects, typically for 2 or more years, and found that among the 80 veterans who had abnormalities on neurological examination, neuropsychological testing, or both, 37 (46 percent) were married when they left military service. Among them the divorce rate was 86 percent in a narrow window of about 1½ years. This is an impact of enormous personal cost. The biggest problem reported was a personality and behavioral change: their families noted that they looked like the same person, but they were not the same person.

Link between PTSD and Impaired Olfaction

The 126 military veterans who had combat-related mTBI with loss of consciousness had a high frequency of deficits on the neurological exam. These deficits were reduced olfaction (65 subjects; 52 percent), impaired balance (14 subjects), abnormal eye movements (13), motor asymmetry (2), and sensory changes (2). Twenty-nine of these veterans had more than one deficit.

An olfaction deficit was the finding of greatest frequency. Among the 65 veterans with impaired olfaction, this was the only neurological deficit for 36

(55 percent), although most did not entirely lose their sense of smell and in fact were not aware that they had a deficit in olfaction. Hence olfactory tests that evaluate only whether an individual can smell are inadequate.

We found that olfaction deficits correlated with PTSD severity in the group with both mTBI and LOC, and that the likelihood of PTSD increases with the number of LOC episodes. Impaired olfaction with mTBI and loss of consciousness may thus be a biomarker for damage to the olfactory bulb and/or the adjacent ventromedial prefrontal cortex, which inhibits the amygdale. The prefrontal cortex and amygdale have different responses to physical injury. In the prefrontal cortex the dendritic tree becomes pruned, whereas the amygdale architecture becomes more elaborate (Radley et al. 2004; Vyas et al. 2002). The ventromedial prefrontal cortex provides inhibition to the amygdale, and its pruning becomes an operational mechanism for PTSD. The proposal is that an uninhibited or overactive amygdale results in an excessive state of fear and anticipation of fear, thus triggering PTSD (Koenigs et al. 2008; Pitman et al. 2012).

Conclusion

We have previously argued that mTBI, not other factors such as smoking, produced impaired olfaction in combat veterans (Ruff et al. 2012a). It has been determined that PTSD itself does not compromise olfaction (Vermetten et al. 2007), and we found that olfactory impairment did not correlate solely with PTSD severity (Ruff et al. 2012a). We conclude that repeated mTBI episodes with loss of consciousness likely reduced olfaction scores.

Further investigation is needed to determine whether our findings linking PTSD and neurological deficits with episodes of loss of consciousness generalize to other populations of military personnel, and to examine how repeated combat mTBI events are linked to both impaired olfaction and the genesis of PTSD.

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Our research on concussion-induced axonal injury may lead to identification of biomarkers that enable noninvasive diagnosis and treatment.

Neuromechanics and Pathophysiology of Diffuse Axonal Injury in Concussion

Douglas H. Smith is the Robert A. Groff Professor of Neurosurgery and director, Center for Brain Injury and Repair, University of Pennsylvania.

Douglas H. Smith

The interchangeable terms *concussion* and *mild traumatic brain injury* (mTBI) denote the phenomenon of a change in brain function associated with blunt trauma to the head or body. Beyond the fact that concussion can occur without the victim losing consciousness, researchers are only just beginning to uncover some of the essential aspects of this major health issue.

Initiated by a biomechanical event, concussion is unique among central nervous system disorders, and humans, more than other species, are particularly prone to brain damage from head impact. For example, if a human and a pig undergo the same head rotational acceleration, the human will fare far worse, as shown by animal and human studies. The approximately 1500 g human brain endures substantially greater mass effects than the 100 g pig brain under similar mechanical loading, where regions of the brain push and pull against each other as the brain is rapidly deformed (Browne et al. 2011; Meaney and Smith 2011; Smith and Meaney 2000; Smith et al. 2003b).

An important finding in animal and human studies of concussion is that selective damage to axons, known as *diffuse axonal injury* (DAI), is a key anatomic phenomenon of mTBI (Johnson et al. 2013; Meaney and Smith 2011; Smith and Meaney 2000; Smith et al. 2013a). Moreover, although in most cases many of the mental function deficits associated with concussion completely resolve, up to 20 percent of individuals with a single mTBI have

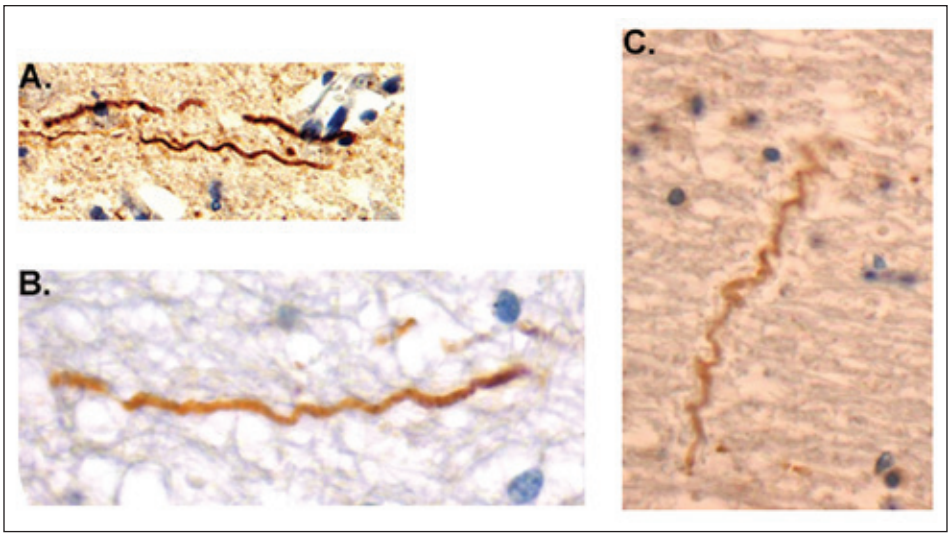

FIGURE 1 Undulations of neurons in the brain shown for three cases after blunt trauma. (A) 3-hour survival in adult swine traumatic brain injury (TBI). (B) 18-year-old human male, 10-hour survival. (C) 18-year-old human female, 22-hour survival. Image (B) is reprinted with permission from Tang-Schomer et al. (2012).

persisting cognitive dysfunction (Hanten et al. 2013; McCauley et al. 2014). There is also growing evidence and concern that one or more concussions can trigger long-term neurodegenerative changes in the brain (Hay et al. 2016; Smith et al. 2013b).

Axonal Injury from Concussion

While the whole brain suffers dynamic tissue deformation during concussion, the white matter is at greatest risk of damage, possibly because of its highly organized, highly directional structure (anisotropy). Axon tracts, the long transmission lines of the white matter, suffer damage in several unique ways from the tensile and shear forces induced by rotational head acceleration. In particular, the classic viscoelastic nature of axons appears to be a major contributing factor (Meaney and Smith 2015; Smith et al. 1999b).

Under normal daily mechanical loading conditions, axons can easily stretch to at least twice their resting length and relax back unharmed to their prestretch straight geometry (Tang-Schomer et al. 2010). However, under dynamic loading with rapid stretch, the axonal cytoskeleton can physically break, evidenced by an undulating appearance upon relaxation immediately afterward (figure 1). These axonal undulations have been observed in an in vitro model of dynamic stretch injury of axons, in preclinical TBI models, and in human TBI (Smith et al. 1999b; Tang-Schomer et al. 2010, 2012).

Using a customized in vitro axonal stretch injury model, we found that the stiffest components of the axon, microtubules, are the structures that most overtly display physical breaking at the time of trauma (Tang-Schomer et al. 2010). The break sites along the microtubule lattice appear to account for the undulating course of injured axons, by impeding the sliding of adjacent microtubules to return back to the relaxed straight geometry after injury.

Because microtubules essentially serve as the anatomical tracks for protein transport, proteins pile up at points of individual microtubule disconnection, resulting in varicose swellings distributed periodically along the injured axon (Johnson et al. 2013; Tang-Schomer et al. 2012) as well as partial transport interruption (Tang-Schomer et al. 2012) rather than complete transport failure in an entire region of the axon. In this scenario, some protein transport can continue through areas of swelling along remaining intact microtubules, but may be derailed farther along the axon because of microtubule disruption there.

Association between Concussion and Neurodegeneration

There is evidence that one or repeated head blows can switch the brains of some individuals from a normal aging track to an accelerated neurodegenerative path, commonly referred to as *chronic traumatic encephalopathy* (CTE) (Hay et al. 2016; Johnson et al. 2010; Smith et al. 2013b).

The initiating source of postconcussive neurodegenerative changes has yet to be identified, but DAI is a leading candidate (Johnson et al. 2013). CTE histopathological occurrences of neurofibrillary tau protein tangles and amyloid-beta plaques found to a greater extent in individuals with histories of multiple concussions (compared with age-matched controls) are similar to tissue accumulations in other neurodegenerative diseases (Hay et al. 2016; Johnson et al. 2010, 2012; Smith et al. 2013b).

Curiously, tau protein and amyloid precursor protein (APP), the parent protein of amyloid-beta, are normally most abundant in axons (Chen et al. 2004, 2009; Johnson et al. 2009; Smith et al. 2003a; Uryu et al. 2007). Therefore, it has been suggested that axonopathy in concussion may lead to the aberrant production and/or aggregation of tau and amyloid-beta (Johnson et al. 2010, 2012).

Role of Tau Protein

Using a new computational model of traumatic axonal injury, we identified a potential viscoelastic spring underlying microtubule breaking, the tau protein (Ahmadzadeh et al. 2014, 2015).

Tau proteins crosslink and stabilize the parallel arrangement of microtubules along the axon. As the axon is stretched under normal loading conditions, adjacent microtubules slide past each other, stretching the stabilizing tau proteins, which must unfold from their resting conformation. We propose that this tau extension includes the breaking of hydrogen bonds along the tau protein. This model predicts that the thermodynamics of hydrogen bond breaking along tau proteins during dynamic axon stretch injury cannot keep up with the rapid microtubule sliding. Thus, the pulling of tau proteins against the microtubules induces enough mechanical strain to rupture the microtubule (Ahmadzadeh et al. 2014, 2015).

While axons themselves rarely disconnect at the time of trauma, large swellings from transport interruption can cause a secondary disconnection of axons (Johnson et al. 2013; Smith and Meaney 2000). There is a broad range in the rate and morphology of axonal swellings identified with undulated axons, varicose swellings, and disconnected axonal bulbs.

The gold standard for postmortem clinical diagnosis of these types of DAI is immunohistochemistry using anti-APP antibodies, which can identify axonal swellings in white matter within hours of injury (Johnson et al. 2013). Although APP+ swollen axonal profiles are indicative of DAI, the vast majority of axons in white matter tracts appear relatively normal after TBI, even in severe cases (Johnson et al. 2013; Smith et al. 2003c). TBI must therefore involve injury beyond axon transport interruption and swelling.

Role of Sodium and Calcium Channels

Ionic concentration disturbances in traumatic axonal injury may play an important role in dysfunction (Iwata et al. 2004; Smith and Meaney 2000; Smith et al. 2003b; Wolf et al. 2001). Our in vitro model revealed that stretch injury impaired regulation of axonal sodium channels, where the channel inactivation gate is disabled and can no longer block excessive sodium influx (figure 2). In turn, the sodium-calcium exchangers are reversed and the high-voltage state maintains open calcium channels, thereby progressively increasing intra-axonal calcium concentrations after injury (figure 3; Wolf et al. 2001). The cascade can continue to the point where high calcium levels activate calcium-dependent proteases, inducing secondary cytoskeletal disruption (Iwata et al. 2004; von Reyn et al. 2012; Yuen et al. 2009).

We propose that the loss of function of axonal sodium channels throughout the brain network underlies common neurocognitive symptoms of concussion, such as loss of consciousness, decreased processing speed, and memory dysfunction. With too much sodium entering the axon, the capacity to generate action potentials (the rapid exchange of ions across the neural membrane) is lost or dysfunctional, interrupting or slowing signaling in the axon and throughout the neural network of the brain (Johnson et al. 2013).

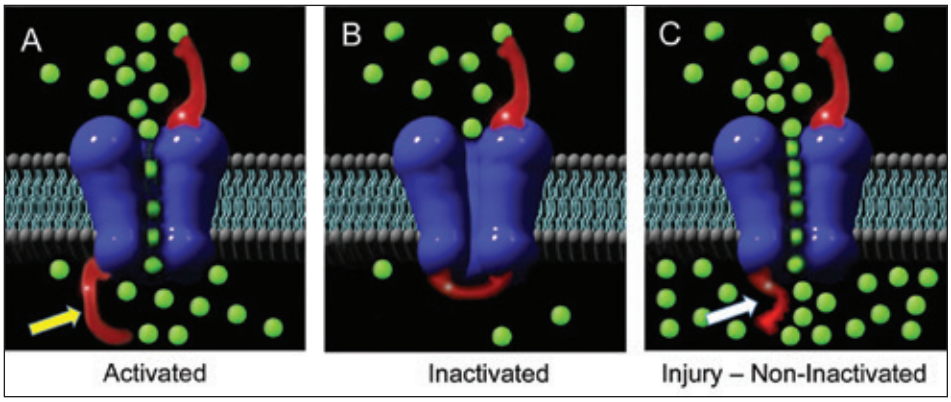

FIGURE 2 Diagram of the axonal membrane showing (A) sodium channel (blue) assemblage with the inactivation gate or "flapper valve" (shown with yellow arrow) with normal sodium influx (green balls) that create an action potential; (B) normal inactivation closes the gate to allow efflux of sodium; (C) upon injury, the inactivation gate is rendered dysfunctional (white arrow), allowing unmitigated influx of sodium ions.

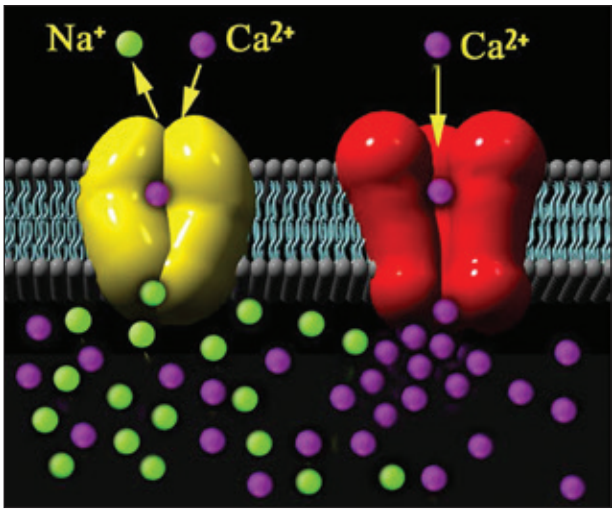

FIGURE 3 After traumatic axonal injury, there is uncontrolled influx of sodium (Na^+) ions (green balls), as illustrated in figure 2, triggering reversal of the sodium-calcium (Ca^{2+}) exchanger (yellow) and sustained opening of the voltage-gated calcium channels (red), resulting in progressive increases of intra-axonal calcium ions (purple). Adapted from Wolf et al. (2001).

Our in vitro model revealed that for some injured axons, sodium channels may remain dysfunctional, resulting in an increase in the number of sodium channels over time (Yuen et al. 2009). This may be a temporary adaptive change to compensate for the dysfunctional channels.

However, this "fix" may come at a cost. With even mild stretch injury of axons in vitro inducing very little sodium or calcium influx, the axons added more sodium channels. With a second very mild stretch injury a day later, massive sodium and calcium influx occurred. If this is also shown to be the case for concussion, it raises the intriguing possibility that sodium channelopathy plays a role in the suggested "period of vulnerability" after concussion.

Potential Biomarkers

In concert with the in vitro model, a swine mTBI model of head rotational acceleration has been developed and scaled to match the brain tissue deformation of human concussion (Browne et at. 2011; Kimura et al. 1996; Meaney et al. 1995; Smith et al. 1997, 2000). With this model, extensive APP+ axonal pathology is produced throughout the white matter with an appearance identical to human DAI (Johnson et al. 2015, 2016; McGowan et al. 1999; Smith et al. 1999a).

The use of this mTBI model in conjunction with examination of human moderate-to-severe TBI has revealed additional axonal injury not seen with APP+ analysis (Johnson et al. 2015, 2016), using an immunostain for the calpain-cleaved spectrin N-terminal fragment (SNTF). The appearance of SNTF generated exclusively in axons implies that the injury induced substantial increases in intra-axonal calcium concentrations, resulting in calpain activation and cleavage of axonal spectrin (Johnson et al. 2016). These observations corroborate the dysregulation of calcium concentrations in axon trauma observed in vitro (figure 3).

Notably, we found that SNTF appears in the blood shortly after concussion in individuals who were later found to have persistent cognitive dysfunction (Siman et al. 2013); its presence thus signals permanent brain damage through the degeneration of axons (Johnson et al. 2016). SNTF and tau protein were also found in the blood of professional ice hockey players after concussions and could remain at elevated levels for days (Siman et al. 2015; Zetterberg et al. 2013).

These studies suggest that SNTF and/or other axonal proteins may serve as blood biomarkers to evaluate the severity of concussion and to specifically diagnose DAI. The identification and validation of a biomarker would be a valuable tool for managing concussed patients as it could provide an objective measure of the effectiveness of treatment. Indeed, biomarkers may allow for the stratification of mTBI patients according to severity, thereby increasing the power of treatment trials.

Conclusion

While substantial progress has been made in understanding the pathophysiology of concussion far beyond this brief overview of our efforts, it is nonetheless certain that the field remains in its infancy. There is no evidence-based practice or medicine for treating concussion, leaving many patients and their families frustrated with their care. And in the absence of noninvasive tests to identify patients at risk, there is little information to provide a long-term prognosis for concussed individuals (Levin and Smith 2013; Smith et al. 2013b).

Research priorities for concussion should include efforts to identify therapeutic targets for DAI (Smith et al. 2013a), characterize the period of vulnerability after concussion for patient management and return to play decisions (Meany and Smith 2011), and uncover the trigger for biochemical events that result in progressive neurodegenerative changes.

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The lack of symptoms or clinically diagnosable dysfunction does not guarantee that an athlete is healthy.

Medical Imaging to Recharacterize Concussion for Improved Diagnosis in Asymptomatic Athletes

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Thomas M. Talavage

The Purdue Neurotrauma Group began in 2009 to study causes and consequences of concussion in youth athletes in an effort to understand why, in a two-player collision that produced a diagnosed injury, it was only one—rather than each—athlete that evidenced symptoms. Our work applies the concept of structural health monitoring (Bond et al. 2014; Kim et al. 2014), without intervention, to characterize how the brain becomes predisposed to presentation of symptoms after exposure to head acceleration events (direct collisions or whiplash movements associated with contact to other portions of the body).

Assessing Concussion

From our initial work (Talavage et al. 2014), it quickly became apparent that although an athlete may be asymptomatic, the lack of clinically diagnosable dysfunction does not guarantee that the athlete is healthy.

Evidence from Brain Scans

Figure 1 illustrates the disparity of health outcomes for three high school football athletes, one from each category of clinically and functionally observed impairment (COI, FOI; identified in Talavage et al. 2014): COI−/FOI− denotes arguably healthy athletes; COI−/FOI+ represents athletes exhibiting neurophysiologic changes in the absence of symptoms; and COI+/FOI+

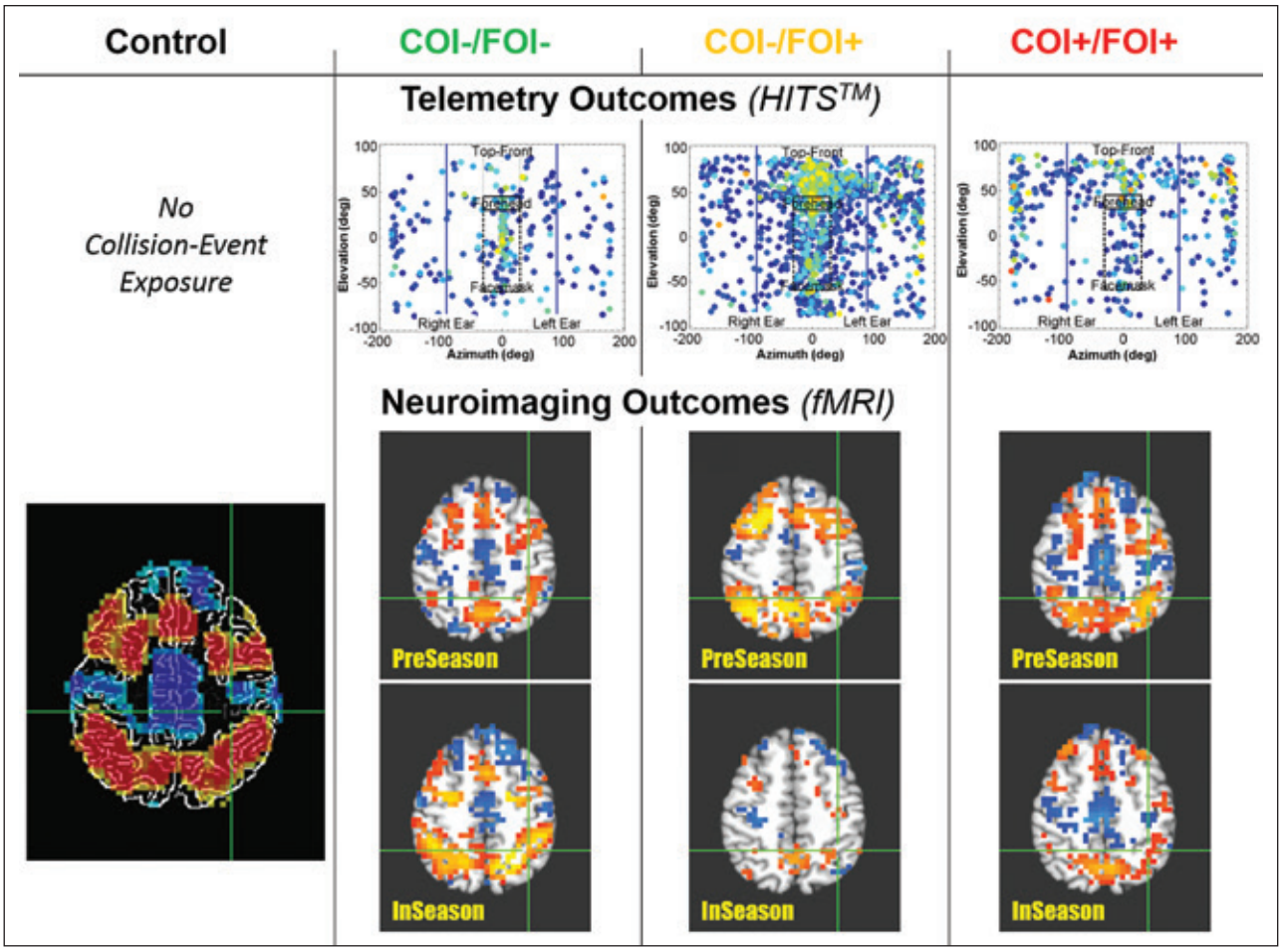

FIGURE 1 Head Impact Telemetry System (HITS) and functional magnetic resonance imaging (fMRI) scans for three high school football athletes before and during the playing season (plus control, left). COI−/FOI− denotes an arguably healthy brain; COI−/FOI+ indicates neurophysiologic changes without symptoms; COI+/FOI+ designates a symptomatic athlete diagnosed with concussion. See text for discussion. COI = clinically observed impairment; FOI = functionally observed impairment.

designates symptomatic athletes diagnosed with concussion. FOI+ classification was based on flagged scores obtained with Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) (Collins et al. 1999; Lovell and Collins 1998), the most commonly used tool at the collegiate and professional level to confirm diagnosis of concussion.

In the top row of figure 1 are plots of the site and magnitude (intensity) of blows (called "events") reported over the entire season by the Head Impact Telemetry System (HITS; Simbex, LLC). The center of each plot represents the face, with facemask and forehead regions denoted by dashed boxes. Each dot is colored (heat map) to indicate the severity of the reported acceleration: dark blue represents the lowest recorded accelerations ("coldest"; HITS recording threshold = 10 g), bright red the highest ("hottest"; roughly 120 g), and yellow-orange an intermediate range of 40–80 g. Note that most of the accelerations are under 30 g (darker blues), with slightly over 60 g (i.e., orange dots) corresponding to the 95th percentile of the accelerations observed in our high school football athlete population.

Below are six functional magnetic resonance imaging (fMRI) contrast maps associated with an n-back working memory task (Ragland et al. 2002) in which subjects view a sequence of letters and press a button if the currently presented letter matches that shown one presentation prior (1-back task) or two (2-back). The imaging sessions were conducted on football players before (PreSeason) and during (InSeason) the competition schedule.

Preferential brain responses are shown using a heat map. Orange indicates brain regions exhibiting greater metabolic activity during performance of the 2-back

task, and blue indicates regions more active during the 1-back task. Areas with no coloration represent regions of the brain that are equivalently active or inactive in the two tasks. We are generally interested in the stability or instability of the spatial pattern of activation valence (i.e., orange, no coloration, blue) more than the absolute level, as changes in metabolic demand typically reflect underlying alterations in neuronal recruitment or health.

Concussed vs. Asymptomatic Athletes

Perhaps the most important observation to make is that some athletes are able to participate in football and remain arguably healthy (COI−/FOI−; figure 1, 2nd column). The depicted athlete was observed to have excellent tackling technique (e.g., kept his head clear from contact, wrapped and rolled with the ball carrier) and played the entire season with just over 200 reported events, of which only one exceeded 60 g. This athlete also exhibited fMRI contrast patterns that were quite consistent with the control population (figure 1, far left column) both before and during competition activities.

In contrast, athletes diagnosed as concussed (COI+/FOI+; figure 1, far right column) exhibit changes in biomarkers consistent with the literature (Lovell et al. 2003; Mayer et al. 2015a,b; Meier et al. 2015; Yeo et al. 2011). Mechanically, the athlete depicted here differs from the arguably healthy (COI−/FOI−) athlete by having experienced a number of large magnitude (above 60 g) events at multiple locations around the head. Although this athlete missed three weeks of the season because of his diagnosed concussion, he still accumulated more than 800 events. Obtained approximately 72 hours after diagnosis of concussion, this athlete's InSeason fMRI shows relatively focal reductions in contrast (Lovell et al. 2003), consistent with the local changes in neuronal metabolic activity expected with injury—either the simpler (1-back) task becomes harder and the two tasks look more similar (i.e., move toward "no coloration" or even "blue" if the 2-back task can no longer be performed), or inputs to the given area are disrupted and it is no longer recruited during either task, resulting in more equivalent nonactivation (again, moving toward "no coloration").

Critically, some athletes exhibit appreciable changes in biomarkers in the absence of symptoms (COI−/FOI+; figure 1, 3rd column). The athlete shown here accumulated over 1,800 events during the season, largely concentrated at the top front of his helmet, as a result of lowering and leading with his head. Obtained after a week in which HITS reported more than 240 events exceeding 10 g, this athlete's InSeason fMRI exhibits more substantial changes in contrast than did the concussed (COI+/FOI+) athlete, with the bulk of the brain now apparently working equally hard to perform the 1- and 2-back tasks. It is important to reiterate that this athlete was asymptomatic, giving no cause to be examined by the team's medical staff.

Variability and Duration of Effects

Taking our 7 years of study as a whole, changes in the neurophysiologic behavior of asymptomatic athletes such as those evidenced in figure 1 are fairly common (Abbas et al. 2015a,b; Breedlove et al. 2012; Chun et al. 2015; Poole et al. 2014, 2015; Robinson et al. 2015; Shenk et al. 2015; Svaldi et al. 2015, 2016; Talavage et al. 2014). This statement is corroborated by work from other research groups evaluating asymptomatic brain health with diffusion-weighted imaging (Bazarian et al. 2014; McAllister et al. 2014) and resting-state fMRI (Johnson et al. 2014).

Of greater concern, many PreSeason measures for the collision-sport athletes in our study suggest that some level of injury is present before they ever take the field (Abbas et al. 2015a,b; Poole et al. 2014). As such, it is possible that imaging them during their collision-sport participation in middle school may be warranted.

Critically, some athletes exhibit appreciable changes in biomarkers in the absence of symptoms, giving no cause to be examined by a team's medical staff.

Moreover, athletes who have experienced many subconcussive events require an exposure-dependent time period before biomarkers recover to more closely resemble those of noncollision-sport peers—i.e., those exposed to more events take longer to recover. As we have shown (Breedlove et al. 2014; Nauman et al.

2015), athletes exhibit higher rates of deviant neurocognitive and neurophysiologic measures during the season than afterward, but even postseason measurements—obtained 3–5 months after participation—reveal a high likelihood of injury for athletes who experienced more than 60–70 events per week (exceeding 10 g, as reported by HITS). This finding is unsurprising, as it may take several days, or even weeks, after injury before repair and a complete return to normal physiology—even if the individual takes time off from activity (Ghaffar et al. 2006).

It may take several weeks for repair and a complete return to normal physiology—even if the individual takes time off from activity.

Appreciable changes in neurophysiology in asymptomatic athletes demonstrate that symptoms are a subset of injury, where the concept of injury must encompass nonstructural alterations (e.g., changes in ionic balance; Hovda 2014). Note that changes in fMRI contrast (figure 1, bottom) are generally concomitant with a high number of HITS-reported acceleration events *even when this number is not coupled to diagnosis of a concussion*. This observation argues in favor of the hypothesis that exposure to subconcussive events plays a critical role in the accumulation of injury (McKee et al. 2009).

Our study suggests that there is a very direct link between changes in the brain and an individual's subconcussive exposure, comprising factors including technique, number of physical head blows experienced, and net occurrence of whiplash-like stresses on the brain from other blows (e.g., tackles not involving a blow to the head).

Current and Future Research

According to the findings reviewed here, evidence exists that some level of subconcussive injury can be sustained without immediate presentation of symptoms. Such injury could range from ionic imbalance (Hovda 2014) to neuronal damage that has not yet precluded delivery of information in the brain. This last is a critical concept for understanding concussion—an individual will not exhibit symptoms until information flow is interrupted or at least sufficiently disrupted so as to reduce the reliability of neuronal summation in place and/or time.

Investigations of the Purdue Neurotrauma Group

Our study seeks to detect these disordered conditions before symptoms arise: while there is obvious value in improving treatment and return-to-life protocols, the greatest benefit is to be gained from preventing the underlying injury. Our study thus has initially been directed at characterization of brain changes associated with subconcussive injury in youth athletes, particularly those exposed to repeated head acceleration events.

Combining neurocognitive testing, advanced neuroimaging, and daily monitoring of head acceleration events, our study tracks athletes before, during, and after exposure to events that are likely to contribute to brain injury. We now have data from football and women's soccer teams at three high schools and one college, comprising 420 athlete-seasons, more than 1,300 MRI sessions, and roughly 1,400 neurocognitive assessments. Partnering with multiple institutions conducting similar research (Bailes et al. 2015), our intention is to evaluate biomarkers derived from these varied assessments to draw conclusions about how impaired individuals are likely to be, based on their exposure to acceleration events.

A key component to all of the findings reported above is the acquisition of a within-subject baseline, either before participation or before an exposure of interest. Most neurophysiologic and neurocognitive measures used to study concussion exhibit appreciable population variance, complicating interpretation of differences between subjects. However, when within-subject changes become larger than the variation in a population, it is straightforward to interpret changes as meaningful.

Needed Research

It is critical to recognize—particularly when assessing outcomes from studies in which only postinjury scans are available—that concussed and asymptomatic athletes with similar histories of head acceleration events can exhibit similar biomarkers, and that both generally exhibit appreciable differences relative to noncollision-sport peers (Abbas et al. 2015a,b; Poole et al. 2014; Svaldi et al. 2015, 2016). Unfortunately, the current

well-funded studies into concussion do not incorporate such a model—their focus is on tracking recovery from symptoms, rather than on understanding how to prevent those symptoms from occurring. Given work by our group and others (Johnson et al. 2014; McAllister et al. 2014), the comparisons made in these large studies are at risk of revealing few differences between concussed and asymptomatic athletes. Lack of biomarker alteration due to concussion must not be misinterpreted to downplay the serious potential for long-term damage associated with this clinically recognized injury.

In conclusion, the structural health monitoring model should be effective in the study of concussion, as it provides a mechanism to quantify both injury and recovery. Assessment of individual athletes before, during, and after exposure to potentially deleterious events will provide the best opportunity to characterize injury and to guide mitigation of these consequences, whether through improved prevention, intervention, and/or therapy.

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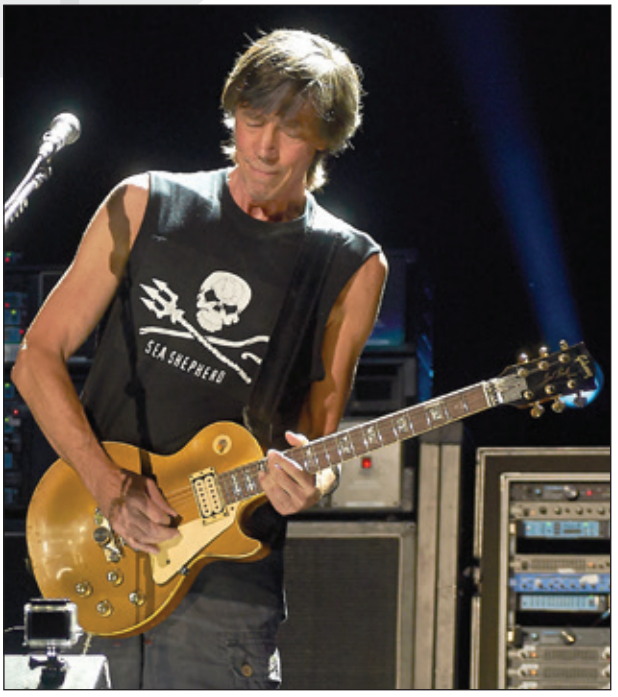
An Interview with . . .

Tom Scholz



Tom Scholz is a musician, inventor, engineer, philanthropist, and founder of the band Boston. Photo credit: Alan Poulin.

RON LATANISION (RML): We are delighted to speak with someone who is both a mechanical engineering student from MIT and a rock icon. Music is certainly part of our social fabric that everyone appreciates, so Cameron and I are grateful to have this opportunity to talk with you.

TOM SCHOLZ: The pleasure is all mine.

RML: Let's begin right at the beginning. Tell us about your choice of mechanical engineering and what led you to MIT.

SCHOLZ: Well, the short answer would be my father, but in reality it was sort of an obvious choice. I was a designer and builder and small-time inventor from my earliest childhood years, which took the forms you might expect—building model airplanes and boats and cars and anything else. I was really fascinated with anything that moved or flew. So I guess I had an aptitude for mechanical devices, if for no other reason than because I had dabbled in so many different ones as a child.

When I got old enough to get a driver's license in high school, I dropped all of those hobbies and started rebuilding cars. I couldn't afford a good car so it was an excellent outlet, because if I wanted a decent car that ran I was going to have to put it back together myself.

From the engineering standpoint, MIT had a reputation even back then when I was out of high school—which now seems like a really long time ago. I was a little shocked that I was accepted, to tell you the truth. I always did well in math and science in high school but I knew that the competition to get accepted at MIT was phenomenal.

I found out just how bad those odds were when I showed up for my freshman orientation. They sat us all in a large assembly area and put up a chart showing everyone's SAT scores. For the English scores there was a bell curve like you'd expect—it was skewed very far up the scale, and I thought, 'well, that's all right, I got in the high 700s in English so I fit in here.' Then they put up the math scores and it wasn't a bell curve. It was just a smooth curve that rose up to the righthand side of a perfect score. I thought, 'now I'm in trouble.'

The good thing is that they were very thorough and careful about how they vetted their new students. Some schools would report how many people they got rid of after the first year, but I don't know if that's something to make public, because if you've chosen them you should be able to teach them. MIT lost only a very, very small percentage of people who just couldn't make the grade.

I was so shell shocked by the end of my first semester that I had already decided—and actually applied—to transfer out because I thought there's just no way I was going to be able to make the grade at this school. Then I got my first report card and I had a 4.8 average. So I thought, 'okay, maybe I can do it. I'll stay.'

RML: And you went on to earn a master's degree in mechanical engineering?

SCHOLZ: They refer to it as a master of science, although it was in the mechanical engineering curriculum. I was very lucky. They offered sort of a "special" for a few students—a scholarship for the tuition, some living expenses, and you could collect your master's

in one additional year. I was very lucky to get picked for that.

I did fine scholastically, but by the end of those five years that was pretty much it for me for scholastic endeavors. I never took another class of any type after that. I decided from that point on if I was going to learn something I was going to do it on my own.

I taught myself how to become a pilot so I could pass both the written and practical tests. I took physical flying lessons but I didn't go to ground school or any of that. And I taught myself Spanish from books—nobody does that anymore, it was sort of a challenge. But that last year was so tough I haven't gone back to school for anything else.

MIT was one of the most difficult things I've ever done, getting through those five years. I can't say I enjoyed it, but it was one of the best things that ever could have happened to me.

MIT was one of the best things that ever could have happened to me.

CAMERON FLETCHER (CHF): Where does your music fit into this? Were you playing guitar and doing other kinds of musical pursuits while you were at MIT?

SCHOLZ: I was. I actually wrote my first piece of music my junior year and it ended up on my first album, which sold 20 million copies. That's probably something of a record for a first composition.

RML: Which one was that?

SCHOLZ: It's an instrumental called Foreplay.

RML: I know that one. You wrote that when you were a junior at MIT?

SCHOLZ: I did. I wrote it on an electric piano in my fourth floor apartment. I had had enough of dynamics and so forth to understand how sound can transfer through a wood floor. The three nurses that lived below us were extremely patient with me because I usually wrote between 12:00 and 2:00 in the morning and every time I pounded on those keys they felt it through the ceiling—and never complained. I think they felt sorry for me because I had to go to MIT.

CHF: Are you a self-taught musician?

SCHOLZ: I am. I did take some piano lessons when I was a little kid, I think between seven and nine years old. I learned how to read a little and I played a little classical music, but then I stopped and I didn't start again until I got to MIT, where they had pianos here and there in the student areas. I started plunking around on those and that's where I got the bug again.

At that point, I began playing by ear and that's when I think my music education began because I began to understand how music was put together. Of course, it started with really simple pop songs but that's when I really started to realize sort of how it went together. Up to that point, having played piano by sight reading, I was basically a glorified piano roll—you know, open the music and I would reproduce the notes on the keyboard.

But I didn't really make the connection between what was on that sheet of paper and what I was doing and what the composer was thinking. Later, I went back to a few of those pieces and then I was really impressed with these classical composers and what they had done. So music was sort of a pastime in school and then I got more serious about it as the years went on.

I play keyboard instruments—piano, organ, and so forth—and fretted string instruments—guitar, bass. I played drums for a bit but then I got an injured back and that became more and more painful so I haven't played drums for quite a while. I learned how to play the standard combo instruments to produce a typical rock-n-roll song of the '60s or '70s. That was not my goal, I did it purely for the enjoyment of playing the music.

I got into guitar because I had joined a really bad band when I was at MIT and the guitar player was just not doing justice to the music—I'm talking important pieces of music like Steppenwolf. I thought, 'how hard can that be?' So I bought a $25 guitar from another student, and the amp, and started trying to learn some songs—and that's when I realized it actually was very hard to do.

It took me a long time to adapt to fretted stringed instruments. To this day I can sit down at a keyboard or an organ or a synth and if I haven't played for six months, I can immediately play any number of complicated pieces that I know. With the guitar, every time I pick it up it's as if I've never played it before and I have to start all over again to get my hand to work. So I find guitar very challenging and it's not easy for me. With keyboards, it was always a piece of cake.

Tom Scholz. Photo credit: Kamal Asar.

RML: Let me understand the transition here. After you got your degree in mechanical engineering you went to Polaroid for a few years.

SCHOLZ: Yes, I spent six years at Polaroid, primarily as a design engineer.

RML: And where was music during this period?

SCHOLZ: When I left school and started a real job, first I was absolutely amazed that I could put in so little time doing something and some company was willing to pay me the kind of money that they did. I thought, 'how is this even possible?' At MIT I didn't even go to class most of the time because I didn't have time to go to class—I was too busy doing the problem sets.

So I was amazed at the amount of free time I had working 40 hours a week. That's when I got much more serious about music. I started trying to record some of it and slowly picked up some pointers on how that could be done. Later, thanks to my Polaroid experience, I learned about the technical aspects of tape recording, including building a recorder.

RML: So the recording was partly a consequence of your experience at Polaroid?

SCHOLZ: Before I knew very much about the technical aspects of recording, I began recording by doing what other people did: buying time at a local studio. Back then, it was a completely different situation. Today, anybody can make a recording on their laptop with 48 or 96,000 tracks if they want to. And it's free, which of course has produced an incredible amount of really bad music.

Back then, if you wanted to record something with close to state-of-the-art audio quality, it cost you an arm and a leg. In today's dollars, you'd be looking at $5,000, $10,000 to make a recording of one song that was of professional quality. If you were going to do it, you were going to pay for it.

So I started slowly. I was working days and saving money and using it for that purpose. Slowly I obtained the technical know-how to build a small demo quality studio in the basement of my apartment house. Polaroid, and of course MIT, where my electronic and mechanical education really started, gave me the tools to be able to do it.

RML: When you were at MIT did you come across Amar Bose?

SCHOLZ: No, I didn't.

RML: He was the founder of Bose, the sound system. I heard him talk about how he founded Bose Corporation. He was studying for his doctoral exam and did not like the quality of the music playing on his hi-fi. He thought there had to be a better way for the listener to enjoy music. Of course, your focus was not so much on the listener as the performer. I'm thinking of the evolution not only of Boston but of Rockman, the device you invented.

SCHOLZ: For everything I got involved in technically that had to do with music, necessity was the mother of invention. It was something that I needed that usually didn't exist, or not in a form that I thought was usable. For instance, back in the early '70s various types of chips started being manufactured. There was one called a bucket brigade. It was an analog device that could provide an analog audio delay, and as soon as I caught wind of this device I got together with an electrical engineer at Polaroid, a friend from MIT, and gave him a block diagram and he drew up a schematic and we built what I called then a doubler.

I wanted something that would make a synthetic second performance of what I was doing without actually having to play it. I was trying to perform my music live in very small venues and I needed to have this doubling thing in the studio since I was very limited in the number of tracks that I had. By doing that, I could build something that reproduced the same performance, slightly off-pitch and slightly off-time.

It turns out you actually need to do a little more than that to make a bona fide fake second performance. And the immediate question is, Why would you want a second performance? The answer to that is that every time you add an instrument or voice doing the same thing,

you completely change the character of the sound, which was discovered a long time ago and is the reason we have symphony orchestras.

I needed that device and there was nothing available at the time that could do it so we built it—put it in a cigar box and used it on the first Boston album and for my demo work. Within a couple of years after that, you could go into any music store and buy that same device, packaged and ready to go—'though not with the same good signal-to-noise ratio as the one we built.

RML: Listening to you speak makes understandable a quote I read about you: "Boston's Tom Scholz has a musician's soul and a scientist's obsession with the phenomena of sound and music."[1]

SCHOLZ: That's pretty accurate.

RML: How many musicians have anything like the science or engineering background to do what you've done?

Knowing basic Newtonian physics gave me a leg up on being able to translate the sound I was dreaming of and make it happen.

SCHOLZ: Having the basic Newtonian physics was such a blessing. I realized when I got out into the world that I understood things about how a guitar worked and why it sounded the way it did and why it responded to various things that you might do with it, and other people had no idea what was actually happening—they knew it would make a sound if they did this but they didn't know why. So it gave me a leg up on being able to translate the sound I was looking for or hoping for or dreaming of and actually get it to happen.

RML: That's a remarkable story, and all the more reason why it's so important for us to have this conversation with you. When we launched this interview campaign we wanted to demonstrate that engineering could be integrated into the culture of the country in ways other than building engineering systems or managing nuclear waste, for example, and this is a wonderful demonstration.

SCHOLZ: Boston music is definitely more fun than nuclear waste.

RML: I have a granddaughter who is nine years old and is taking cello lessons. I volunteered to take her to music school on the very first day, and her teacher handed her a book of music and said, "This is something I'd like you to work on between lessons." I looked at my granddaughter and said, "Scarlett, can you read music?" And she looked at me and said, "Of course." I was pretty impressed with that.

SCHOLZ: It is an admirable skill and, having dabbled in it when I was a little kid, now I look back and think, 'boy, I wish I'd kept that up,' because if you put a piece of music in front of me now it's a foreign language again. I can sit down and decipher it over a few hours but there's no playing from sheet music.

CHF: What are you doing with music these days, Tom?

SCHOLZ: I'm preparing for the 40th anniversary tour of Boston this summer, and coming up with arrangements for half a dozen songs we're going to add to our set and writing segues to go between the songs. I'm also having to invent some gear because a couple of these songs are pretty challenging to play and I was doing things in the studio, double tracking, and now I have places where I have to play or sing a part myself and I have to do both at the same time, so I'm coming up with ways to do that. And I'm working on some lighting effects. There's an enormous amount that goes into a tour and I'm busy trying to get as many loose ends together as possible before our first rehearsal.

RML: When does the tour begin?

SCHOLZ: It starts the last day of April in Fort Lauderdale. Don't ask me why, but we've started every tour at the Hard Rock in Fort Lauderdale for the last however many years and it's become a tradition. So we head down there at the end of April and the tour goes through the 14th of August.

RML: On a slightly different topic, tell us about the DTS Foundation, your charitable foundation.

SCHOLZ: I set it up as a way to keep track of what I was doing with my charitable donations. Actually, after

[1] *GuitarWorld*, "Tom Scholz Releases Boston's Last Recordings with Brad Delp, 'Life, Love & Hope,' an Album 11 Years in the Making," April 2, 2014.

I had become successful for a few years in the music business, I was pretty demoralized with what I saw. It wasn't the most admirable group of individuals I had been involved with. I made a lot of people fairly wealthy from the work I did, and I didn't like seeing what they did with the money.

So after the second album and tour in the early 1980s, I did a little soul searching because I was at that point contemplating getting out of the music business entirely. Then I had an epiphany: instead of letting every snake in the grass run off with the money generated by these recordings I'm making, if I can channel that into the right hands, I could actually see some really good things happen. That became my reason for remaining in the music business—and of course I loved playing music, especially live, and I loved writing it and hearing it come to completion on an album.

So I made a conscious decision that from then on my goal, from a professional or financial standpoint, was to make money to help bankroll people who were trying to make a difference. The areas I was aiming at were animal protection, efforts to help children—I wanted to do what little I could to reduce suffering. And as I learned more about it I became a vegetarian.

So the charitable foundation I set up was a way for me to keep track of where the donations went and how much. My goal was to give away more than I spent on myself, and a lot of really good things ended up happening from that. There was an effort to try to stop tuna fishing vessels from catching dolphins, and I provided funding to run ads on the East Coast that turned the tide and got Starkist to finally agree to dolphin-safe tuna. And over a million dollars was given to the Humane Farming Association to educate people about veal crates and pig crates.

I also used the band's name itself on tours to try to generate awareness and funding for various organizations; for example, in 1987 we did something for the National Hospice and in 2003, I think it was, we raised money for the Sierra Club. Most recently we did a combination promotion and benefit for the Shriners Children's Hospital and Sea Shepherds.

When all else fails, if things are going badly or I'm down in the dumps or wonder why I'm doing what I'm still doing, I always remember that I am doing something that's really helping a lot of other living things.

RML: Do you have someone who manages the day-to-day operations of the foundation?

SCHOLZ: My wife and I do it. We do as much vetting as we can. We've been donating to many of the organizations for a long time and we try to pay attention as much as we can, we get a feel for who is really doing something special with the money. It's amazing what some of these people can do with very little in the way of resources. A lot of the individuals who staff these organizations, they live that job, some of them for 20-plus years. It's just amazing to me.

I set up my foundation to use the money I make from my music to help people who are trying to make a difference.

My part is very small even though in some cases I provide a lot of the funding; all I do is write a check, but some of these people, their whole life is spent living these jobs that they do. I'm very pleased that I can do that much. Some people can speak publicly or become a spokesman for some effort or organization or their goals, but I've never had the knack for that. This is something I can do.

RML: That's a wonderful thing—not only to be able to do it but to follow up and do it.

SCHOLZ: I've always been a subscriber to the thought that people should live simply so that others may simply live, and I think I have a wonderful life. I have a nice home in a nice place but I don't need a lot of stuff. I drive a 20-year-old Camry that I love. I do have to admit I got a second one that's newer—it's a 19-year-old Camry that's lower in mileage. I love old stuff. I should qualify that: I love well-engineered old stuff.

RML: What do you do when you're not involved in music, in your downtime?

SCHOLZ: I've been putting in a large patio behind my house that has taken me about three years. It's flagstones with pea stones in between, but the pea stones don't move like they do with a regular flagstone patio because I put in a network of grout that's reinforced with graphite fibers and then pea stones on top. It's been a very cool process.

And I spend half of my summer trimming back huge trees and bushes on my property. I planted a lot of them over the years. I have massive amounts of flowering shrubs and so forth and I love going out and taking care of them and pruning and doing all the things you have to do.

I like working outside and I have a dog that I take for a couple-mile walk/run every day. And a wife I love. Whenever I have a little bit of time, I spend it doing one of those things that I really enjoy.

CHF: And those are all interests that you can pursue indefinitely—it's not as though you have to anticipate and plan for retirement and what you'll do after that.

SCHOLZ: Oh God, no. I have so many things that I haven't gotten to do!

CHF: What are some of those things?

SCHOLZ: Well, I'm looking at this airplane that I built. It looks like one of the Bell rocket planes from the mid-50s. It's a delta wing airplane with about a 4-foot wingspan and it's about 4–4½ feet long. It's got a radio control that I designed in 1972 and built and have flown for many, many years. I love this thing. It takes off vertically out of a chute so you fire it up—it makes all kinds of ungodly racket, it's really scary—and hit the release with your foot and off it goes, straight up in the air. Very cool. But it hasn't been started now in a few years and I have to replace the engine and the radio, too, because it's no longer compliant with the frequency allocation for radio-controlled models. I'm dying to get that back up in the air.

RML: I get the launch, Tom, but how do you land it?

SCHOLZ: No landing gear. So I really want to fly this thing somewhere where there's grass or weeds because asphalt is not good. Most places that are approved for flying radio-controlled models have grass. It just bellies in. It actually slides—it's blisteringly fast but has a very, very slow stall speed. It's got a huge wing.

Tom's delta wing plane in his studio. Photo credit: Kim Scholz.

CHF: And what are some of the other activities you're looking forward to when you get a spare minute?

SCHOLZ: I'm trying to get my double toe loop back and double Salchow. I had a really old pair of skates and I took one of them and built a hinged support system. You're probably not real familiar with figure skates but traditionally they're super heavy and super hard—they're like little mini ski boots because you need the ankle support. But at the same time you need to be able to use your calf muscle if you want to get maximum elevation for jumps. So I built a hinge into one of the boots to try it out—I didn't get too esoteric with it, I just used aircraft aluminum—and did a little experimentation to find out where the best point was on my ankle to have the thing flex. It was successful and now I only wear those skates. I always say I get an extra 2–3" of elevation because I have the magic skate. The engineering came in very handy for figuring out where the stresses were going to be.

CHF: You have really maximized that MIT education in ways I'm sure they never anticipated.

SCHOLZ: I use it every day. Honestly, in everything I do. It's so ingrained. I am always thinking about the easiest way to open a refrigerator or—well, everything is so automatic now—and it all was from that training. That's why I say the years I spent at MIT, as hard as they were, were the best use of time of anything I think I've ever done.

CHF: It really makes you the ideal engineering student.

RML: It really does. Tom, I know you have an incredibly busy life, but have you ever had time in your agenda to talk with students, engineering students at universities?

SCHOLZ: I have had very little opportunity to do that. But recently I was invited to join a visiting committee at MIT and I got to see and hear from some of the current students. It was very interesting. I thought, things really haven't changed that much. The place looks different but the students are still the same. They are driven. They are incredibly talented and they are putting up with the same things and are bugged by the same things, but living through it and improving their minds in ways that are hard to fathom.

RML: What strikes me in your story and our conversation is that you are a great demonstration of someone who has something that you enjoy very much—music—and you've found the right path to maximize all of your experiences in a wonderful career as a musician. There's got to be an enormous amount of satisfaction in all of that.

SCHOLZ: I consider myself incredibly lucky. Not that I didn't work very hard and take some enormous risks to do it, but I never expected success at it. My description of success, had you asked me back in the mid-70s, would have been 'well, if I can get a song on a local radio station and play in some local places and have anybody recognize a song, that would be my ultimate dream.' I never for a moment thought that my father would have a platinum record hanging over his fireplace.

And by the way, my father lobbied very hard against me having anything to do with a band or music. But he did hang the platinum record. My father and mother were both brilliant people. I learned later in life that he had his own band—he was a trumpet player—so I guess he had formed his own opinion about the likelihood of being successful with that or about what kind of a life it would lead you into.

On the other hand, he was very happy to see things work out for me in music even though he gave me quite a hard time about dabbling in it. I remember telling him that I was doing one last demo because I just couldn't spend any more time or money on it, I was almost 30. And I remember him berating me for wasting my time on recording this music when I should be concentrating on my engineering career, I could have been a senior principal engineer by now. And then I had this really unexpected success.

About five years later I decided, almost as a hobby but as a sideline, to start a little engineering company to build novel gear for rock musicians. I told my dad about it and I remember him saying, "Why are you wasting your time on this engineering crap"—his actual words—"when you could be writing another hit album?"

RML: Well, I can't imagine another American rock musician who can top what you're describing. This is a great story. And coupled with all of that is the fact that your background is in engineering and you've put it into practice in ways that are pretty extraordinary. Is there anything you'd like to say or any comment directed to the engineering practice in the United States today?

SCHOLZ: While the amazing advances made possible by modern microprocessors are undeniable, the overuse, inappropriate use, and poor design implementation of digital technology in the 21st century have done more than just make life more aggravating, distracting, and complicated. They have created new unforeseen lethal dangers. Whether it is "safer" airliners with overly complex automation falling from the sky, cars speeding out of control due to malfunctioning "drive by wire" accelerator and drivetrain controls, or drivers running over pedestrians while either one of them is distracted by texting, it should be obvious that engineers need to resist the doing-it-because-it's-possible bells and whistles design philosophy. The current love affair with designing a microprocessor into everything may be driven by marketing departments and gullible consumers; engineers need to speak up for simplicity of design, which translates naturally to understandability, reliability, and control response.

Engineers need to speak up for simplicity of design, which translates naturally to understandability, reliability, and control response

On a personal note, the de-evolution of recorded music audio quality brought about by digital recording and digital consumer delivery means that MP3 files have probably been a major factor in the demise of the music industry, and hence the quality of new music. The fact that true audio enthusiasts go to great lengths to preserve their vinyl collections and turntables is a testament to this.

Within the last three years, sound reinforcement (the really big speakers) has increasingly been processed through digital mixing consoles, meaning there are only two places you can go to hear a musical production in the analog domain that the instruments, and your ears, inhabit: small symphonic productions without sound reinforcement, and Boston in concert. We don't use digital mixers.

RML: We've now taken an hour of your time and we promised to do no more than that.

SCHOLZ: It's been great talking with you guys.

NAE News and Notes

Class of 2016 Elected

In February the NAE elected 80 new members and 22 foreign members, bringing the total US membership to 2,275 and the number of foreign members to 232.

Election to the National Academy of Engineering is among the highest professional distinctions accorded to an engineer. Academy membership honors those who have made outstanding contributions to "engineering research, practice, or education, including, where appropriate, significant contributions to the engineering literature," and to "the pioneering of new and developing fields of technology, making major advances in traditional fields of engineering, or developing/implementing innovative approaches to engineering education."

Individuals in the newly elected class will be formally inducted during a ceremony at the NAE's annual meeting in Washington, DC, on October 9, 2016. A list of the newly elected members and foreign members follows, with their primary affiliations at the time of election and a brief statement of their principal engineering accomplishments.

New Members

Kevin R. Anderson, Mercury Fellow, corporate research and development, Mercury Marine, Fond du Lac, WI. For advances in metals recycling through invention of innovative aluminum alloys.

Thomas E. Anderson, Warren Francis and Wilma Kolm Bradley Endowed Chair in Computer Science and Engineering, University of Washington, Seattle. For contributions to the design of resilient and efficient distributed computer systems.

Zhenan Bao, professor of chemical engineering, Stanford University, CA. For synthesis, design, and application of organic semiconductors for flexible electronics.

Steven J. Battel, president, Battel Engineering Inc., Scottsdale, AZ. For engineering design and implementation of space flight systems.

Neal Bergano, chief technology officer, TE SubCom, Eatontown, NJ. For innovation and leadership in undersea optical communications.

Charles P. Blankenship Jr., president and chief executive officer, GE Appliances and Lighting Division, General Electric Co., Louisville, KY. For contributions to the incorporation of new technology in consumer products and aircraft engines.

Dan Boneh, professor of computer science and electrical engineering, Stanford University, CA. For contributions to the theory and practice of cryptography and computer security.

Antonio J. Busalacchi Jr., director, Earth System Science Interdisciplinary Center, and professor, Department of Atmospheric and Oceanic Science, University of Maryland, College Park. For understanding of tropical oceans in coupled climate systems via remotely sensed observations and for international leadership of climate prediction/projection research.

Emily A. Carter, Gerhard R. Andlinger Professor in Energy and the Environment and professor of mechanical and aerospace engineering and applied and computational mathematics, Princeton University, NJ. For development of quantum chemistry computational methods for the design of molecules and materials for sustainable energy.

Michael A. Celia, Theodora Shelton Pitney Professor of Environmental Studies and professor of civil and environmental engineering, Princeton University, NJ. For contributions to the development of subsurface flow and transport models in groundwater remediation and CO_2 sequestration.

Frederick R. Chang, director, Darwin Deason Institute for Cyber Security, Bobby B. Lyle Endowed Centennial Distinguished Chair in Cyber Security, and professor, Department of Computer Science and Engineering, Lyle School of Engineering, Southern Methodist University, Dallas. For leadership in cybersecurity research in the intelligence community and advancing the importance of cybersecurity science in academia.

Simon R. Cherry, distinguished professor, Department of Biomedical Engineering, University of California, Davis. For development of nuclear emission imaging and magnetic resonance technologies for medical science.

Morton Collins, managing partner, Battelle Ventures LLC, Ewing, NJ. For accomplishments as a builder and manager of technology-based companies and as an advisor to government and universities.

Thomas M. Connelly Jr., executive director and chief executive officer, American Chemical Society, Washington, DC. For leadership of interdisciplinary innovations in chemical engineering including cellulosic ethanol, polymers, and related materials being used worldwide.

Gérard P. Cornuéjols, IBM University Professor of Operations Research, Tepper School of Business, Carnegie Mellon University, Pittsburgh. For contributions to the theory, practice, and application of integer programming.

Juan J. de Pablo, Liew Family Professor in Molecular Engineering and deputy director of education and outreach, University of Chicago. For design of macromolecular products and processes via scientific computation.

Scott L. Delp, James H. Clark Professor of Bioengineering, Mechanical Engineering, and Orthopaedic Surgery, Stanford University, CA. For computer simulations of human movement and their applications to treatment of clinical movement pathologies.

Paul E. Dimotakis, John K. Northrop Professor of Aeronautics and professor of applied physics, California Institute of Technology, Pasadena. For contributions to the fluid mechanics of jet propulsion and other processes involving turbulence, mixing, and transport.

Michael F. Doherty, professor of chemical engineering, University of California, Santa Barbara. For the design of methods for complex distillation and crystallization processes.

Fiona M. Doyle, Donald H. McLaughlin Professor of Mineral Engineering, Department of Materials Science and Engineering, and dean, Graduate Division, University of California, Berkeley. For contributions to environmentally benign hydrometallurgy leading to separation of metals from solutions and for leadership in engineering education.

Adam J. Ellison, corporate research fellow, Science and Technology Division, Corning Inc., Corning, NY. For invention of advanced glasses with widespread use in mobile device displays.

Hans K. Fauske, president (ret.) and Regent Advisor, Fauske and Associates Inc., Burr Ridge, IL. For contributions to nuclear and chemical reactor safety.

Clark W. Gellings, principal, Electric Power Research Institute, Palo Alto. For leadership in demand-side management and for the application of digital technology to improve efficiency and reliability in electric power systems.

Richard A. Gottscho, executive vice president, Global Products Group, Lam Research Inc., Fremont, CA. For solutions to plasma etch technology and productivity challenges in scaling semiconductor devices from the micro- to nanometer levels.

Albert G. Greenberg, Distinguished Engineer and director, Azure Networking, Microsoft Corp., Redmond, WA. For contributions to the theory and practice of operating large carrier and data center networks.

Mehdi Hatamian, senior vice president of engineering, Broadcom Corp., Irvine, CA. For contributions to development of integrated circuits for video, communications, and digital signal processing.

William A. Hawkins III, lead director, Immucor Inc., Norcross, GA. For leadership in biomedical engineering and translational medicine.

Mary Cynthia Hipwell, vice president of engineering, Bühler, Plymouth, MN. For leadership in the development of technologies to enable areal density increases in hard disk drives.

Teh C. Ho, retired senior research associate, ExxonMobil Research and Engineering Co., Bridgewater, NJ. For contributions to catalytic removal of sulfur and nitrogen compounds from hydrocarbon fuels.

James E. Hubbard Jr., Samuel P. Langley Distinguished Professor, Department of Aerospace Engineering, University of Maryland, College Park, and University of Maryland Langley Professor, National Institute of Aerospace, Hampton, VA. For advances in the modelling, design, analyses, and application of adaptive structures.

Paul E. Jacobs, executive chair, Qualcomm Inc., San Diego. For leadership in the design, development, and worldwide commercialization of wireless products and services.

Anil K. Jain, University Distinguished Professor, Department of Computer Science and Engineering, Michigan State University, East Lansing. For contributions to the engineering and practice of biometrics.

Basil Louis Joffe, senior operations research consultant, Spiral Software Ltd., Houston. For leadership in optimization-based production planning systems for the petroleum and petrochemical industry.

David S. Johnson, visiting professor of computer science, Columbia University, New York City. For contributions to the theory and practice of optimization and approximation algorithms.

Kristina M. Johnson, cofounder and chief executive officer, Cube Hydro Partners LLC, Chevy Chase,

MD. For development and deployment of liquid crystal on silicon display technologies, the basis for high-speed optoelectronic 3D imaging.

Brian D. Kelley, vice president of bioprocess development, US Biologics Pharma Technical Development, Genentech Inc., South San Francisco. For leadership in the development of bioprocess technology and cost-effective manufacturing processes for clinically effective recombinant protein therapeutics.

Peter S. Kim, Virginia and D.K. Ludwig Professor of Biochemistry, Stanford ChEM-H, Stanford University School of Medicine, CA. For leadership in the discovery and development of novel drugs and vaccines used worldwide.

Gary J. Klein, executive vice president and senior principal, Wiss, Janney, Elstner Associates Inc., Northbrook, IL. For investigations of national and international infrastructure and conveying knowledge from these investigations to the profession.

John J. Koszewnik, chief technical officer, Achates Power Inc., San Diego. For improvements in the design, development, and production efficiency of vehicle engines.

Philip T. Krein, professor of electrical and computer engineering, and director, Grainger Center for Electric Machinery and Electromechanics, University of Illinois, Urbana-Champaign. For contributions to power electronics technology and education.

Charles E. Leiserson, Edwin Sibley Webster Professor, Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge. For theoretically grounded approaches to digital design and parallel computer systems.

Bruce G. Lindsay, chief data scientist, Paradata, San Jose, CA. For the design and implementation of high-performance distributed and extensible database systems.

Yilu Liu, Governor's Chair Professor, Oak Ridge National Laboratory and University of Tennessee, Knoxville. For innovations in electric power grid monitoring, situational awareness, and dynamic modelling.

Jon D. Magnusson, senior principal, Magnusson Klemencic Associates, Seattle. For building designs that enable high-rise buildings in seismic sensitive regions and for innovations in modern structural engineering practice worldwide.

David R. Maidment, Hussein M. Alharthy Centennial Chair in Civil Engineering, Center for Research in Water Resources, University of Texas, Austin. For the development of geographic information systems applied to hydrologic processes.

Michael Maloney, manager of structural alloys, hot section materials, and coatings, Pratt and Whitney, East Hartford, CT. For contributions to the development and implementation of low-conductivity thermal barrier coatings for advanced aircraft engines.

Charles W. Moorman, retired chair and chief executive officer, Norfolk Southern Corp., Norfolk, VA. For leadership in the development of computerized freight railroad tracking system in North America.

Warren C. Oliver, president, Nanomechanics Inc., Oak Ridge, Tennessee. For contributions to the development and commercialization of nanomechanical testing technology.

Shmuel S. Oren, Earl J. Isaac Professor in the Science and Analysis of Decision Making, Department of Industrial Engineering and Operations Research, University of California, Berkeley. For contributions to the integration of decisions and cooperative market mechanisms for adaptive multisource electrical power systems.

Arati Prabhakar, director, US Defense Advanced Research Projects Agency, Arlington, VA. For national leadership to advance semiconductor and information technologies.

David Y.H. Pui, Distinguished McKnight University Professor and L.M. Fingerson/TSI Inc. Chair in Mechanical Engineering, University of Minnesota, Minneapolis. For contributions to aerosol and nanoparticle science and engineering for air pollution control.

James B. Rawlings, Paul A. Elfers Professor and W. Harmon Ray Professor, Department of Chemical and Biological Engineering, University of Wisconsin, Madison. For contributions to control engineering theory, practice, and education.

Gabriel M. Rebeiz, Wireless Communications Industry Chair Professor of Electrical and Computer Engineering, University of California, San Diego. For contributions to radio frequency microelectromechanical systems (RF MEMS) and phased array technologies.

Wanda K. Reder, vice president, Power Systems Services Division, S&C Electric Co., Chicago. For leadership in electric power delivery and workforce development.

Rodolfo R. Rodriguez, chief scientific officer and founder, Advanced Animal Diagnostics, Morrisville, NC. For inventions to analyze blood and separate blood

components that enable widespread clinical therapies.

Emanuel M. Sachs, scientific advisory board chair, 1366 Technologies, Bedford, MA. For contributions and commercialization in photovoltaics and three-dimensional printing.

Ann Beal Salamone, president, Rochal Industries LLP, San Antonio. For development of materials for biomedical applications, personal care, electronics, and water purification.

José G. Santiesteban, manager, Catalyst Technology Division, Process Technology, ExxonMobil Research and Engineering Co., Annandale, NJ. For development and commercialization of catalytic systems for petrochemical manufacture and cleaner fuels production.

Bridget R. Scanlon, senior research scientist, Sustainable Water Resources Program, Bureau of Economic Geology, University of Texas, Austin. For contributions to the evaluation of groundwater recharge and aquifer depletion.

David L. Sedlak, Malozemoff Professor in Mineral Engineering, codirector of the Berkeley Water Center, and director, Institute for Environmental Science and Engineering, University of California, Berkeley. For contributions to environmental aqueous chemistry, especially in the areas of water reuse, water contaminants, and urban water infrastructure.

Mohammad Shahidehpour, Bodine Chair Professor of Electrical and Computer Engineering, director, Robert W. Galvin Center for Electricity Innovation, and associate director, Wanger Institute for Sustainability and Energy Research, Illinois Institute of Technology, Chicago. For contributions to the optimal scheduling of generation in a deregulated electricity market with variable renewable energy sources.

Michael K. Sinnett, vice president of product development, Boeing Commercial Airplanes, the Boeing Co., Woodway, WA. For leadership in commercial aircraft and aircraft systems development, creating improvements in performance and cost.

K.R. Sridhar, principal cofounder and chief executive officer, Bloom Energy Corp., Sunnyvale, CA. For contributions to transport phenomena and thermal packaging of electrochemical systems and generation of clean, reliable, and affordable power.

Robert L. Steigerwald, power electronics consulting engineer, Adirondack Power Processing LLC, Burnt Hills, NY. For development and deployment of power electronics for medical, transportation, and industrial applications.

Adam Diedrich Steltzner, manager, Planetary Entry, Descent, and Landing and Small Body Access Office, Jet Propulsion Laboratory, Pasadena, CA. For development of the Mars *Curiosity* 2011 entry, descent, and landing system and for contributions to control of parachute dynamics.

Grant H. Stokes, head, Space Systems and Technology Division, MIT Lincoln Laboratory, Lexington, MA. For innovations in systems for space situational awareness and the discovery of near-Earth asteroids.

Kathryn D. Sullivan, undersecretary of commerce and administrator, National Oceanic and Atmospheric Administration, Washington, DC. For service to the nation through flight in space and leadership of federal oceanography and meteorology.

Yongkui Sun, executive director of business development and licensing, Merck Research Laboratories, Merck & Co., Rahway, NJ. For contributions to green, economical processes for pharmaceuticals and for developing business strategies in emerging markets.

Kenneth R. Swartzel, William Neal Reynolds Distinguished Professor Emeritus, Department of Food, Bioprocessing, and Nutrition Sciences, North Carolina State University, Raleigh. For advances in thermal processes of food preservation.

Ganesh C. Thakur, president, Thakur Services Inc., Houston. For leadership in the implementation of integrated reservoir management techniques.

Leonard Kent Thomas, consultant, Bartlesville, OK. For contributions to the development and application of reservoir simulators to enhance production from complex reservoirs.

Michael F. Tompsett, retired president and owner, TheraManager LLC, Chatham, MA. For the design and development of the first charge-coupled device imagers.

John R. Treichler, president, Raytheon Applied Signal Technology, Sunnyvale, CA. For contributions to digital signal processing and its applications to national intelligence gathering.

Stephen M. Trimberger, fellow, Xilinx, Inc., San Jose, CA. For contributions to architectures and programming tools for field-programmable gate arrays (FPGAs).

Chris G. Van de Walle, Herbert Kroemer Chair in Materials Science and professor, Materials Department, University of California, Santa Barbara. For contributions to the theory of semiconductor interfaces and its impact on optoelectronic devices.

David A. Weitz, Mallinckrodt Professor of Physics and Applied Physics and director, Materials Research Science and Engineering Center, Harvard University, Cambridge, MA. For discoveries of complex fluids, colloids, and emulsions, which have resulted in new products and companies.

David F. Welch, cofounder and president, Infinera Corp., Sunnyvale, CA. For contributions to high-power semiconductor lasers and photonic integrated circuits.

Jennifer L. West, Fitzpatrick Family University Professor of Engineering and professor, Departments of Biomedical Engineering and of Mechanical Engineering and Materials Science, Duke University, Durham, NC. For developments in photothermal and theranostic therapies and bioabsorbed scaffolds for tissue regeneration.

Alan E. Willner, Steven and Kathryn Sample Chair in Engineering, Department of Electrical Engineering, and associate director, Center for Photonics Technology, University of Southern California, Los Angeles. For significant advances in high-capacity optical communication systems.

Michael I. Yarymovych, president, Sarasota Space Associates, Osprey, FL. For contributions to space programs and for leadership of national and international aerospace organizations.

New Foreign Members

Hiroshi Amano, professor, Department of Electrical Engineering and Computer Science, and director, Akasaki Research Center, Nagoya University, Japan. For development of p-type gallium nitride (GaN) doping, enabling blue semiconductor LEDs.

Mukesh D. Ambani, chair and managing director, Reliance Industries Ltd., Nariman Point, Mumbai. For engineering and business leadership in oil refineries, petrochemical products, and related industries.

Göran Andersson, professor, electric power systems, Swiss Federal Institute of Technology, Zürich. For contributions to the development of high-voltage direct current (HVDC) technology and methods of power system voltage stability analysis.

John Boscawen Burland, emeritus professor and senior research investigator, Department of Civil and Environmental Engineering, Imperial College, London. For contributions to geotechnical engineering and the design, construction, and preservation of civil infrastructure and heritage buildings.

Emmanuel Detournay, professor, Department of Civil, Environmental, and Geoengineering, University of Minnesota, MN. For advances in hydraulic fracturing and drilling dynamics.

Masao Doi, professor, 1000 Foreign Expert Program, Beihang University, Beijing. For contributions to the rheology of polymeric liquids, especially the entanglement effect in concentrated solutions and melts.

Peter Gumbsch, professor, Institute for Applied Materials–Computational Materials Science, Karlsruhe Institute of Technology, Germany. For multiscaled modelling techniques that improve fracture and deformation behavior of structural materials.

Geoffrey E. Hinton, Distinguished Emeritus Professor, Department of Computer Science, University of Toronto, and Distinguished Researcher, Google Inc., Toronto. For contributions to the theory and practice of artificial neural networks and their application to speech recognition and computer vision.

Keith W. Hipel, University Professor, Department of Systems Design Engineering, University of Waterloo, Ontario. For development and application of conflict resolution techniques from a systems engineering perspective.

Lei Jiang, dean, School of Chemistry and the Environment, Beihang University, and professor, Institute of Chemistry, Chinese Academy of Sciences, Beijing. For development and commercialization of superphilic and superphobic coatings.

Willi A. Kalender, professor and chair, Institute of Medical Physics, University of Erlangen-Nürnberg, Erlangen, Germany. For development of spiral computed tomography methods that enable modern high-speed 3D medical imaging with X-rays.

Bruno Michel, manager, advanced thermal packaging, IBM Zürich Research Laboratory. For sustainable technologies to improve data centers and improved efficiencies of energy conversion systems.

Joachim Milberg, retired chair of the board, BMW AG Munich, and professor, Technical University of Munich. For development of computer integrated design and production engineering.

Satyan (Sam) G. Pitroda, chair, The Pitroda Group, Oakbrook Terrace, IL. For development of rural telecommunications infrastructure for India.

Rui Luis Reis, professor of tissue engineering, regenerative medicine, and stem cells, Department of Polymer Engineering, and director, 3B's Research Group, University of Minho, Guimarães, Portugal. For

contributions to biomaterials and tissue engineering in regenerative medicine.

R. Kerry Rowe, professor, Department of Civil Engineering, Queen's University, Kingston, Ontario. For advances in knowledge of the performance of waste containment facilities.

Molly Shoichet, University Professor of Chemical Engineering and Applied Chemistry, Chemistry, and Biomaterials and Biomedical Engineering, University of Toronto. For contributions to neural tissue engineering and design of polymers for cell and drug delivery.

Julia Slingo, chief scientist, Met Office, Exeter, Devon, UK. For contributions to modelling of the Earth's climate system and for leadership in the weather and climate community.

Peter Stoica, professor in systems modelling, Department of Information Technology, Uppsala University, Sweden. For contributions to array signal processing in communications, sensing, and imaging.

Kirsi K. Tikka, president and chief operating officer, ABS Europe Division, American Bureau of Shipping, London. For contributions leading to internationally recognized standards for ship structural design, construction, and maritime safety.

Peter Whittle, Emeritus Churchill Professor of Mathematics for Operational Research, University of Cambridge, UK. For contributions to the mathematics of operations research and statistics.

Yuzhuo Steve Zhang, chair of the board, Shenhua Group Corp. Ltd., Dongcheng, Beijing. For development and commercialization of coal to chemicals/fuels and for leadership in environmental responsibility for the coal industry.

NAE Newsmakers

On November 5, 2015, **Robert D. Allen**, senior manager, IBM Almaden Research Center, Chemistry and Advanced Materials Research, was inducted into the Virginia Tech College of Science **Hall of Distinction**. He is credited with helping launch IBM's Smarter Planet initiative, emphasizing the areas of water, the environment, health, and energy. Research projects under his watch include membranes for improved separations, antimicrobial surfaces to battle against infectious diseases, and materials for the encapsulation and delivery of medicine.

B. Jayant Baliga, director, Power Semiconductor Research Center, North Carolina State University, was recognized by the IEEE Electron Devices Society in Washington, DC, as a **Celebrated Member**. The EDS Celebrated Member was established in 2010 and is intended to recognize and honor legendary individuals in the field of electron devices. Only six people, including three Nobel laureates, from among the 10,000 members have been given this distinction so far.

Rudolph Bonaparte, president and CEO, Geosyntec Consultants, was honored by the American Society of Civil Engineers with the **2016 Outstanding Projects and Leaders (OPAL) Leadership Award for Design**. He received the award March 17, 2016, during ASCE's annual OPAL Gala in Arlington, Virginia.

Terry Boston, a former executive vice president for the TVA, received a **Lifetime Achievement Award** during the Platts Global Energy Awards ceremonies in New York City on December 9. Platts noted Mr. Boston's accomplishments of the past eight years as CEO of PJM, the largest power system in North America and largest electricity market in the world, as well as his long career at the Tennessee Valley Authority.

Federico Capasso, Robert Wallace Professor of Applied Physics and Vinton Hayes Senior Research Fellow in Electrical Engineering, Harvard University, and **Alfred Y. Cho**, vice president (retired), Semiconductor Research Laboratory, Bell Labs, Alcatel-Lucent, are the recipients of the **2015 Rumford Prize** in recognition of their contributions to the field of laser technology. The award is presented by the American Academy of Arts and Sciences.

Chau-Chyun Chen, Jack Maddox Distinguished Chair Professor, Department of Chemical Engineering, Texas Tech University, has been elected an **AIChE Fellow**. Candidates are nominated by their peers, must have significant chemical engineering practice, and must have been a member of AIChE for at least 10 years, three of them as a senior member.

George M. Church, Robert Winthrop Professor of Genetics, Harvard Medical School, has been named one of *Foreign Policy*'s **Leading Global Thinkers of 2015** for

his investigation into adapting genetics to sustain species in the face of extreme environmental and climate changes.

Robert P. Colwell, president, R&E Colwell & Associates, was selected by the IEEE Computer Society Awards committee to receive the **2015 B. Ramakrishna Rau Award** for "contributions to critical analysis of microarchitecture and the development of the Pentium Pro processor."

Earl H. Dowell, William Holland Hall Professor of Mechanical Engineering at Duke University, has been named this year's recipient of the American Institute of Aeronautics and Astronautics (AIAA) **Reed Aeronautics Award**. The award is the highest honor an individual can receive for notable achievement in aeronautics. Dr. Dowell is being recognized for his "pioneering contributions to aeroelasticity, structural dynamics, and unsteady aerodynamics which have had a tremendous influence on aerospace technology." The award will be presented in Washington, DC, on June 15, 2016, at AIAA's annual Aerospace Spotlight Awards Gala held in conjunction with the AIAA Aviation and Aeronautics Forum and Exposition.

Ann Dowling, president of the Royal Academy of Engineering, has been admitted to the **Order of Merit** in the Queen's 2016 New Year's Honors list. Dame Ann joins just 23 other members of the prestigious order, presented as a personal gift of the sovereign.

Robert S. Langer, David H. Koch Institute Professor, Massachusetts Institute of Technology, was named the **Scheele Award Laureate for 2015** in a ceremony that took place during the Scheele Symposium in Stockholm on November 19. Additionally, the Franklin Institute has announced that Dr. Langer will receive the **2016 Benjamin Franklin Medal for Life Sciences**, to be presented at a gala at the institute in April 2016.

J. David Lowell, chair and CEO, CIC Resources Inc., was one of three honored with the **2015 Regents' Award for Outstanding Service to Higher Education** by the Arizona Board of Regents.

Cherry A. Murray was confirmed by the Senate on December 10, 2015, as **director of the Department of Energy's Office of Science**.

Rex W. Tillerson, chair and CEO of ExxonMobil Corporation, has been honored by the Maguire Energy Institute at SMU Cox School of Business with the **L. Frank Pitts Energy Leadership Award**. The award was presented at a ceremony on January 14. Mr. Tillerson, who has helped steer ExxonMobil through four decades of dynamic growth, was selected because he represents the spirit of entrepreneurship, ethical leadership, and energy industry innovation personified by L. Frank Pitts, the late oilman for whom the energy award is named.

The following NAE members have been elected **AAAS fellows**: **R. Byron Bird**, Vilas Professor Emeritus, University of Wisconsin–Madison; **Shu Chien**, University Professor of Bioengineering and Medicine, Y.C. Fung Professor of Bioengineering, and director, Institute of Engineering in Medicine, University of California, San Diego; **James W. Demmel**, professor, Computer Science Division, University of California, Berkeley; **Dennis E. Discher**, Robert D. Bent Professor, Chemical and Biomolecular Engineering, Mechanical Engineering & Applied Mechanics, University of Pennsylvania; **Timothy L. Killeen**, president, University of Illinois; **Babatunde A. Ogunnaike**, William L. Friend Chaired Professor and dean, College of Engineering, University of Delaware; and **Victor W. Zue**, professor of electrical engineering and computer science, Massachusetts Institute of Technology.

The following members are among the **2016 inductees to the National Inventors Hall of Fame**: **Victor B. Lawrence**, Batchelor Chair Professor of Electrical Engineering and associate dean for special programs, Stevens Institute of Technology; **Radia J. Perlman**, fellow, EMC Corporation; **William J. Sparks** (posthumously); and **Ivan E. Sutherland**, visiting scientist, Portland State University.

The **National Academy of Inventors** has elected the **2015 Class of Fellows**. Election is accorded to academic inventors who have demonstrated a prolific spirit of innovation in creating or facilitating outstanding inventions that have made a tangible impact on quality of life, economic development, and the welfare of society. NAE members inducted in 2015 were **Kristi S. Anseth**, Howard Hughes Medical Institute Investigator and Distinguished Professor, University of Colorado, Boulder; **B. Jayant Baliga**, director, Power Semiconductor Research Center, North Carolina State University; **John E. Bowers**, director, Institute for Energy Efficiency and professor, Department of Electrical and Computer Engineering, University of California, Santa Barbara; **Selim A. Chacour**, professor, Institute for Advanced Discovery and Innovation, University of South Florida; **Shu Chien**, University Professor of

Bioengineering and Medicine, YC Fung Professor of Bioengineering, and director, Institute of Engineering in Medicine, University of California, San Diego; **Robert C. Dean, Jr.**, president, Synergy Innovations Inc.; **Christodoulos A. Floudas**, director, Texas A&M Energy Institute and Erle Nye '59 Chair Professor for Engineering Excellence, Texas A&M University, College Station; **George Georgiou**, professor, Departments of Chemical Engineering, Biomedical Engineering, and Molecular Genetics and Microbiology, University of Texas, Austin; **Victor B. Lawrence**, Batchelor Chair Professor of Electrical Engineering and associate dean for special programs, Stevens Institute of Technology; **Tobin J. Marks**, Vladimir N. Ipatieff Professor of Catalytic Chemistry and professor of materials science and engineering, Northwestern University; **Radia J. Perlman**, fellow, EMC Corporation; **H. Vincent Poor**, dean of engineering and applied science and Michael Henry Strater University Professor, Princeton University; **Kenneth L. Reifsnider**, director, Institute for Predictive Methodology and Presidential Distinguished Professor, University of Texas, Arlington; **Ben A. Shneiderman**, professor, Department of Computer Science, University of Maryland; **Ivan E. Sutherland**, visiting scientist, Portland State University; **Paul K. Wright**, director, Berkeley Energy and Climate Institute, University of California, Berkeley; and **James C. Wyant**, professor emeritus, College of Optical Sciences, University of Arizona.

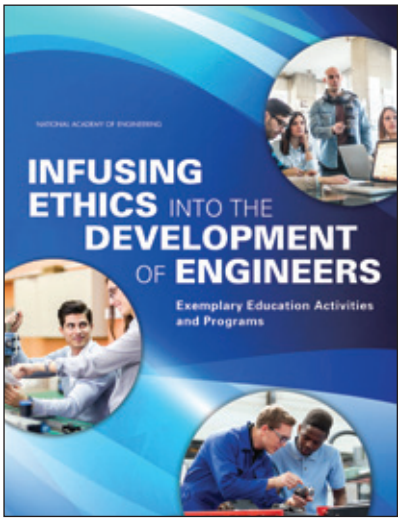
News from the Center for Engineering Ethics and Society

New Online Ethics Center for Engineering and Science

In the second year of the project to expand the National Academy of Engineering's Online Ethics Center (OEC; onlineethics.org) to be the go-to online source for critical resources and support for ethics and ethics education in science and engineering, the site was revised and relaunched. It has been redesigned to (1) connect resources; (2) provide resources on ethics topics and on how to teach ethics; (3) allow searching and browsing by type of resource, topic, or science and engineering field; and (4) enable better recognition of those who author and contribute resources. Over the next three years six content editorial boards will identify, develop, and evaluate materials to expand the collection; and, together with the Outreach and Engagement Group, will reach out to meet the needs of site's the wide range of audiences. The focus areas of the content editorial boards are engineering; life and environmental sciences; computer, math, and physical sciences; social and behavioral sciences; research ethics; and international ethics. The project's advisory committee includes leaders in ethics, the sciences, and engineering, and members of the three academies. The project is funded by the National Science Foundation, with the cooperation of the NAE's sister Academies of Sciences and Medicine, and in collaboration with the Ethics Education Library (EEL) of the Center for the Study of Ethics in the Professions at the Illinois Institute of Technology.

Infusing Ethics into the Development of Engineers: Exemplary Education Activities and Programs

An essential part of the development of engineers is their training to understand and recognize ethical



issues in engineering. Research on ethics education in engineering reveals a variety of approaches; some activities focus on ethical decision making, others on awareness of ethical and social issues, and still others on professional standards, rules, and regulations. This report recognizes and describes 25 exemplary programs that prepare students for ethical practices, research, or leadership in engineering. These *NAE Exemplars in Engineering Ethics Education* range from short activities inserted in engineering courses to multiyear programs required of all students. This report will be a resource for institutions and educators to strengthen and expand their ethics programs and thus improve the capabilities of practicing and future engineers. Additional information about and materials from the exemplars in the report will be included in the NAE's Online Ethics Center for Engineering and Science (OEC) collection (onlineethics.org). Information about the project is available at www.nae.edu/InfusingEthics.aspx.

Overcoming Challenges to Infusing Ethics into the Development of Engineers

This new project will convene a workshop for current and emerging leaders in ethics and engineering who are working to improve the ethical development of engineering students, to (1) share their work, experiences, and lessons learned; (2) discuss strategies for overcoming institutional and cultural challenges; and (3) develop plans and collaborations for advancing efforts to infuse ethics into the development of engineers. Research on instructional and cultural challenges for infusing ethics in engineering instruction has begun to identify issues, suggest strategies, and test approaches to changing institutional culture. At the workshop, practicing engineers, engineering educators, and engineering ethics scholars will have both informal and guided opportunities to strategize and develop plans for incorporating ethics in engineering curricula. The information, expertise, mentoring, and facilitated discussions and collaboration at the workshop will help attendees advance their work and develop effective plans for their own institutions. Ultimately, these attendees will form the basis for a cohort of leaders and agents of change across the country. The workshop will be held in the second half of 2016. Information is available at www.nae.edu/overcomingchallenges.aspx.

Mirzayan Fellows Join Program Office

On January 21 the NAE Program Office welcomed three Mirzayan S&T Policy Fellows who will be with us through April 8, 2016.

Kavita Chandra

KAVITA CHANDRA is completing a PhD in materials science and engineering, focusing on nanoparticle synthesis for cancer therapeutic applications, at Northwestern University. She earned a bachelor's degree in materials science from MIT. Aside from research, Kavita has a passion for science outreach, specifically promoting women in STEM fields. She serves on the executive board of the Graduate Women across Northwestern and participates in two year-long mentorship programs at Niles High School and Science Club of the Boys and Girls Program in Uptown. She is excited to learn about a career in science policy as a Mirzayan Fellow with the NAE, specifically through improving access to STEM education for all K–12 students. Kavita loves traveling around the world, especially trying new foods. And because of this fervent love for food, she is also a runner and dancer. She is working with Greg Pearson on the Link Engineering project.

Corinna Raimondo

CORINNA RAIMONDO, J. Herbert Hollomon Fellow with the Center for Engineering Ethics and Society, received her PhD in physical chemistry from the Institut

de Science et d'Ingénierie Supramoléculaire of the University of Strasbourg (France) after completing her BA and MA in chemistry at the University of Genoa (Italy). Her Marie Curie Fellowship in partnership with BASF-SE Corporation afforded her the opportunity to collaborate with researchers in Switzerland, Italy, Germany, the Netherlands, and the United Kingdom. She also performed research at the University of Leuven (Belgium). Corinna's early research focused on the synthesis, characterization, and application in devices of light-sensitive nanomaterials. Subsequently, she started working as a postdoctoral fellow in the Chemical and Chemical Engineering Departments at Northwestern University, studying the synthesis and application of nanomaterials in diverse fields ranging from pure electrochemistry to cell biology. Now a postdoc in the Chemical Engineering Department, her main focus is developing novel heterogeneous catalysts for epoxidations and carbonylations. During her very diverse research experience and collaboration with experts in many different fields and countries, she realized that there are complicated problems of ethics in science, with enormous implications. Corinna has cotaught a course on responsible conduct of research, and is currently working on an MS in law from the Pritzker School of Law at Northwestern University. As a Mirzayan Fellow, she hopes to learn from policy leaders in the area of science and engineering and to discover ways she can apply these lessons to affect policy decision making. She works on the NAE Online Ethics Center (OEC), assisting Frazier Benya.

Rochelle Williams

As director of programs and research at ABET headquarters in Baltimore, ROCHELLE WILLIAMS is responsible for partnering with faculty and industry in robust, relevant technical education research and for providing educational opportunities worldwide on continuous improvement and sustainable assessment processes. This includes ABET's Institute for the Development of Excellence in Assessment Leadership (IDEAL), program assessment workshops, and symposia. Rochelle joined ABET with extensive project management skills and a passion for broadening participation in technical education. She was science laboratory manager at Baton Rouge Community College, where she was responsible for the day-to-day operations of the physics, biology, and chemistry labs. She also taught developmental mathematics as an adjunct faculty member in the Mathematics Department. Before completing her doctoral work, Rochelle served as a graduate assistant at Southern University, teaching composite materials, materials science, and metallurgy. She received her BS in physics from Spelman College, and her master's in mechanical engineering and PhD in science and mathematics education from Southern University. Her research interests include assessment and quality management systems and broadening participation in technical education. Rochelle works with Amelia Greer and Ken Jarboe on the Role of Engineering Societies in Undergraduate Engineering Education and related projects.

The IOM Is Now the Health and Medicine Division

On March 15, 2016, the program unit of the National Academies of Sciences, Engineering, and Medicine that focuses on health and medicine was renamed the Health and Medicine Division (HMD) instead of the Institute of Medicine (IOM). The new name builds on the heritage of the IOM's work in medicine while emphasizing its increased focus on a wider range of health matters.

HMD is fully integrated into the broader work of the National Academies of Sciences, Engineering, and Medicine, which is facilitating more collaborative and interdisciplinary approaches to the most pressing challenges facing the nation and the world. The division will continue to conduct consensus studies and convening activities through the six core boards that were part of the IOM. Clyde Behney continues as executive director of the division.

A Message from NAE Vice President Corale L. Brierley

Corale Brierley

I am pleased to report on a healthy fundraising year. Thanks to the generosity of over 730 members and donors, we were able to raise over $3.7 million in new cash and pledges in 2015 to support our efforts to strengthen the engineering profession and engage the public about the opportunities that arise from engineering. Over $1.7 million (almost 50 percent of the funds raised) was for unrestricted purposes, including $1.3 million to the NAE Independent Fund and $377,000 for the President's Initiatives Fund. This would equate to a $38 million endowment equivalent assuming a 4.5 percent draw that could be used as flexible funds.[1] These unrestricted funds are vital to the NAE. They not only provide core support but allow us to initiate important new projects that lack federal funding and help expand the scope and impact of current programs.

We also received $2 million for projects (restricted) including EngineerGirl, the Next MacGyver, public awareness and understanding of engineering, K–12 education, the Frontiers of Engineering (FOE) symposia, prizes, and other programs. Approximately $1.4 million (74 percent) of the restricted funding came from corporations and/or foundations. We also had 100 percent giving participation from the NAE Council—a sincere gesture of commitment by our leadership.

This extraordinary philanthropic support provides for 30 percent of the NAE's annual budget, and we are grateful for our donors' confidence in our ability to use their contributions to serve the engineering community, students, policymakers, and the public. Below is a sampling of what the NAE accomplished with philanthropic support in 2015:

- With support from Chevron, created ***LinkEngineering***, a new website (*www.linkengineering.org*) launched in January 2016 to help preK–12 educators in the United States implement engineering education in classrooms and out-of-school settings. It provides the first-ever platform for K–12 teachers and informal educators to work and learn as a community toward improving the reach and quality of US precollege engineering education.

- With support from the Lockheed Martin Corporation, we successfully cohosted the second annual **Global Grand Challenges Summit** with the Chinese Academy of Engineering (CAE) and Royal Academy of Engineering (RAE). It was held in September 2015 in Beijing and had record attendance of 700. Increased philanthropic support allowed us to expand the program to include a student business plan competition where 15 undergraduate teams presented entrepreneurial ideas tackling one or more of the NAE Grand Challenges for Engineering.

- We hosted the second **E4U Video Contest** that encouraged students and the public to learn about and get interested in engineering. Funded by a $250,000 gift from ExxonMobil, the winners were announced at the 2015 Annual Meeting.

- We published four highly acclaimed issues of ***The Bridge***. This popular publication is primarily funded by your contributions to the NAE Independent Fund. In 2015 your support allowed us to make it more visually appealing by providing the resources to print this flagship publication in color.

- With support from the United Engineering Foundation (UEF), we launched the ***Next MacGyver Competition***. Top Hollywood producers teamed with the NAE, the University of Southern California's Viterbi School of Engineering, and the MacGyver Foundation to engage the worldwide public in a competition to crowdsource ideas for a scripted TV series featuring a female engineer as the leading character. Less than 20 percent of engineering bachelor degrees are granted to women and recent trends have been declining. White House officials have asked, "What could Hollywood and our creative talent do to help make engineers and entrepreneurs the rock stars of the 21st century?" Much like CSI did for forensic science, positive

[1] It would be $34 million assuming a 5 percent draw.

portrayal of engineers in popular culture can help young people consider themselves in such a role. The top 5 finalists are currently shopping their scripts to various networks to pilot their scripts.

After the blockbuster year of 2014, contributions slowed in 2015, especially in the first two quarters. This could be attributed to donor fatigue after the 50th Anniversary 4-year fundraising effort, for which many donors stretched their giving, and the tumultuous stock market at the end of December and into January.

Some Highlights from 2015

The Fran and George Ligler Challenge for Section 2 got off to a great start in 2015. NAE member Fran Ligler and her husband George created this challenge to raise $100,000 by 2019 from Section 2 members and hopefully inspire other members to fund challenges for their sections. Of the 51 Section 2 members who gave in 2015, 22 increased their giving from 2014, 11 were new or lapsed donors, and 33 qualified for the Ligler Match. With close to $35,000, we are 1/3 of our way to reaching the goal—and this is only the first year of the 5-year effort. This is great news, and if we can keep up this pace of contributions we will exceed the goal for this challenge by the end of 2017.

We launched the **Ming and Eva Hsieh $250,000 Challenge** at the Annual Meeting. This is a wonderful first gift from the Hsiehs, especially since Ming was just inducted in October 2015—it is great to see that they decided to get involved early. Their gift benefits the President's Initiatives Fund. Over **$800,000 is eligible to be matched** by the Hsieh Challenge, surpassing the $250,000 goal. In response to the challenge 291 members made gifts; 140 were new or lapsed donors and 151 increased their giving from 2014. This was also a good tool to spur contributions at the end of the year, and helped bring about several new pledges, including four $80,000 pledges to reach the Einstein Society for a total of 8 new Einstein members and 25 new Golden Bridge Society members for the year.

February Council Dinner and Financial, Tax, and Estate Planning Session

In February 2015 the NAE hosted its annual Council dinner in Newport Beach the night before the National Meeting with over 100 attendees. This dinner has become a tradition where members, donors, and friends in the area can interact with the NAE Council and meet, socialize, and hear about developments at the NAE. Art Geoffrion was presented with his Heritage Society Medal. For the third time, the NAE also hosted a Financial, Tax, and Estate Planning seminar just before the dinner, led by Cindy Sterling, certified financial planner. This seminar has become popular during the Annual Meeting and we wanted to offer members on the West Coast opportunities to learn more about making tax-wise estate plans and how best to incorporate their philanthropic priorities.

Golden Bridge Society Dinner

In conjunction with the 2015 Annual Meeting, President C. D. Mote, Jr. and his wife Patsy hosted some of the NAE's most generous members and friends at the Golden Bridge Society Dinner at the Organization of American States on October 4. Among the supporters present, the newest donors were welcomed into the Academy's three lifetime recognition societies, including 3 Einstein, 1 Golden Bridge, and 1 Heritage.

Noteworthy Contributions

The NAE received some remarkable gifts in 2015. While all contributions are greatly appreciated and make a difference in the work of the NAE, the following gifts show extraordinary leadership and commitment to the NAE.

- **Dan ('76) and Frances Berg** for pledging $80,000 to benefit the NAE Independent Fund in honor of his 40th anniversary as a member.
- **Virginia Bugliarello** for making a gift in memory of her late husband, NAE member George Bugliarello, in support of EngineerGirl.
- **Chevron Corporation**, which generously provided over $330,000 for EngineerGirl and LinkEngineering.
- **Ross ('02) and Stephanie Corotis** for pledging $80,000 to benefit the NAE Independent Fund.
- The **Charles Stark Draper Laboratory** for contributing $236,000 to cover operating costs of the Draper Prize for the advancement of engineering and public education about engineering.
- **Dotty and Gordon ('12) England** for their $60,000 gift in support of the NAE Independent Fund.
- **Martin E. ('96) and Lucinda Glicksman** who pledged $80,000 to benefit the NAE Independent Fund.
- **Ming and Eva Hsieh** who gener-

ously funded a $250,000 giving challenge to encourage others to support the NAE. Their gift benefitted the President's Initiatives Fund.

- **The William R. Kenan Institute at NC State** for a $150,000 pledge in support of EngineerGirl.
- **Jane and Alan ('97) Mulally** for directing Alan Mulally's $50,000 prize monies from the J.C. Hunsaker Award back to the Academies.
- **Ohio University Foundation** for contributing $636,000 to cover operating costs associated with awarding the Russ Prize recognizing engineering achievements that have a significant and widespread impact on society.
- **Lockheed Martin** for a $500,000 pledge payment for the 2015 Global Grand Challenges Summit in Beijing.
- **Robin ('07) and Rose McGuire** for $50,000 in support of K–12 engineering education.
- **Microsoft** for its annual gift to support the Frontiers of Engineering (FOE) program.
- **James M. Tien ('02) and Ellen S. Weston** for pledging $80,000 to help increase the public's awareness and understanding of engineering.
- **United Engineering Foundation** for a $150,000 gift in support of the Next MacGyver, a project that leverages the power of Hollywood to get students interested in engineering.

If you are interested in making a gift to the NAE, please contact Radka Nebesky, NAE director of development, at 202.334.3417 or RNebesky@nae.edu.

Loyal Donors

Gifts made regularly each year to the NAE demonstrate genuine commitment to our mission and goals. As a long-time donor who understands that every donation to the NAE is a choice to support an organization whose work I believe matters greatly, I thank the Loyalty Society members (page 117) who have contributed to the NAE for 20 years or more.

Looking Ahead

In 2016 we will focus on building the endowment to ensure the NAE's long-term financial strength and to provide a sustained stream of income for keystone programs. We plan to offer more opportunities to learn about deferred giving and estate planning by hosting seminars in conjunction with selected Regional Meetings in addition to the estate planning brunch during the NAE Annual Meeting and other regular communication. If you are interested in making a planned gift to NAE, or if you have already made a gift provision in your estate plans but have not yet notified us, please contact Jamie Killorin, director of gift planning, at 202.334.3833 or JKillorin@nas.edu.

Without your philanthropic support, the NAE would not have a solid foundation from which to sustain its most successful projects and spearhead the creation of new and timely programs. The energetic participation of our members has always driven the NAE forward with crucial time, effort, and ideas. Our members are also vital to our fundraising success, both by making financial contributions of their own and by serving as advocates for the NAE and engineering to their peers. We sincerely appreciate your generosity and continual support.

On behalf of the NAE Council, President Dan Mote, and myself, thank you very much for your contributions in 2015. Our supporting members, friends, partner corporations, foundations, government sponsors, and other organizations make all the difference in our ability to positively impact our world by being an advocate for engineering. I am grateful for your contributions, and look forward to your continued involvement in 2016.

2015 Honor Roll of Donors

Annual Giving Societies

The National Academy of Engineering gratefully acknowledges the following members and friends who made charitable contributions to the NAE, and those NAE members who supported the Committee on Human Rights, a joint committee of the three academies, during 2015. The collective, private philanthropy of these individuals has a great impact on the NAE and its ability to be a national voice for engineering. We acknowledge contributions made as personal gifts or as gifts facilitated by the donor through a donor-advised fund, matching gift program, or family foundation.

New member Ming Hsieh ('15) and his wife Eva challenged all members and friends to increase their giving to the NAE in 2015 with a $250,000 challenge. This generous gift provides resources to programs aligned with the new NAE Strategic Plan. Donors who participated in the Hsieh Challenge are noted with the ◊ symbol.

Fran Ligler, a member of the NAE Council and Section 2, and her husband George pledged $100,000 to encourage giving by Section 2 members over the next 5 years or until the $100,000 goal is reached. The members who participated in the Ligler Challenge are noted with the # symbol.

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$50,000+

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Ross and Stephanie Corotis◊
Dotty and Gordon England◊
Ming and Eva Hsieh
Robin K. and Rose M. McGuire◊
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Rosette Society

$25,000 to $50,000

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Bharati and Murty Bhavaraju
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Frances and George Ligler
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Challenge Society

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$1,000 to $9,999

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We have made every effort to list donors accurately and according to their wishes. If we have made an error, please accept our apologies and contact the Development Office at 202.334.2431 or giving@nae.edu so we can correct our records.

In Memoriam

GENE M. AMDAHL, 92, retired chair, Commercial Data Servers Inc., died November 10, 2015. Dr. Amdahl was elected to the NAE in 1967 for development of large computer systems.

DAVID ATLAS, 91, Distinguished Visiting Scientist Emeritus, NASA Goddard Space Flight Center, died November 10, 2015. Dr. Atlas was elected to the NAE in 1986 for contributions, inventions, leadership, and public service in the application of radar and electromagnetic engineering to meteorology.

CHARLES CRUSSARD, 91, retired scientific director, Pechiney (France), died January 14, 2008. Dr. Crussard was elected to the NAE as a foreign member in 1976 for contributions to metallurgical science and technology and its applications.

ELIO D'APPOLONIA, 97, professional engineer, died December 30, 2015. Dr. D'Appolonia was elected to the NAE in 1977 for contributions to design and construction procedures for foundations of complex facilities subjected to heavy loadings.

JOSEPH F. ENGELBERGER, 90, chair, HelpMate Robotics Inc., died December 1, 2015. Mr. Engelberger was elected to the NAE in 1984 for his inventive design and development of the industrial robot which has brought about a new industrial revolution—one that has culminated in an automated factory.

FAZIL ERDOGAN, 90, G. Whitney Snyder Professor of Mechanical Engineering and Mechanics, Lehigh University Packard Laboratory, died October 2, 2015. Dr. Erdogan was elected to the NAE in 1997 for contributions to fracture mechanics.

BRIAN L. EYRE, 80, professor and senior visiting fellow, University of Oxford, died July 28, 2014. Professor Eyre was elected to the NAE as a foreign member in 2009 for understanding of neutron irradiation–induced damage in materials and for developing technologies and policies for the UK nuclear industry.

MORRIS E. FINE, 97, Technological Institute Professor Emeritus, Northwestern University, died October 1, 2015. Dr. Fine was elected to the NAE in 1973 for contributions to education, research, and development in the field of materials science and metallurgical engineering.

RENATO FUCHS, 72, independent consultant, died September 7, 2015. Dr. Fuchs was elected to the NAE in 1994 for engineering contributions in the design, construction, and operation for large-scale manufacturing of recombinant DNA proteins.

JOHN H. HORLOCK, 87, fellow and former vice chancellor, Open University, United Kingdom, died May 22, 2015. Sir John was elected to the NAE as a foreign member in 1988 for distinguished contributions to knowledge of the thermodynamics and fluid dynamics of gas turbines and for innovations in engineering education.

HERBERT H. KELLOGG, 95, Stanley Thompson Professor Emeritus of Chemical Metallurgy, Columbia University, died January 16, 2016. Mr. Kellogg was elected to the NAE in 1978 for strengthening the scientific base of metallurgical processes, and ability to unite theoretical studies with practical industrial needs.

LOUIS C. LUNDSTROM, 100, retired executive director of environmental activities staff, General Motors Corporation, died August 6, 2015. Dr. Lundstrom was elected to the NAE in 1977 for leadership in the development of the systems approach to safe highways and in the development of test technology for improvement in auto safety.

HUDSON MATLOCK, 95, professor emeritus of civil engineering, University of Texas, died October 8, 2015. Mr. Matlock was elected to the NAE in 1982 for outstanding leadership in research and design related to offshore engineering.

SEYMOUR (CY) L. MEISEL, 93, retired vice president of research, Mobil Research & Development Corporation, died December 28, 2015. Dr. Meisel was elected to the NAE in 1981 for integrating basic exploratory research and process engineering developments leading to successful commercialization of important new technology.

GEORGE E. MUELLER, 97, retired chief executive officer, Kistler Aerospace Corporation, died October 12, 2015. Dr. Mueller was elected to the NAE in 1967 for electronic systems engineering.

F. ROBERT NAKA, 90, retired president and CEO, CERA Inc., died December 21, 2013. Dr. Naka was elected to the NAE in 1997 for the development of national security systems and for contributions in materials and sensor technologies for advanced military systems.

TSUNEO NAKAHARA, 85, former vice chair of Sumitomo Electric Industries, died January 8, 2016. Dr. Nakahara was elected to the NAE as a foreign member in 1999 for contributions and leadership in the development and industrialization of materials for optical communications.

NORBERT PETERS, 72, professor, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen University, died July 4, 2015. Dr. Peters was elected to the NAE as a foreign member in 2002 for contributions to the field of combustion modelling of turbulent flames and the development of chemical kinetic mechanisms for hydrocarbon oxidation.

HENRY M. ROWAN, 92, chair, Inductotherm Group, died December 9, 2015. Mr. Rowan was elected to the NAE in 1998 for developing and commercializing induction melting and for advancing engineering education.

VICTOR H. RUMSEY, 95, professor emeritus, University of California, San Diego, died March 11, 2015. Dr. Rumsey was elected to the NAE in 1980 for research in practical applications of electromagnetic theory, especially in design of radio antennas insensitive to frequency and polarization.

DONALD G. RUSSELL, 84, chair, Russell Companies, died December 19, 2015. Mr. Russell was elected to the NAE in 1982 for technical

contributions and leadership of professional and business organizations that have contributed significantly to the engineering profession.

OLEG D. SHERBY, 90, emeritus professor, Stanford University, died November 9, 2015. Dr. Sherby was elected to the NAE in 1979 for research to improve the understanding of high-temperature deformation of metals and technical materials leading to their improved performance.

WILLIAM H. SILCOX, 93, retired manager, offshore technology development, Chevron Corporation, died August 6, 2015. Mr. Silcox was elected to the NAE in 1986 for the development of original subsea drilling and completion systems, and offshore compliant deepwater structures.

MORRIS A. STEINBERG, 95, retired vice president for science, Lockheed Corporation, died January 6, 2016. Dr. Steinberg was elected to the NAE in 1977 for contributions to the introduction of new and improved structural materials into aircraft and space vehicles.

JOSEPH F. TRAUB, 83, Edwin Howard Armstrong Professor, Columbia University, died August 24, 2015. Prof. Traub was elected to the NAE in 1985 for initiating optimal iteration theory, for creating significant new algorithms that solve diverse problems, and for educational leadership in computing.

ROBERT M. WHITE, 92, former president, National Academy of Engineering, died October 14, 2015. Dr. White was elected to the NAE in 1968 for development of methods of weather forecasting and leadership in the evolution of the World Weather Watch System.

MIRANDA G. YAP, 67, retired professor, National University of Singapore, died October 14, 2015. Professor Yap was elected to the NAE as a foreign member in 2006 for her outstanding achievements in education, research, and management in the field of mammalian cell culture.

Calendar of Meetings and Events

April 1	Deadline for NAE Awards Nominations for 2016–2017
April 6	Symposium: Exploring a New Vision for Center-Based, Multidisciplinary Engineering Research
April 14	NAE Regional Meeting: Engineering Now: Insights from the Labs at MIT Cambridge, Massachusetts
April 15	Gordon Prize Award Ceremony Worcester Polytechnic Institute, Massachusetts
April 18–19	NAE/AAES Professional Engineering Societies Convocation
April 26	NAE Regional Meeting Microsoft Corporation, Redmond, Washington
April 28	NAE Regional Meeting: Innovation in our Energy Systems National Renewable Energy Laboratory, Golden, Colorado
May 2–3	NAE Regional Meeting: Preparing a STEM Workforce for Tomorrow: Academic and Industry Viewpoints Ohio State University and Battelle, Columbus
May 10–11	LinkEngineering Committee Meeting
May 12–13	NAE Council Meeting
May 24	NAE Regional Meeting: Driverless Cars and Connected Transportation University of Michigan, Ann Arbor
June 8–10	Fourth Annual Integrated Network on Social Sustainability (INSS) Conference Charlotte, North Carolina
June 14	Robert M. White Memorial Symposium
June 16–18	2016 Japan-America Frontiers of Engineering Beckman Center, Irvine, California

All meetings are held in National Academies facilities in Washington, DC, unless otherwise noted.

Most of humankind's biggest endeavors are mega-engineering projects that provide solutions spanning disciplines, geographies, and cultural boundaries.

The National Academy of Engineering has launched its third

Engineering for You Video Contest (E4U3): MEGA ENGINEERING

We're looking for short videos (1-2 minutes) that:

1. Introduce a particular mega-engineering project,
2. Highlight its importance/contribution to people and society, and
3. Suggest contributions to its development.

The Grand Prize of $25,000 will go to the most inspiring 1- to 2-minute video.

The submission deadline is May 31, 2016 at 12:00 PM. Anyone can enter, so grab your phone, camera, or tablet and start filming!

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HOW YOU CAN BENEFIT

IRA Rollover

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Congress has extended the **IRA charitable rollover** and made it permanent. With the IRA charitable rollover, you can make a gift from your IRA to help support the work of the NAE and benefit. Gifts made from your IRA (up to $100,000 per year) are not reportable as taxable income. They also qualify for your required minimum distribution (RMD), which can lower your income and taxes.

To learn more about the benefits of making an IRA charitable rollover gift, please contact Jamie Killorin at JKillorin@nae.edu or 202.334.3833.

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