The Mechanics of Traumatic Brain Injury: A Review of What We Know and What We Need to Know for Reducing Its Societal Burden

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Traumatic brain injury (TBI) is a significant public health problem, on pace to become the third leading cause of death worldwide by 2020. Moreover, emerging evidence linking repeated mild traumatic brain injury to long-term neurodegenerative disorders points out that TBI can be both an acute disorder and a chronic disease. We are at an important transition point in our understanding of TBI, as past work has generated significant advances in better protecting us against some forms of moderate and severe TBI. However, we still lack a clear understanding of how to study milder forms of injury, such as concussion, or new forms of TBI that can occur from primary blast loading. In this review, we highlight the major advances made in understanding the biomechanical basis of TBI. We point out opportunities to generate significant new advances in our understanding of TBI biomechanics, especially as it appears across the molecular, cellular, and whole organ scale. [DOI: 10.1115/1.4026364]

Introduction

Traumatic brain injury (TBI) presents a significant public challenge in today's society. Approximately 1.7×10^6 people in the U.S. each year suffer some form of TBI that requires at least a visit to the hospital [1]. The relative fraction of severe TBI patients—estimated as 3% of the total annual cases—requires the most intensive medical care and is often complicated by injuries to other body regions. Moderate brain injury represents 22% of the annual incidence and commonly leaves patients with persistent deficits that they carry for the remainder of life. Mild TBI has the highest incidence rate in the population (75% of total injuries) and may be even higher than reported in epidemiological studies, owing to substantial underreporting in young populations, athletes, and members of the military [2,3]. In aggregate, the socioeconomic toll is significant—TBI remains the most prevalent cause of death in adults aged less than 45 years and is also the highest cause of long-term disability [4,5]. As the population ages, we are also seeing the relative incidence rise in the elderly population, where it is now only second to cancer as a cause of death in people aged 65 and over [4]. With the growing awareness of TBI in both the civilian and military population, TBI is no longer a silent epidemic.

With the longstanding knowledge of neurodegenerative changes in boxers now expanding to include repeated TBI in other professional athletes and soldiers [6–8], it is also clear that TBI is both an acute disorder and, for some patients, a chronic neurological disease. This awareness, however, also exposes the need for far more clarification on many issues in the scientific literature because it brings to light many questions that center on defining the exposure for possible at-risk populations that include civilians (e.g., athletes in contact sports) and members of the military. As we answer these questions, we will have the opportunity to use some of the same tools we describe below to tackle the looming challenge of mitigating the chronic effects of trauma to the brain.

The focus of this review is to provide a summary of past efforts to understand key points in the TBI neurophysiological injury cascades, which include:

- defining the environments in which these injuries occur
- understanding how mechanical loads are transferred to the brain structures during the loading conditions that occur in these environments
- using the mechanical, physiological, and pathophysiological response of the brain—at multiple length scales—to identify the critical mechanisms for damage, including necessary interspecies scaling between animal models and humans
- identifying the key acute mechanisms of injury that cause the most significant functional impairments, and testing if these primary mechanisms contribute to the long-term changes associated with injury

We present both past and ongoing work addressing these central questions. We also identify several areas that need more study. Several excellent reviews provide some historical context and additional information on efforts across the length scale; we refer the reader to these articles for further detail [9–14]. We structure the review by (a) reviewing the existing knowledge to define when traumatic brain injuries occur in the civilian and military environments and (b) the separate work identifying how immediate mechanism(s) of injury mediate acute impairments after injury.

An Integrated, Multiscale Approach for Understanding Traumatic Injury to the Brain

Drawing on several decades of research with applications primarily in producing protective headgear, developing head protection standards, and designing of safety systems in motor vehicles, there is a considerable literature that has defined the scenarios causing TBI. The work spans multiple scales and forms a natural research cycle (Fig. 1)—from population-based surveys

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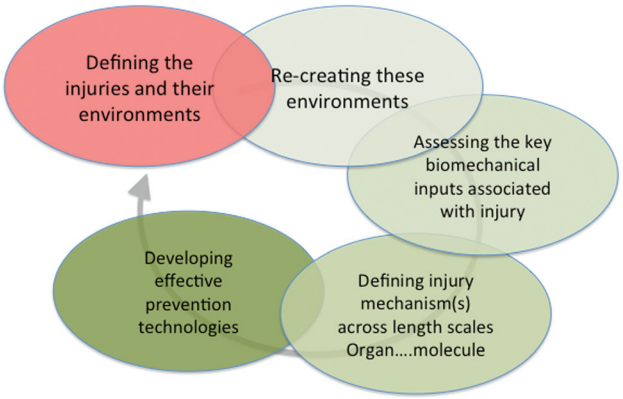

Fig. 1 The research cycle of reducing the societal burden of traumatic brain injury. Epidemiological evidence collected from clinical studies, and analysis of motor vehicles crashes, forms part of the first tier for defining where the most significant brain injuries occur and if these injuries change over time (red). The work transitions to the research laboratory (green) for defining how these injuries occur, establishing key relationships between the physical inputs in these environments and their resulting injuries. The inevitable translation of this new knowledge into the next generation of protection technologies completes the cycle and also triggers the next research cycle for focusing efforts on the most significant injuries in the population. One broad research cycle has already occurred for moderate and severe brain injuries, resulting in advances in helmet protection technologies and passive safety systems. Emerging efforts have now shifted to include more focus on mild TBI, which occurs across both the civilian and military population.

identifying significant injuries [15–17] down to tissue/single cell-based work for detecting key molecular signatures of the injury [18–20]. The work begins with the clinical environment to define injury incidence, transitions to the laboratory environment to replicate and study both injury mechanisms and tolerance, and proceeds to the translational environment for developing effective countermeasures to reduce or eliminate injury incidence. A central component in this past work is using experimental and analytical tools to draw relationships between the physical input (acceleration, impact force, duration, etc.), the resulting mechanical response of the brain/skull, and to integrate thresholds for damage to the brain and its coverings to identify the mechanical loading scenarios most often associated with injury. Ongoing work to study blast-induced traumatic brain injury is following a similar trajectory, although the tolerance criteria for blast loading are in the early developmental stages [21–23]. A defining characteristic of this research cycle is to address the most significant injuries occurring in the population, to implement new technologies for reducing the incidence of these injuries, and generate new surveys of the population for focusing future research efforts.

In general, the primary mechanical response of the brain to either impact, impulsive, or blast loading is driven on the macroscale by the brain/skull geometry, the partitioning of the brain within the skull, and the material properties of the cranial tissues. Although general principles of the brain response to mechanical loading can be developed, an important caveat is that every traumatic brain injury occurs under unique mechanical loading conditions. Perhaps one of the greatest challenges is to consider how the unique mechanical inputs associated with each injury can be coalesced into a single, universal approach for determining when injuries occur in the population.

To date, the most complete approach for predicting the incidence of TBI in humans requires several key steps: (1) defining the external mechanical loads experienced by the head during situations that cause injury, (2) using models of the brain (either physical, analytical, or computational) to estimate how these external mechanical loads transfer to mechanical conditions (e.g., stress, strain, etc.) in the brain at the tissue and cellular scale, and (3) using tissue and cellular tolerance criteria to determine the regions of the brain that will be injured or impaired as a result of the external applied loading. In the remainder of this paper, we will review the work in support of this approach and discuss emerging areas of research that will significantly extend the ability to predict TBI incidence in the future.

Characterizing the Causal Environments of TBI. Historically, motor vehicle crashes were a primary environmental focus for TBIs because they consistently ranked as the most frequent cause of TBI-related deaths in civilians [24,25]. However, a broader view of TBI across the severity spectrum (Fig. 2(*a*)) shows that falls are the leading cause of emergency department visits and hospitalization stays related to TBI; the second leading cause is where the individual is struck by or strikes another object [1]. For visits that require either hospitalization or only an emergency department visit, motor vehicles are the third leading cause of injury [1,2]). The loading scenarios for head impacts occurring in the automotive environment are well developed and embedded into vehicle safety testing protocols used in the U.S. and elsewhere [26]. These testing procedures specify collision speeds and impact directions that are linked to common accident scenarios associated with death and disability in motor vehicle crashes. As the focus of the field shifts to more moderate and mild TBIs, we must continue to expand our test conditions and include more scenarios associated with the injuries that occur in nonvehicular environments (Fig. 2(*b*)) [27]. In particular, concussions in sports, including youth, need better biomechanical testing scenarios.

Recent evidence of a large risk of mild/moderate TBI in military scenarios associated with blasts (bTBI; Fig. 2(*a*)) [22,28,29] (i.e., blast-induced traumatic brain injury (bTBI)) lacks a comparable level of epidemiological detail. For example, recent work shows many of the scenarios causing TBI in the military are from the motor vehicle crashes, falls, and the head striking another object, similar to the civilian population (e.g., Ref. [30].). Of course, the initiating event for injury is different from the civilian population: ~67% of the TBI injuries requiring hospitalization in U.S. military operations in Iraq and Afghanistan were from explosions (Fig. 2(*b*)), with direct blunt trauma contributing ~19% and penetrating injuries contributing ~11% of the injuries. Even within the injuries attributable to explosions, many are linked with low rate blunt trauma following the blast event [31].

Although this may initially downplay the importance of primary blast in military TBI, there is other evidence showing a substantial number of injuries occur with direct blast exposure, including primary blast exposure of dismounted service members (Fig. 2(*b*)) [31,32]. Recent evidence suggests that civilians exposed to large blasts also have the potential for sustaining bTBI without pulmonary injury [22,33]. Together, these reports demonstrate that our perspective on the mechanisms of TBI in the military population is still evolving. Some confusion on the relative role of blast-induced traumatic brain injury may arise because the classification system for bTBI was designed to encompass any physical phenomena that could cause brain injury [34]. Primary blast injury, defined as the damage occurring as the blast wave travels through the brain, is unique to bTBI. However, the secondary and tertiary forms of bTBI—in which the injury is caused by direct laceration of the brain from fragments or shrapnel (secondary) or the head moves suddenly and may strike another object (tertiary)—shares a common mechanistic base with injuries observed in the civilian population. Therefore, mechanisms of blast-induced TBI may have a mixture of mechanisms from primary, secondary, and tertiary blast injury. Unknown, though, is how effects of the primary blast wave interact with the injury mechanisms caused by the secondary and tertiary phases.

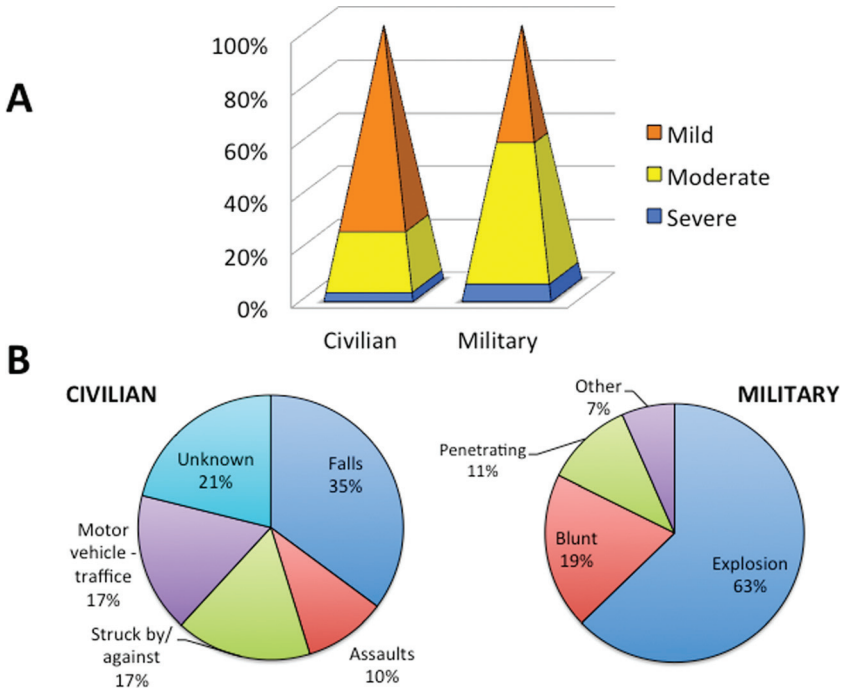

Fig. 2 (*a*) The relative incidence of TBI in the civilian and military population, and their causes. Excluding penetrating TBI and unclassified injuries, the relative incidence rates for the military and civilian population appear distinct. However, the possible underreporting of mild TBI in the military may alter the relative incidence rates significantly. (*b*) Within each population, the causes of TBI span a broad range. Primary blast TBI is unique to the military environment.

Defining the Injuries in the Clinical Context. From a clinical standpoint, brain injuries are often categorized as either focal or diffuse [35]. These general descriptions apply for both the civilian and military environment. Focal injuries are readily visible using standard imaging techniques (CT; MR). Primary vascular injuries that cause bleeding within the brain (intracerebral hematomas; tissue tears), on the surface of the brain (acute subdural hematoma; subarachnoid hemorrhage; extradural hematoma), or in the cortical gray matter (cerebral contusion) are common examples of focal brain injuries that appear in the severely and moderately head-injured population. With the exception of subarachnoid hemorrhage, these focal injuries do not appear in the mild TBI population. Moreover, the number of mild TBI cases with subarachnoid hemorrhage is rare. Therefore, diffuse injuries are considered the predominant category of injury in mild TBI.

Diffuse brain injuries are, as the name implies, not localized to one area of the brain but are more distributed throughout the brain. Diffuse brain swelling is one form of injury that can appear over time following the injury and is not often the focus of studies for predicting how the mechanical forces can cause subsequent injury throughout the brain. An ongoing discussion in the bTBI literature suggests that diffuse brain swelling may be a more common component of the injury pattern after bTBI [36,37].

The most common diffuse brain injury receiving attention for TBI biomechanics is diffuse axonal injury (DAI), which is the appearance of axonal injury at the microscopic scale in selected regions of the brain [38]. The mechanisms and progressive changes to the cytoskeleton, organelles and membrane within the axonal compartment is an ongoing area of study with DAI, as this would point towards possible therapeutic intervention [39]. Strictly defined as an entity that appears in humans, DAI is often the subject of study in mild traumatic brain injury (mTBI) patients because of the widespread disruption of brain networks that can appear in these patients without any other sign of brain damage. The continuum of DAI in humans is well described, and the general conditions that cause DAI in the human are providing a template for studying these same types of injures in animal models. There is some evidence of diffuse injury to axons in primary blast TBI models [21,22,40,41], but a complete description of DAI in human primary blast TBI is not yet available. The closest demonstration of DAI in blast TBI shows alterations in directional diffusion within white matter measured by diffusion tensor imaging [42], changes that are presumed to reflect areas of microscopic axonal injury based on earlier work in animals [43,44]. However, the distribution of DAI patterns in humans following blast exposure, similar to the definition of DAI in human patients after falls, assaults, and motor vehicle accidents [45], would help shape future biomechanical studies to understand primary blast TBI more completely.

Emerging Key Issues. With the dramatic change in the passive safety technologies for motor vehicles, there is a shift in the distribution of the types of specific brain injuries observed in the moderate and severely brain injured population [46,47]. The most extensive clinical study that detailed the distribution of severe head injuries is over three decades old [15], and an updated set of data would point toward specific populations that are potentially at risk for different types of brain injuries, and also different scenarios leading to these injuries. Perhaps most significantly, the distribution of these injuries in the military population is extremely vital as it can shape priorities for the next decade, yet this distribution is not completely defined. Moreover, there is a well-recognized paucity of assessment techniques for mild TBI that achieve both good sensitivity and specificity over the time course of TBI. Without these specific and sensitive measures to record the accurate incidence of mild TBI, the overall fraction of mild, moderate, and severe TBI in either the civilian or military population remains to be defined.

For military injuries associated with blast, there are potentially large numbers of exposed personnel, especially for mild bTBI. It is unclear for mild severities how to differentiate between bTBI

and common, potentially comorbid, syndromes such as posttraumatic stress syndrome (PTSD) with similar symptomology [48].

Estimating the Primary Mechanical Response: Modeling the Structure. Knowing the accurate size and shape of the brain, the brain deformation, and the brain movement relative to the skull during an exposure is a critical factor in developing an ability to accurately predict when injuries will occur. The human brain varies in size across the population, across age, and across gender. In particular, the brain size decreases over the latter part of the lifespan and, therefore, the subdural space may increase to increase the risk of TBI with age [49]. The variation in size and shape alone means there is a broad range in the primary brain mechanical response to blunt, acceleration-based, or blast loading. Although there is a well-developed anatomical description of the human brain, less clear is how these anatomical regions vary among individuals. Recently, magnetic resonance imaging (MRI) technologies make it possible to explore the variation in size, shape, and organization of the brain across any desired population, especially using imaging techniques without ionizing radiation (i.e., MRI). Alternatively, existing public data sets[2] provide high-resolution images that can be used for any subsequent biomechanical examination.

Perhaps the most important new element to consider in the brain structure is its organization across regions, i.e., the connectome. Imaging technologies to examine the direction of white matter tracts, in combination with techniques to measure local blood flow changes in the brain, provides a way to connect brain regions and assess how the brain connection map changes following TBI [50]. Public data sets of the human connectome are available[3]. This technology presents interesting opportunities for understanding the biomechanics of TBI, as it could provide insight into the regions of the brain damaged in mild TBI patients. Not only will we need to consider the distribution of stress and strain throughout the brain during an impact/blast exposure, we will also need to predict if these patterns of acute changes in the brain may be influenced greatly by the initial connection map in the brain at the moment of injury [50]. Therefore, understanding the evolving relationship between functional networks and structure is critical to making progress in understanding neurotrauma.

The physical properties of the brain tissue within the cranial vault are a critical determinant of how the brain moves and deforms during impact. Some physical properties are either well characterized and do not appear to vary across the population [51] or they likely do not contribute to the motion of the brain during blast/acceleration/impact conditions. The most critical factors contributing to the mechanical response are the mechanical properties of skull, brain parenchyma, brain coverings, and the supporting vessels. Estimates of the scalp properties stem back several decades and include estimates for the failure limits during impact [52]. The mechanical impedance of the scalp to an incoming blast wave, though, is not defined. Similarly, the mechanical properties of dura are also known [53–57] but the dynamic properties are not well described, especially for high rate loading. Although there is some discussion on the relative importance of the cerebrovascular network providing mechanical integrity to the brain [58], only the mechanical properties and failure limits of the parasagittal bridging veins are known [58–63].

Brain tissue, by far, is the most extensively characterized of these tissues, but unfortunately has large unresolved differences among reported values (overview of the range in material properties shown in Fig. 3). Early work on brain tissue stiffness showed that it was primarily elastic and nearly incompressible under cyclic, dilatational loading up to 100 kHz. Although initial estimates of shear properties revealed a moderately compliant, viscoelastic material with a complex modulus of ~20 kPa at loading

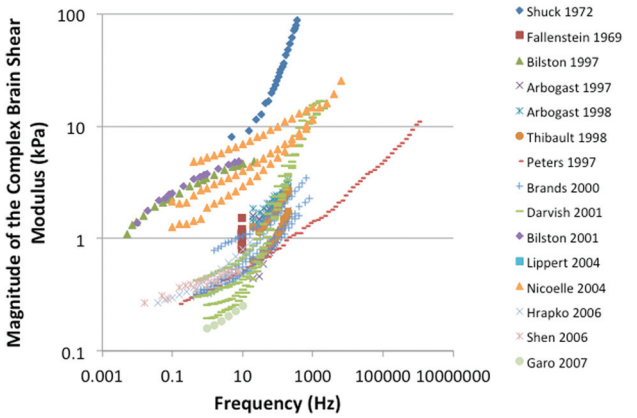

Fig. 3 Large variance in reported white matter and brain material properties by study. Early work estimated both bulk and shear modulus. In the past two decades, work has shown that brain is one of the softest biological tissues, more than ten times more compliant than the earliest measurements.

frequencies up to 120 Hz [64,65], these studies are now replaced with a larger complement of studies that demonstrates brain is one of the softest biological solid tissues measured (complex modulus ~.3–2 kPa), can be nonlinear viscoelastic, and varies across species (recent reviews: [66,67]). A remarkable characteristic is that the brain material softens at finite strains and that this softening response is repeatable across many consecutive loading cycles. Less clear, though, are the properties of brain, including the criteria for functional failure of brain tissue, at the much higher strain rates associated with blast loading [68,69]. Measures of bulk elastic properties at ultrasonic frequencies produce estimates that are nearly 1000 x stiffer than shear properties at much lower loading frequencies, and the stiffness of the brain at these loading rates is under ongoing examination [70]. Where possible, direct measures of brain material properties in vivo are complementing past studies. For example, recent results using brain MR elastography provides estimates of the changes that occur in vivo and are in the range of properties derived from previous in vivo and in situ measurements [11,71–75].

In selected studies, the regional and local anisotropic variation in brain material properties was examined [76–81]. At small strains, the relative stiffness of highly oriented brain stem samples showed modest anisotropy [81]. Gray matter properties show less directional dependence but more heterogeneity than previously appreciated, even within anatomical structures with several fold differences at large strains [82]. Moreover, white matter and gray matter show some significant differences in their relative shear properties, although these changes are within twofold to threefold. The regional properties for blast loading conditions are virtually absent from the literature, although it remains an active area of study. In work motivated by blast-TBI, a key concern is how to measure these material properties under high strain rate conditions. Hopkinson bar-based methods are now scaled to examine shear properties at very high rates, but the soft nature of brain tissue makes this a very challenging set of experiments [83–85]. Though values are reported at high strain levels (to 50% engineering strain, an overwhelmingly destructive loading condition), the experiments lack sufficient resolution to estimate the response at more realistic strain levels associated with primary blast injury (~1% strain).

The development of macroscopic material properties, combined with recent advances in computer modeling capabilities and a desire to know which components of the brain are injured in response to a macroscopic loading conditions, now provide an opportunity to develop more precise material models of the brain that reflect both the underlying cellular structure of the material and the unique macroscopic material behavior. Anatomical descriptions of

[2]Allen Brain Atlas: http://www.brain-map.org/: Visible Human Project: http://www.nlm.nih.gov/research/visible/

[3]http://humanconnectome.org

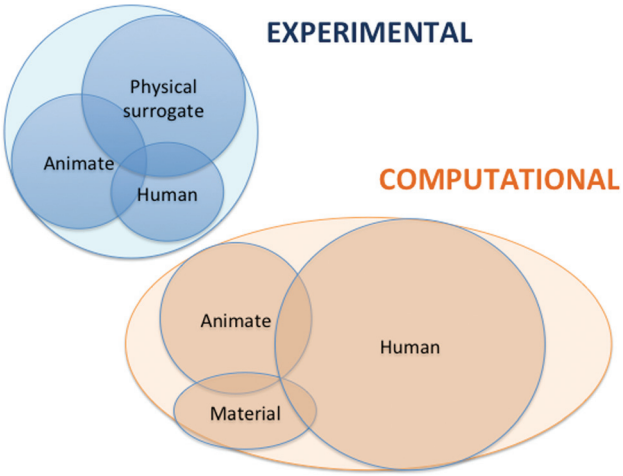

Fig. 4 Multimodal modeling approaches for defining the structural response of the brain to applied mechanical loading. Historically, experimental approaches led to insight into the most important types of mechanical loading associated with severe brain injuries. These experimental approaches span both human and animate models and use physical surrogates to complement either scale. The most significant development in the past decade is the growth of computational approaches to examine the biomechanics of TBI in both experimental models and humans. However, the need to validate these models for numerical issues (e.g., mesh convergence, mesh quality) as well as biofidelic output is even higher given their increased complexity and proliferation.

brain tissue are easily obtained using standard histopathological techniques. In some cases, existing material models gleaned from the composite materials community can help assist in interpreting anisotropic material behavior [79,80]. Some models of the white matter already suggest how different cell types may couple to each other and propose how structural elements of the tissue interact in complex manner to expose a subpopulation of axons to high mechanical loading [86–90]. Continuum-based nonlinear material descriptions are also available to correlate with these structurally-based material models [87,89]. With their continuum formulation, the integration of these models into existing finite element software packages is possible. Currently, though, there are no efforts to model the complex mixture of cell types found in other areas of the brain (e.g., hippocampus) and the relative change in the macroscopic/microscopic transformation that underlies any injury patterns that occur in these areas. A recent set of measurements show that material properties of the hippocampus in situ differ significantly, yet the cellular mechanism(s) for this difference is not clear [76–78]. Potential reasons for this difference include a change in the relative balance of excitatory and inhibitory neurons, each of which possess a different morphology that could contribute to a difference in the kinematics of deformation at the cellular level. Additionally, this difference may also reflect a change in the neuron/glial ratio among the regions, given the material properties of these two cell types are distinct. An inability to track different cell types in living tissue over the microseconds to milliseconds time scale remains a major technical impediment to validating any structure-based model of the brain.

Emerging Key Issues. In comparison to our current knowledge of the geometry and the multiscale structure of the brain, the material properties are better known but vary in their magnitude over a broad range (Fig. 4). The consistent use of these material property measures, and not stiffer values from very early studies, remains problematic. In addition, the specific material properties in some, but not all, brain regions are known and the expansion of this data set to include more brain regions and more anisotropic properties would significantly help in the predictive ability of models. Extending these properties to blast loading conditions must be done, but we already have information that can be applied to both the secondary and tertiary forms of bTBI. The bulk dilatational response as the primary blast wave transmits through the tissue is key, but may already be described with early work in the field [52]. The associated deviatoric response under the high loading rates associated with blast, however, is not fully described. More insightful findings could come from studying the underlying role of the vasculature in contributing towards the macroscopic material properties of the brain conditions across the loading spectrum; early works suggest intriguing changes that could map the macroscopic response to the underlying structural failure of the vascular elements [58]. Additionally, there is evidence that material properties of individual cell types within the brain are distinct [91–96], and these variations may contribute greatly to our understanding of cell types within specific brain regions that would be mechanically vulnerable. Extending the structural descriptions of brain tissue to reflect the transmission of the macroscopic mechanical input during blast loading may provide unique insights into how the extremely rapid events during blast extend to the cellular scale. Moreover, the heterogeneity of the macroscopic to microscopic transformation will inevitably extend to the subcellular scale—e.g., do synapses from the same neuron (or same dendrite from within a neuron) show the same local deformation that is applied macroscopically? Undoubtedly changes at the synaptic scale will be important in decoding how the network function can be compromised after injury.

Estimating the Primary Mechanical Response: Role of Physical Models, Human Surrogate Models, and Computational Models. With a primary goal of linking an external mechanical input to injury patterns within the brain, investigators have commonly used tools from both experimental and computational mechanics (Fig. 4). With such a complex geometry, though, it is not surprising that the earliest efforts to achieve this overall goal were experimentally based. Seminal studies by Holbourn demonstrated the value of using simple photoelastic materials to illuminate areas of a brain surrogate that experience high shear strains during rapid rotational motions [97]. Holbourn's models highlighted that cortical regions were most vulnerable to injury when the head was rapidly rotated about the sagittal plane (anterior-posterior head motion), while structures deeper within with the brain were more vulnerable with rotations along the coronal plane. Subsequent studies using similar technologies highlighted how high stresses can also appear at the craniocervical junction [98]. Direct visualization of grid patterns or embedded markers within a transparent silicone gel also provided direct evidence for the unique patterns of deformations that occur with accelerations imposed in different directions and the influence that different skull/gel boundary conditions and ventricular structures have on intracranial strains, showing that the ventricles can redistribute and, in some regions, reduce the strains appearing within the brain after impact [99–102]. In some instances, these models have been used to assess the effectiveness of different animal models to recreate the deformation patterns that appear during impact and have led to a redesign of animal models to produce deformation patterns that more closely resemble the strains within the hemispheres during injury [103–105]. These same techniques are now extended to blast loading conditions [102–109], where the efforts will yield significant information on the manner that external blast waves transfer to the brain simulant, how these pressures are distributed throughout the surrogate, and how these pressures dissipate over time. Although providing a direct window into the possible response of the brain to any external mechanical loading condition, it is worth noting that the highly elastic material properties of brain tissue surrogates will need to be considered in extending or interpreting these results for the viscoelastic, nonlinear brain tissue.

Some of the disadvantages associated with physical models of the brain within the skull are mitigated with human surrogate

tests. By using cadaveric material with minimal material degradation, neutrally buoyant markers placed within the brain, and high speed X-ray imaging technologies, one can track motions at any point within the brain during an impact event [110]. Depending on the location of the markers within the brain, these data can provide direct measures of the relative motion between the cortical surface and the skull, the relative motion within the deep white matter, and the differential motion across the hemispheres [110–116]. Key results from these studies include the demonstration that the cortical surface of the brain can move relative to the inner skull surface, thereby creating conditions that can cause bridging vein rupture. Perhaps most significantly, Hardy and colleagues provided a well-characterized data set of neutrally buoyant markers in the brain that illustrate how many points in the brain move simultaneously during impact. In blast loading, these same approaches can provide estimates of how the blast wave transmits throughout the parenchyma. These data are critical in bridging the physical models with more realistic in situ measurements and linking computational models with the in vivo environment.

To date, the only direct visualization of living brain motion in humans has been accomplished with cyclical, noninjury motions. Using a well-developed MR technology to place magnetic "lines" within an anatomic plane, it is striking to see how much the brain can move under a simple, repeated rotation in the horizontal plane [117,118]. Estimates of the intracranial strains that appear during physiological head rotations in volunteers show the shear strains can reach 0.05 mm/mm, which is near the thresholds for axonal damage but at much lower deformation rates. Until this work appeared, it was not clear if there were any methods to cross-correlate the experimental database on tolerance criteria for the tissue with deformations that occur in vivo. These data provide yet more validation data for finite element models of the brain within the skull, especially since it is the only data available for the in vivo brain response. Although these data are not for injurious situations, they will also provide an opportunity to match skull/brain boundary conditions and assess the need for anatomic detail and proper material descriptions for the brain.

The experimental work across physical models, human surrogates, and human volunteers forms an extensive database of information for developing computational models of the brain response to impact or blast exposure. An excellent set of reviews details the early development of these models, which focused on modeling impact testing in human surrogates and developing estimates of tolerance under simple impact conditions [119,120]. These models quickly expanded into efforts for modeling the brain mechanical response under more complex conditions, and the need to accurately model the structure, material properties, and developing new material formulations for the soft brain material properties became evident. The extensive array of computational models developed in the past decade for the study of injury in the human brain is nothing short of remarkable [109,113,121–158].

Existing models can be roughly grouped into human and nonhuman species. Human-based models contain different level of complexity, depending on their purpose. A significant effort by the National Highway Traffic Safety Administration to build a finite element model of the human brain/skull structure aims to compute a solution to any impact condition within hours on a desktop computer [159]. For this reason, the geometry is less refined than other existing models. The reduction in complexity suits the long-term goal of the model, which is to provide a tool for evaluating brain injury specific risk in motor vehicle collisions and, ultimately, inclusion of this tool in assessing passenger car safety [157]. In comparison, models that use high resolution images and details of the anatomy require more solution time but offer more ability to interpret the predicted response and match the multiscale aspects of TBI. For example, accounting for the highly complex cortical gray matter and the underlying white matter structure yields insight into how the stress patterns can match the exact patterns of injury observed in animal models and patients [158,160]. In general, the material properties used in these human-based models have migrated over the past decade into estimates more consistent with the soft material characteristics measured experimentally. A continuing effort to use accurate material properties in these models is challenging, as the resulting deformations can be large and the algorithms for computing the forces at interfaces must be monitored carefully. Moreover, it is well known that the soft material properties of the brain, when coupled with its nearly incompressible dilatational behavior, present significant computational challenges. Unanticipated mesh warping must be carefully considered to avoid error propagation in these models.

Investigators continue to use experimental data to validate the models, complementing early data showing the pressures during blunt impact with more recent data showing motions within the brain during impact. Currently, publicly available models show an increasing sophistication in their anatomical detail and their correlation with available validation data. In the past five years, these same models were extended to study blast exposure [105,109,124,128,131,134–136,138–140,143,144,157,161–164]. In many cases, though, the absence of validation data remains a key concern and must be addressed with each model before the models can be meaningfully used to correlate blast exposure with specific injury risk.

Given its importance as a linking process to accurately predict the incidence of TBI, the *process* of validation needs better definition. Although the intent of validation is centered on the goal of building virtual, computationally based models that accurately describe the human mechanical response to impact, the specific levels of validation for a model should always be considered in its use for predicting injury. For example, finite element models developed over two decades ago often used impact response data from human cadaveric testing conducted by Nahum and colleagues to validate the model. This validation process is best suited to evaluate the dilatational response of the finite element model and is, therefore, a key step in evaluating finite element models that use pressure as a metric for predicting injury. One could view this as an initial validation level in the model development process. However, injury mechanisms caused by deformation, and not pressure, would be more difficult to study with these models validated at this level because the deformation response can vary widely over a range of deviatoric material properties that would not significantly influence the pressure distribution in the brain during impact. The data on the displacements of points within the brain during impact or, alternatively, the strains within the living human brain during repeated, slower rotations form the basis for a second validation level that concentrates on matching the motion of the brain during impact. Given the relationship between the displacement and resulting deformations in the brain, models that achieve this validation level would improve the confidence that the model could be used to study injuries in the brain caused by different deformation mechanisms. However, there is no standardized performance specification for a model matching the data in this second validation level. Currently, the motion of several points within the brain and the comparison to model predictions leads to a more generalized statement on the performance of the model instead of a specific performance parameter. The clear addition of more experimental data on the movement of points within the brain under different impact conditions, directions, and with different-sized brains would significantly improve the process of validation at this second level. A third validation level to consider in the future would match patterns of damage observed in human surrogate studies with predictions of damage from the computational model. This validation level would test the accuracy of applying a model to predicting some injuries appearing in the moderate and severely head injured population. This validation level, much like the first two levels, would need a standardized scoring metric to assess the performance of the model. Similar to how performance test criteria for protective headgear resulted in a continuing improvement in performance

over decades of development, including this validation level would eventually ensure the improving correlation between computational models and the injury patterns they are designed to predict.

For nonhuman models, much of the work was an examination of existing experimental models of TBI. Species include rodents [109,128,135,138,140,143,144,161–167], pigs [168–173], and sheep [174–176]. These experimental models offered a measure that human physical models and human surrogate tests often could not provide—an estimate of the injuries that occurred throughout the brain as a result of the mechanical loading. Although some vascular injuries can be captured in human surrogate tests, much of the underlying pathobiology of TBI at the microscopic scale must be examined directly in the living brain. Similar to the human models, an extensive series of models appeared in the past decade to provide insight into the relative risk of injury to the living brain. Spatial descriptions of material properties may be necessary to explain the relative injury risk in the hippocampus that occurs commonly in rodent models of TBI [76,77,82]. Moreover, the distribution of stress and deformation is key for predicting areas of blood-brain barrier compromise, an injury often overlooked in biomechanical investigations [177]. These models also provide to opportunity to design new features into experimental models of TBI—e.g., the shape of an impounder tip or the speed of impact in the well described cortical impact model of TBI can significant change the cortical lesion volume in this TBI model [177]. These models offer a direct translational path for studying blast exposure, and early results indicate that these models are transferrable when attention to details such as mesh size and material properties are made [22,164]. However, a systematic correlation of model results with the histopathology of injury is warranted to assess the efficacy of these models. Perhaps most importantly, these models lack the extensive model validation data sets that exist for the impact/acceleration-based models.

Linking the Physical Response to the Biological Response: The Eventual Definition of Human Tolerance. With efforts to identify the most common environments that cause TBI, the relevant mechanical loading scenarios that occur in these environments, and the subsequent physical response of the brain during these loading scenarios, one is faced with the next logical question—when will these conditions cause injury to the brain? And, relatedly, where will the injury occur? In some instances, the direct correlation between the mechanical input and the resulting pathobiological response will be made possible through a close comparison of the computational/physical model and the histopathological description of the injury pattern. However, the direct comparisons between model and injury patterns will provide little insight into the functional consequences of the injury patterns presented in any TBI. For example, although one may correlate strains at the tissue level to different levels of axonal damage at the microscopic level [178–182], an unanswered question is the threshold of damage needed to cause impairment of electrophysiological activity in the cell body, in the pathways connecting these circuits, or any alterations in circuit plasticity that would be the basis for impairments in learning and memory. Moreover, these correlations do not provide insight into the direct mechanisms of injury, an element that is critical for successful treatment.

Simplifying the Physical Inputs of the Injury for in Vitro Study or "Reduced" in Vivo Models to Determine Injury Mechanisms. With the clear need for coupling mechanical input into functional consequences, work in the past decade has responded and provided more direct insight into the mechanisms that cause the resulting functional changes. Motivated by the early work using physical models and finite element simulations, several investigators developed microscope-based systems to study directly the relationship between the mechanical deformation and resultant biochemical signaling [183–189]. As a result, we now know that both neural and glial cells respond to mechanical deformation, that synaptically localized receptors are uniquely mechanosensitive, show immediate alterations in their physiological properties, and changes occur across both excitatory and inhibitory neurons [190–195]. At higher loading conditions, an additional mechanism of injury appears, which is the nonspecific, transient opening of pores within the membrane [183,186,196–202] after cellular deformation. In contrast to our knowledge on the effects of mechanical deformation on neural and glial cells of the central nervous system (CNS), the role of dynamic pressures in affecting cellular function is not well described. In nearly all cases of deformation-based mechanisms, the in vivo evidence matches the in vitro observations. New models to mimic only the blast wave transmission in cell cultures open up an entirely new opportunity for discovery in the blast loading regime in which several potential mechanisms of injury can be tested precisely with in vitro analogues [14,23,203–211].

Perhaps the most informative and relevant in vitro model for directly coupling mechanical inputs into brain tolerance and injury mechanisms will be the organotypic, in vitro models or the reduced in vivo models [18,23,212–219]. Organotypic brain cultures are sections of the brain isolated from the postnatal rodent brain and cultured over days to weeks. With the isolation from a living brain and without dissociation of the tissue common to other culturing methods, the in vivo architecture is well preserved in this model. Moreover, the combination of cell types within the brain is also maintained. Although organotypic cultures can be generated from different regions of the brain (cortex, thalamus, hippocampus, cerebellum), the most complete data for tolerance exists for the cortex and hippocampus [173,207,209,213,214,217]. Because these cultures are not vascularized, however, they do not provide an estimate of the selective change in the tolerance in cases where blood flow is compromised (ischemia; relative ischemia) or vascular damage occurs (blood-brain barrier breakdown; vasospasm). The use of in vitro models to study the effects of blast exposure is in its early stages, and estimates for blood-brain barrier opening, alterations in glial signaling, and the recovery of function are starting to appear in the literature [23,203]. A key issue that will need more clarification is the correlation of these loading conditions used in vitro to the loading environment in situ during blast.

Reduced in vivo models are the next most informative method for establishing links between input and resulting functional impairment. The optic nerve is a highly aligned cranial nerve that is part of the CNS, is accessible and can be injured directly to estimate thresholds for tissue tolerance [181,182]. Similarly, dorsal nerve roots are also accessible and provide a method to measure directly the electrophysiolgical impairment after tensile stretch, and data show that injury is linked to both the strain and strain rate applied to the nerve roots [178–180].

Interspecies scaling to translate experimental model results to the human from in vitro and in vivo testing plays a role on both the macroscale and the microscale. Biomechanical scaling on the macroscale is well established (e.g., Ref. [220].), but it is unclear how brain scaling works on the microscale. Scaling principles for bTBI are in their infancy (e.g., Refs. [22,221].), but investigation is crucial to establish realistic exposures in models and scalable endpoints for correlation with human clinical outcomes.

Key Emerging Issues. A growing concentration of efforts are aimed towards understanding the tolerance of mild TBI, and these efforts are critically reliant on defining conditions that will cause some change in either the wiring of a neural network, a compromise in the network's mechanisms to adapt in response to an incoming signal (plasticity), and the ability of the network to shape or control activation patterns. Therefore, the mechanisms of injury over the mild spectrum will span the cellular level—e.g., the direct changes to the plasma membrane, channels, and receptors on the neuronal surface, the accompanying changes to surrounding glial cells and the vascular cells—and the network level

that includes both the neural circuit formed by neuronal ensembles within a brain region and the coordination of signaling among these brain regions. Based on current published work, the extension of these tolerance criteria and injury mechanisms in vitro to functional impairment is limited [218,219,222,223]. These predictions of network impairment will be facilitated with better descriptions of the material behavior that embed neuronal and glial connectivity and will also be very reliant upon measures of impairment made in experimental models of TBI. In this way, the prediction of function will be a significant and natural extension of ongoing activities in the field.

Scaling network results, especially functional microscale behavior from the models to humans, remains uncertain. Investigation of this unexplored territory may increase relevance of models and lead to insights into the interface of structure, network and functional outcome.

Estimating Human Tolerance Through the Playing Field. Rather than using a coordinated series of physical surrogates, computational simulations, and in vitro models of traumatic brain injury, a new concept has surfaced in the past decade that uses a profoundly different approach—using the sports playing field and other sources of exposure to TBI as a "passive" biomechanics laboratory where one collects data to eventually estimate the human tolerance to mild TBI. Rather than relying on approximations across several steps in the laboratory, accurate measures of individual exposure will yield a direct estimate of the human tolerance over time. In one approach, the effort is made possible by novel monitoring technologies that allow one to estimate the key mechanical exposures that an athlete experiences over a practice or game [224]. When a concussion occurs, the exposure that led directly to the concussion would be archived and a distribution of loading inputs would emerge over time to yield the aggregate human tolerance. The most widely used monitoring technology (head impact telemetry system, or HITS) allows investigators to record the estimated exposures in an American football game [225]. As of this writing, nearly 2×10^6 exposures have been recorded with this technology, and over 200 concussion events are contained in this data set [226–228]. New recording technologies are under active development, especially as the advantages of microelectronic fabrication technologies make these sensors smaller, less expensive, and potentially more widely available.

An alternative approach reconstructs the scenarios causing concussion, as captured on videotape, using anthropomorphic test dummies in a testing laboratory. Based on the pre- and postimpact positions of the striking and struck test dummies, the most likely loading conditions are estimated [149,152,229–231]. A comparison of the average peak accelerations associated with concussion in this data set, compared to the concussion data set collected with the helmet-based recording technologies, show reasonable agreement, especially given the uncertainties involved in both approaches.

A review of these approaches best puts into relief the challenges presented with the "human laboratory." At a broad level, neither approach is designed to measure the unique tolerance for each individual. Alternatively, measuring a range of conditions causing concussion will inevitably raise the question of whether we can conclusively assign a concussion risk function for an individual, based on data from a population. From a simple biomechanical viewpoint, normal variations in brain shape, material properties, and loading direction can each produce significant variations in the deformations at any point within the brain. With this variability, even in the absence of any biological variability, the corridor of conditions associated with concussion can be large. Even if this concussion risk curve were constrained to a single individual, the role that previous impacts occurring minutes, hours, or even days prior to a given impact has given rise to great speculation about the potential for repeated impacts leading to increased vulnerability. Recently, the uncertainty of the measurements from the helmet recording systems has shown to exceed earlier estimates, which would further contribute to the range of conditions recorded for concussions in the field [232,233].

Separate from developing human-based concussion thresholds, one may choose to use exposure measurements to take players out of a game or practice for medical evaluation or simple rest. Already, evidence shows that allowing players to self-report concussion leads to a significant underestimate of the actual concussions occurring in a game. Therefore, this monitoring system would provide a possible approach to better capture participants that should receive medical evaluation. Once again, though, the uncertainty of a unique concussion threshold and the potential uncertainty in the measurement accuracy could lead to both false positive and false negative events.

Is this key concept of the human laboratory useful for other injury situations, like blast? Technology is already developed for detecting threshold blast overpressures in the field [234–236]. Acting as a sensor for deciding if a soldier warrants medical evaluation, this application is not designed as a precise recording technology. Even if such precise monitoring for blast overpressure was available, though, one must also consider simultaneously recording key mechanical parameters that contribute to secondary and tertiary blast injury (e.g., linear and rotational acceleration) so that a recording of the complete blast exposure is recorded. Many of the same caveats applied to the use of helmet recording systems in sports would apply equally to the blast environment. Helmet-mounted systems present even more critical challenges for use in assessing exposure in the military environment. Blast waves are highly directional [22] and produce helmet motions with small peak displacements with very high accelerations ($>1000\,g$ or more in the helmet) [237,238] with much lower resultant accelerations of the head ($\sim$200–300 g). It is not clear that a helmet to head transfer function is even possible for omnidirectional blast exposure. Understanding blast biomechanics of neurotrauma is even more complicated because we are only beginning to understand how these mechanical input conditions contribute to the primary injury response.

Using These Efforts to Reduce the Societal Burden of TBI. With this collection of tools to examine how traumatic brain injury occurs in both the civilian and military environment, it is worth considering the broader impact of how new knowledge will eventually ease the burden of this disease on society. Some of the general benefits are clear, as a more detailed understanding of injury causality will inevitably lead to better protective headgear, automobiles designed to reduce TBI incidence, and even safer sporting environments. With the current projections of the economic consequences of traumatic brain injury and disability in the U.S., these benefits can become more specific. For example, even a 25% reduction in the incidence of TBI would translate to an economic savings of 25×10^9 U.S. dollars per year. The same reduction in incidence, if applied equally over the severity spectrum, would save 10,000 lives annually and result in a decrease of 250,000 emergency department visits each year. The number of lives saved would compare to almost halving the deaths due to prostate cancer in the U.S., or reducing the overall accident-related deaths by more than 10%.

Perhaps equally compelling is the potential long-term effects of providing a safer environment. The potential link between TBI and Alzheimer's disease (AD) provides a useful case study. If there is significant increase in the risk for developing AD in people with a history of TBI, we could see a meaningful decline in the incidence of AD over the ensuing decades with better protection against TBI. Developing a specific estimate of the benefit is difficult, as there are a range of studies that show a clear link between TBI and enhanced risk for AD, while others show no significant increase in the risk [239]. Clearly, the net benefit of better protection would be a product of the decreased incidence rate of TBI and the relative enhanced risk of developing AD in people

with a history of TBI. For example, assume 1/6 of a population has a history of head injury and that the relative increase in risk for developing AD in the TBI population is twice the risk for a population with no prior TBI. If protection technologies led to a 50% reduction in the incidence rate of TBI, then 1/12 of the future population would have a history of head injury and we would see an approximate 7% reduction in the incidence of AD in society. Although this may seem modest, the growing economic burden of Alzheimer's disease means this reduction in incidence would save $11–15 \times 10^9$ U.S. dollars per year in healthcare costs. As the exact relative risk for AD in patients with a history of TBI becomes more fully developed, this illustrative case study will be replaced with more specific estimates of how better protection technologies in the future will not only save lives but also contribute towards lowering the burden of diseases that could be triggered or accelerated with a history of TBI.

Areas of Opportunity in the Future. Although foundations of the mechanics of neurotrauma are over 70 years old, we still face significant challenges in merging the structural mechanical response and human pathophysiological response across the length scales. This gap is especially true for mild TBI, in part because we are just beginning to understand the mechanisms responsible for acute and long-term impairment for mild TBI. Using the outline presented in this review, we identify several critical unanswered questions that would accelerate our understanding in the next decade.

For defining the environments associated with TBI, we see a need to maintain a current working knowledge of the incidence rates for focal and diffuse brain injuries, and to critically define injury subgroups that are either declining in incidence or significantly increasing in incidence in specific environments. Achieving this goal would keep research foci relevant as the injurious environment changes either through new threats or the consequences of improved safety systems.

Similarly, we see a significant shortcoming in our clinicopathological understanding of primary blast injury to the human brain. Our definition of research priorities for brain injuries suffered in motor vehicle crashes was made possible by a systematic description of the injuries in the human condition (e.g., skull fracture, intraceberal hematoma, diffuse axonal injury), leading to the replication and careful study of these injuries in the laboratory. A similar, systematic description of the key injury features for primary bTBI in the human would significantly focus research efforts and consequently accelerate our understanding of their causation as well as how to protect against these types of injuries.

In estimating the primary mechanical response, several open areas of opportunity exist along the length scales:

- At the tissue scale, the continuum descriptions of material behavior are maturing but the deviatoric properties at high loading rates ($>500\,s^{-1}$) are lacking.
- At the cellular scale, the nonlinearity of material behavior is nearly absent. Although we know some key transduction events, we know far less about how these force transducers and cellular inhomogeneities will affect the circuit function.
- At the molecular scale, some evidence shows key molecular domains within receptors can control their mechanosensitivity, but detailed molecular-level study across all force-responsive receptors and channels is lacking. Knowing these key molecular and atomic scale interactions would reveal potentially new insights into how forces are transduced across the mechanical loading spectrum
- At the organ and organismal scale, there remains a strong need to develop rational interspecies scaling relationships for bTBI that account for the primary mechanical response, the interspecies differences in the connectome, and any resulting changes in behavior for networks across the phylogenic spectrum

Finally, we also see an opportunity in the far term to move these efforts for exploring two interrelated questions—how does the acute injury progress into a chronic disease, and can we better identify individual risk-curves instead of relying on estimates for the population? As we learn more about the key biological events or, alternatively, key brain regions that are important in the progression of some acute injuries into chronic impairments, we will be positioned to develop more specific tolerance criteria and protection strategies to reduce the long-term burden of TBI. Additionally, as more data become available from the human laboratory, we will see an opportunity to identify how the individual features—e.g., brain size, shape, the unique exposure profile, etc.—can lead to a better estimate for customizing protection technologies for an individual rather than relying on one design for an entire population, akin to the emerging efforts to customize treatment options based on genetic profiles in cancer patients. These efforts, although admittedly in the distant future, would represent an important evolution in our efforts to reduce the burden of TBI on the population by understanding it in each of us.

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