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Mitigating the Consequences of Subconcussive Head Injuries

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Abstract

Subconcussive head injury represents a pathophysiology that spans the expertise of both clinical neurology and biomechanical engineering. From both viewpoints, the terms injury and damage, presented without qualifiers, are synonymously taken to mean a tissue alteration that may be recoverable. For clinicians, concussion is evolving from a purely clinical diagnosis to one that requires objective measurement, to be achieved by biomedical engineers. Subconcussive injury is defined as subclinical pathophysiology in which underlying cellular- or tissue-level damage (here, to the brain) is not severe enough to present readily observable symptoms. Our concern is not whether an individual has a (clinically diagnosed) concussion, but rather, how much accumulative damage an individual can tolerate before they will experience long-term deficit(s) in neurological health. This concern leads us to look for the history of damage-inducing events, while evaluating multiple approaches for avoiding injury through reduction or prevention of the associated mechanically induced damage.

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INTRODUCTION

The topic of subconcussive head injury introduces a concept that requires collaboration between clinical neurology and biomechanical engineering. As characterization and evaluation of brain injury over the last decade have evolved, the engineering and clinical communities have begun to build on the inference by McKee et al. (1) that the presence and severity of long-term neurodegeneration associated with chronic traumatic encephalopathy (CTE) (2) was not well correlated with the history of diagnosed concussions. Rather, a critical contributor to such injuries is taken to be subconcussive head injury—a subclinical pathology in which underlying cellular- or tissue-level damage (here, to the brain) is not severe enough to present readily observable symptoms.

For clarity, we wish to briefly emphasize the congruence of the clinical and engineering definitions of both injury and damage. Both of these concepts are intended to refer to potentially recoverable changes in cellular health. Generally, it is interpreted that damage alters the integrity or behavior at a cellular level, which may aggregate to manifest at the tissue level as injury—i.e., achieve sufficient alteration that one may readily detect pain or dysfunction. Note that these definitions are superficially different from common neurological parlance of a brain injury being a pathology that may naturally recover, and brain damage generally being associated with a pathology that, at best, requires intervention to be overcome but may be permanent. We argue that the more traditional viewpoint equating the nature of injury and damage lends itself well as a general framework for all medical researchers and clinicians trying to understand traumatic brain injury (TBI).

Given the potential for subclinical damage to manifest as clinically observable injury, multiple investigations and contextual analysis of extant data emphasize that the clinical diagnosis of a concussion is inadequate to characterize the presence or extent of alterations to brain structure, function, or chemistry. Supporting this contention requires a gold standard capable of linking the engineering definition to the neurological definition of injury. Medical imaging research demonstrated that alterations in all three of brain structure, function, and chemistry are statistically correlated with repeated exposure to head acceleration events (HAEs)—either direct blows or whiplash movements by the head, arising from participation in contact sports. As initially reported in 2010 (3), Talavage et al. (4) used functional magnetic resonance imaging (fMRI) to document that near-term alterations in the brain's health—assessed by responses to relatively simple working memory tasks—were well correlated with significant recent exposures to certain numbers, types, and magnitudes of HAEs. This finding has subsequently been corroborated

(5–7) and extended by deploying other MRI-based modalities, including resting-state functional connectivity (8–11), diffusion-weighted imaging (12–16), perfusion (17), neurovascular coupling (18–20), and magnetic resonance spectroscopy (21–23).

Therefore, medical imaging presently serves as the gold standard against which other potential measures of neurological function or anatomical compromise must be evaluated. Given what is at stake for persons affected by TBI, we should also seek external (direct or surrogate) measures of brain health that accurately predict the presence or absence of underlying pathophysiology.

WHY WE SHOULD CARE ABOUT SUBCONCUSSIVE EXPOSURES

It is valuable to understand how subconcussive head injury and concussion are posited to be related to each other and to TBI, in general. Initially considering the latter two, it is important to note that there remains debate as to how the diagnosis of concussion reflects the presence of—or is even synonymous with—a TBI and associated alterations in brain behavior. As McCrory et al. (24) observed, concussion and TBI likely should not be viewed as strictly equivalent, and the requirement of the immediate presence of symptoms associated with a TBI is inappropriate, given the historical lack of a gold standard by which to assess various diagnostic criteria. Supporting this interpretation are multiple survey-based studies of collegiate athletes that have uncovered appreciable underreporting or underdiagnosis of concussions (25–31) in collision-based sports, with the detection/reporting rate of true events possibly being below 25% (32). Given the inability to easily detect symptoms (see **Table 1**), it is unclear whether McKee's hypothesis relating subconcussive exposures to long-term neurological consequences can yet be substantiated by recording of clinical symptoms. However, modeling efforts have documented that the likely history of exposure to HAEs is, in fact, an effective predictor of later-in-life neurological health (33–38).

It remains to be determined if there is a demonstrable physical difference between subconcussive and concussive exposures. The physiological mechanism by which energy is dissipated during an HAE is known to affect cellular sequelae, as in the contrast between a blast wave versus a direct mechanical impact or an acceleration event. However, from the moment of damage onward, the actual source of the disruption is no longer relevant—the cellular behavior has been disrupted, and a healing process potentially initiated. While there may be potential for a specific injury process to initiate a particular subsequent pathological event (such as injury-specific inflammation or necrosis), we consider these postacute event complications as outcomes of the induced damage rather than remote consequences of the specific injury mechanism.

In light of this perspective, the engineering-based argument would be to care that acute damage has occurred, and not be overly concerned with observation of symptoms that result after an accumulation of insults, and perhaps only at a significant temporal delay. We have

Table 1 Easily observable and often hidden or ignored symptoms of concussion

Easily observable	Often hidden or ignored
Loss of consciousness	Metallic taste
Amnesia	Seeing stars
Inability to concentrate	Sensitivity to light
Fainting	Tinnitus
Stuttering speech	Headache or migraine
Balance difficulty	Itchy extremity
Uncontrolled tears, rhinorrhea	Blindness in an eye
Seizure	Altered perception of odors

hypothesized that asymptomatic populations should not be expected to have coherent alterations in brain health measures over large, contiguous extents of tissue or else they would almost certainly not be asymptomatic (16). The sequence of HAEs experienced by each individual should be expected to produce a unique pattern of compromised tissue—representing the superposition of the patterns of tissue strain induced by each event in the sequence. A key consequence of this intersubject variability would be that a population average may not benefit from sufficient overlap to reveal a particular characteristic pattern of injury. This prediction is largely consistent with the heterogeneity of neuroimaging findings in concussed athletes reported by Klein et al. (39). Furthermore, accumulation of compromised tissue will progress in an individual-specific manner, in terms of both location and time. Therefore, the specific neural tissues that eventually become incapable of normal behavior are going to be unique to each individual, meaning that each individual will exhibit a unique set of deviations from their personal baseline performance. However, in a larger population, this might appear as an early and increased incidence of a common clinical presentation, such as mood swings, parkinsonism, or dementia.

Following from this argument, our concern becomes not simply whether an individual has a (clinically diagnosed) concussion, but rather, how much cumulative damage an individual can tolerate before they will experience long-term deficit(s) in neurological health. The former question leads one to look for the (typically assumed to be singular) hit that caused the concussion. In contrast, the second question allows us to evaluate a variety of techniques for preventing injury, because we must accept that we cannot necessarily know the individual contribution of any single event, or when a threshold for eventual neurological demise has been breached.

A growing appreciation of the importance of understanding which HAEs most contribute to changes in brain structure, function, and chemistry opens the door to the engineering community of validating additional methods to reduce long-term consequences of repeated exposure to these events. Intuitively, any effort that reduces the number of sustained HAEs—be it reduced participation, early detection of brain function or anatomical changes, or modeling of individual risk—has a reasonable chance to lead to reduction in the deleterious effects of these HAEs. We here explore all of these approaches, highlighting how the melding of medicine and engineering is essential to both development of appropriate protective measures, including activities and equipment, and evaluation of the efficacy of activity changes that may allow athletes to participate in collision-based sports with reduced risk of adverse outcomes.

BIOMECHANICS OF INJURY

The ultimate motivation for studying the biomechanics of brain trauma is to elucidate the relationship between kinematics of the entire intact skull and cellular-level impairment. Skull kinematics have been characterized for American football (hereafter termed football), lacrosse, women's soccer, and ice hockey (4, 5, 40–47) using a variety of sensor systems to quantify translational and rotational accelerations (48–50). Gross-level head movements are important inputs to the system and, somewhat surprisingly, exhibit similar ranges among multiple sports and across levels of competition. There are fundamental confounding factors when estimating deformations of brain tissue associated with HAEs. One is the complicated geometry of the skull, especially near the base, which contributes to a similarly complicated strain pattern. The second is the tissues that tether the outside of the brain to the inside of the skull at various points, making it possible for an HAE with even a small angular component to induce large strains in tissues all over the brain (51). A third complicating factor is that white matter is highly anisotropic and its load-deformation curve is highly asymmetric, while gray matter typically behaves isotropically. The surfaces at which these two tissue types interface are thus complex and difficult to quantify. It should be noted, as

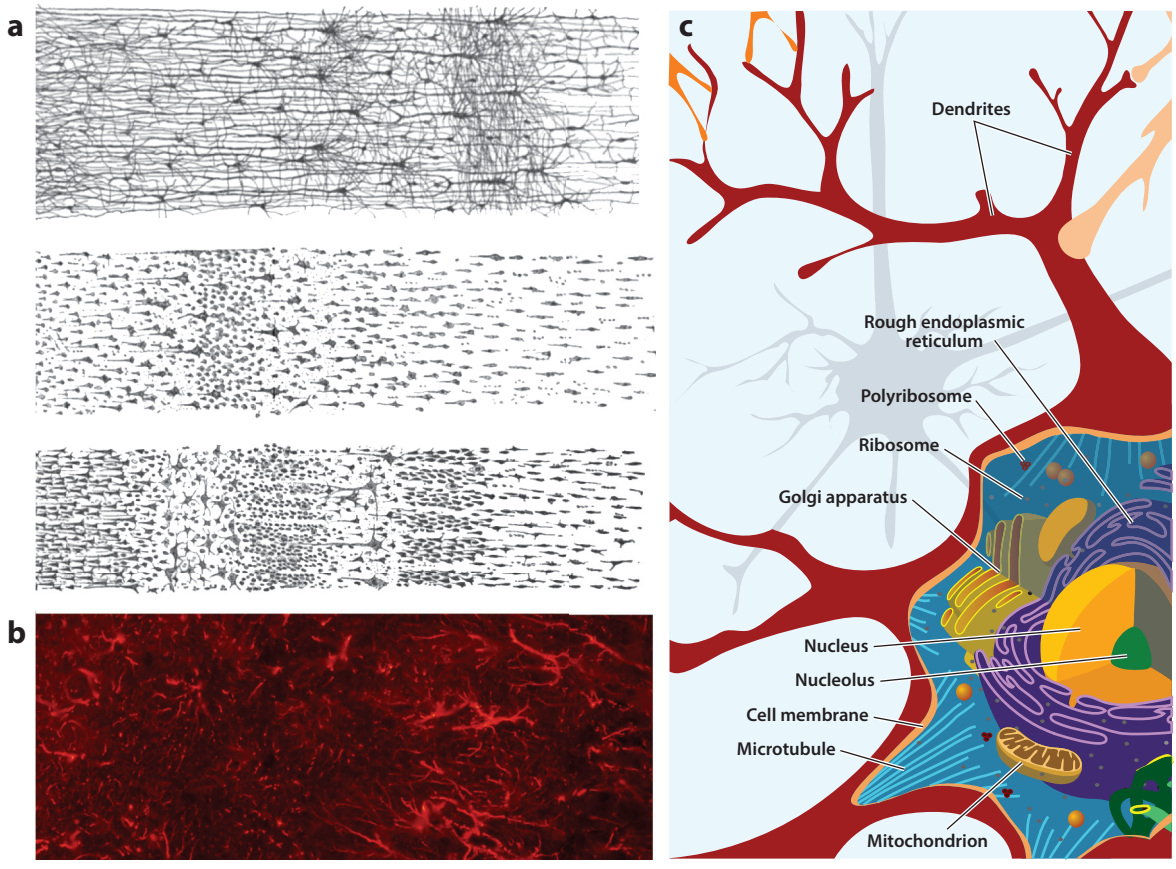

Figure 1

Density and structure of central nervous system tissues. The microscopic structure of nerve cells in the brain. (*a*) Nissl-stained cells from the adult human visual (*bottom*) and motor cortex (*middle*) demonstrate regional variations in density and structure, while those from a human infant (*top*) demonstrate changes with age. There are approximately 160 billion cells in the human brain, almost half of which are support cells such as the (*b*) glial fibrillary acid protein (GFAP)-stained astrocytes. (*c*) Understanding the structure of neurons and their intercellular connections is crucial for mapping energy transfer throughout the system.

well, that the most important aspect of energy transfer actually occurs at the cellular and subcellular levels. To date, computational models have incorporated white matter orientation, viscoelastic effects, and rapid rotations (52–56), but future computational models will have to integrate the microscale cellular structure (57–59). Roughly 160 billion cells comprise the human brain. Half of these cells are heterogeneously distributed neurons (**Figure 1**). The remainder are mostly astrocytes, oligodendrocytes, and microglia that aid in maintaining the biochemical environment needed for normal neuronal activity. Physical insults directed at any of these cell phenotypes or their myriad interconnections can result in altered neurophysiology; however, little is known about the mechanisms by which skull motions generate damage at the cellular level.

While multiscale biomechanical problems are challenging to solve under the best of circumstances, a primary difficulty with brain biomechanics is that there exist a number of misconceptions about the transfer of energy from the whole skull to the individual cells. One is that HAEs cause the brain to strike the inside surface of the skull. In truth, the brain presses and shears against the soft tissue layers that make up the meninges. Another misconception is that only coup-contrecoup

injuries generate brain damage during an HAE. Bayly et al. (51) demonstrated quite effectively that, in addition to compression waves, numerous regions of high tensile and shear stresses are induced at and around the brain's tethering points. Taken together, these data strongly indicate that every HAE has the potential to affect much, if not most, of the brain and that it is important to understand the effects not only of compression but also of tension and shear.

The energy delivered by violent head accelerations affects more than just the neuronal cell population, and it dissipates in a variety of ways. Dissipation mechanisms consist of elastic and permanent deformations (including rupture) of the soma, axons, dendrites, synapses, myelin, and interconnections between glial cells and the microvasculature. Simple engineering models suggest that the most compliant structures in the brain will deform the most and serve as the primary sources of energy transfer. Unfortunately, this approach neglects the fact that tearing of the extracellular matrix, rupture of cell membranes, and other forms of failure absorb tremendous amounts of energy. The takeaway is that the brain's macro- and microstructure are sufficiently complicated that predicting the type of failure for a given HAE is extraordinarily difficult.

Modeling energy transfer to the brain requires a thorough understanding of the mechanics of white matter and gray matter, both of which are nonlinear, strain-rate-sensitive materials (57–59) with significant water content. White matter in the brain and spinal cord is highly anisotropic due to the presence of fiber bundles and, in the longitudinal direction, is considerably stiffer than gray matter (58). In a landmark study, Galle et al. (57) were the first to correlate the applied macroscopic compressive stress (perpendicular to the fiber bundles) directly to cell membrane disruption. A subsequent study demonstrated that the compound action potentials were not substantially affected until 50–70% compression was achieved, and that the reduction in action potentials directly correlated to the level of membrane damage (60). Transverse impact loading of intact spinal cords (61) indicated that debonding of the axon-myelin interface absorbs the most energy, and relatively little permanent damage occurs to the axon—an outcome consistent with stiffness measurements obtained using atomic force microscopy (62). Despite the lack of direct damage to the axon, however, the function of that cell may be compromised due to effective elongation of the node of Ranvier. Compression of cortical neurons embedded within hydrogels demonstrates that bleb formation, mechanoporation, and cell death depend on overall strain, strain rate, and hours elapsed since loading (63). Slow axial loading induces neurite outgrowth (64), while rapid axial loading tends to induce cell membrane tears (65).

Little has been done to examine the effects of mechanical loading on synapse function, despite the obvious importance to neuronal signaling, and these synapses' often precarious mechanical tethering (see **Figure 1*c***)—especially involving axosecretory, axoextracellular, and axosynaptic synapses. The fact that there is a marked response in synapse structure and function postinjury (66) suggests that there is likely a short-term effect that has not yet been well characterized. The integrated effects of synaptic disruption might be observable with electroencephalography (EEG), but detailed characterization will likely require histologic evaluation.

Likewise, characterization of capillary mechanics and vasculature disruption is crucial to understanding both the short-term and long-term physiologic responses of the brain. However, only a handful of researchers have attempted to perform the necessary experiments (67–71) or develop relevant models (72, 73). Better understanding of the damage and repair mechanisms of the brain's microvasculature will be crucial to developing predictive models of brain recovery. Characterizing this response in animals and humans will require detailed computational models combined with advanced imaging techniques, such as MR-based perfusion imaging and spectroscopic characterization.

Another energy dissipation mechanism that is often overlooked is the viscous shear stress resulting from the relative motion between the extracellular fluid, which makes up approximately

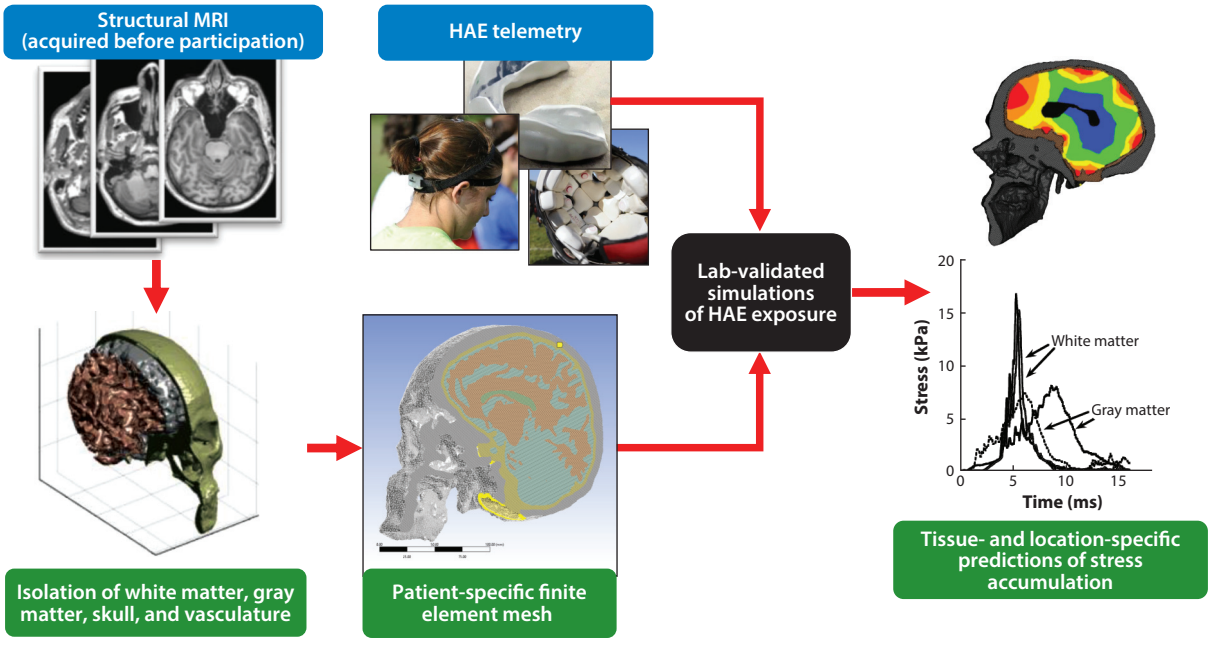

Figure 2

Characterization of the accumulation of injury in the brain will require validated computational models that can operate on preexposure structural information (e.g., as acquired using MRI) and a known history of exposures to HAEs to produce individual-specific maps of strains, which are expected to be tightly correlated with the accrual of neural tissue injury. Future work in animals is expected to provide a linkage between the accumulation of strain and dysfunction at the neuronal and vascular levels, resulting in prediction of short-term risk of neural injury. Such an approach can enable the healthcare team to hold an individual out of lower-value activities (e.g., practices as opposed to games) or to highlight an individual in need of additional training to reduce use of risky techniques. Abbreviation: HAE, head acceleration event; MRI, magnetic resonance imaging.

25% of the tissue volume (74, 75), and the matrix of cells. This mechanism has been noted in a variety of mixture theory models of mechanics in bone and cardiovascular tissues (76–78). The results of this interaction are difficult to predict, because they depend on the direction of fluid movement relative to the orientation of the axons, microvasculature, and synaptic connections. However, integration of MR-based diffusivity measures should make it possible to designate boundaries on the stresses generated by fluid–solid interactions for various loading regimes.

As a whole, the literature indicates that cellular-level damage can take many forms and produce a complex array of cellular, tissue, and whole-brain-level deficits. Understanding the relationship between mechanical insult, energy dissipation mechanisms, and the corresponding level of cellular damage will be accomplished by a thorough integration of animal and human data, linked by a combination of computational models and medical imaging (see **Figure 2**).

MITIGATION OF BRAIN TRAUMA

There are two fundamental options for ameliorating the effects of HAEs on the brain: repair the damage after the fact or make an effort to prevent the damage from occurring in the first place. While some progress has been made in the treatment of brain plaques (such as those putatively associated with CTE) using invasive and noninvasive methods (79), neurologists and engineers agree that preventing brain injuries is a more efficient and cost-effective approach to the problem.

We next focus on a variety of methods aimed at prevention, focusing on the current state of the data supporting each method and its overall potential for mitigation. These include: reducing the number of HAEs through changes in participation and training, head impact monitoring, improving protective systems, and readily accessible injury detection. We believe that preventing subconcussive injury is an important part of the discussion.

Reduce HAEs

HAEs experienced by athletes have been measured with a variety of helmet-based and head-based sensors, demonstrating that the number of HAEs per week varies considerably between sports. There are two interesting, if often overlooked, aspects of these data sets. The first is that HAEs can occur from direct impact with another player, the ground, or a whiplash event without any direct head contact. Noncontact HAEs in the range of 10–20 g often occur with a sudden change of direction, with a jump, or even with kicking a ball (45). 20 g is often assumed to be a lower bound on the types of HAEs likely to cause human brain damage, but this assumption will require validation with exquisitely sensitive biomechanical measurements of alterations in brain structure, function, and/or chemistry. The second important aspect of the HAE data sets collected thus far is that they exhibit remarkably consistent frequency histograms across sex and sport. Given that most detection systems use a threshold of 10 g to record events, the assumption of a true lower bound for damage at 20 g, combined with what appear to be sport-independent distributions of HAEs, makes it likely that a fair estimate of overall exposure may be achieved even when low-resolution sensors are used simply to count the total number of HAEs.

Recent studies have demonstrated that there may be floor thresholds in HAE magnitude, beyond which HAEs are particularly deleterious (16, 17, 20, 23). While additional work is required to elucidate the specific ranges at which the neurophysiological changes become damaging, these data suggest that it may be possible to modify team practices and monitor individual participation in a manner that reduces both individual and accumulative HAEs.

It is not unusual for high school and college athletes participating in certain contact sports to experience at least 100 HAEs exceeding 10 g of linear acceleration in a week. It has been suggested that, in football conferences or leagues that do not limit the number of contact practices, or with coaches who encourage frequent hitting, the numbers are even higher. Early studies in high school football demonstrated that, when computer-based cognitive testing and task-based fMRI analysis were jointly performed, 21 of 22 evaluations conducted during the competition season were flagged by at least one of the two measures (80). A subsequent study found that, in the postseason, athletes were more likely to be flagged by one or both measures if they had experienced an average of more than 50 HAEs per week (again, exceeding 10 g of linear acceleration) during the season (81). Clearly, reducing the number of HAEs in practices and games is important. This goal can be accomplished in a variety of ways (82).

A simple and cost-effective method of reducing HAE exposure is to decrease the number of contact practices and ensure that such practices do not occur on consecutive days, so that some (as yet unknown) amount of healing can occur. Many states mandate no more than two contact football practices per week at the high school level (typically occurring on Tuesdays and Wednesdays), with games on Friday nights or Saturdays. Regardless of coaching style, reducing the number of such contact practices to one per week should reduce HAEs by approximately one-third and add the benefit of eliminating consecutive contact practices. There are often fewer regulations for younger participants, possibly arguing for greater examination of the consequences of participation in youth leagues—a concern partially addressed by USA Soccer when it prohibited heading for players 10 years of age or younger and restricted heading to (controlled) practices for players ages 11–13 years.

Similar, easy-to-implement rules changes for football include not allowing players to play both offense and defense, and limiting overtime periods (or allowing tie games during the regular season). Such rules changes could have a huge potential benefit. For instance, an athlete who plays both ways in a double overtime game may experience three times the number of HAEs compared to a player who played on one side of the ball during a normal regulation-length game.

All contact sports might benefit from a less egalitarian approach to postseason play. States whose high school playoffs include all teams (regardless of regular season record) generate additional rounds of competition, increasing the accumulative HAE exposure by adding multiple weeks to the competition season. By example, only allowing the top quarter of the teams into postseason play would eliminate two games and the associated practices.

The aforementioned methods for reducing the number of HAEs are essentially free of additional financial cost (other than revenue generation from spectators and sponsors) and quick to implement, whereas adding technological solutions (e.g., improved protective equipment, HAE sensors) might add benefits, but at a financial cost. Nonetheless, these costs may represent an acceptable trade-off. Monitoring HAEs during practices requires some form of sensor attached to the head or the helmet (48–50) and provides a range of options for reducing HAE exposure. Tracking which drills and forms of game play result in the greatest number of HAEs is a method for evaluating the opportunity to make activity changes, such as modifying practices and rules. With currently available sensor technology, individual players can be tracked and HAE monitoring data can be used to determine which of them are particularly in need of focused observation, training, and behavior modification.

Further interventions that merit further study include altering the stance of linemen, and modifications to tackling instructions and technique. A recent study of football players in a professional developmental league participating in a structured scrimmage demonstrated reduction in HAEs when offensive linemen began in a two-point stance as opposed to a three- or four-point stance (83). Tight ends were observed to be particularly vulnerable to HAEs because they may block and act as receivers on the same play. Future studies should examine the effects of changing lineman stance patterns in less structured and more realistic game environments, especially in situations where they have had prolonged practice time to acclimate to the new technique (84, 85). USA Football's Heads Up program has endeavored to empower coaches of youth football to teach safer tackling techniques and provide greater awareness of concussions (86). While results from these various initiatives have been mixed, modifications to lineman stance and tackling technique hold promise for future improvements, especially if they are coupled with head impact monitoring and video feedback to augment the ability of coaches to deliver quality instruction.

More active instructional tools include the MVP robotic tackling system (87). It enables the coaching team to simulate game speed movements and improve the way that tackling technique is taught. Future work should evaluate the ability of robot-assisted tackling drills to transfer technique improvements from the practice field to game situations.

Monitoring Technology

In the absence of a direct physiological means to assess neurological health on the sidelines, the body of literature argues that deviations from normal measures of brain health (here, referring to the preactivity baseline for an individual) may be roughly predicted by the accumulation of HAEs. This finding agrees with intuition. That is, knowledge of the direction and magnitude of incident forces (or whiplash-like accelerations) should permit prediction of strain fields in the brain, with greater accumulation (over time) of strain being associated with a greater risk of tissue injury. Therefore, monitoring aggregate accelerations would, when coupled with meaningful models of an individual's specific anatomy, be anticipated to have the greatest predictive power (e.g., 53, 55).

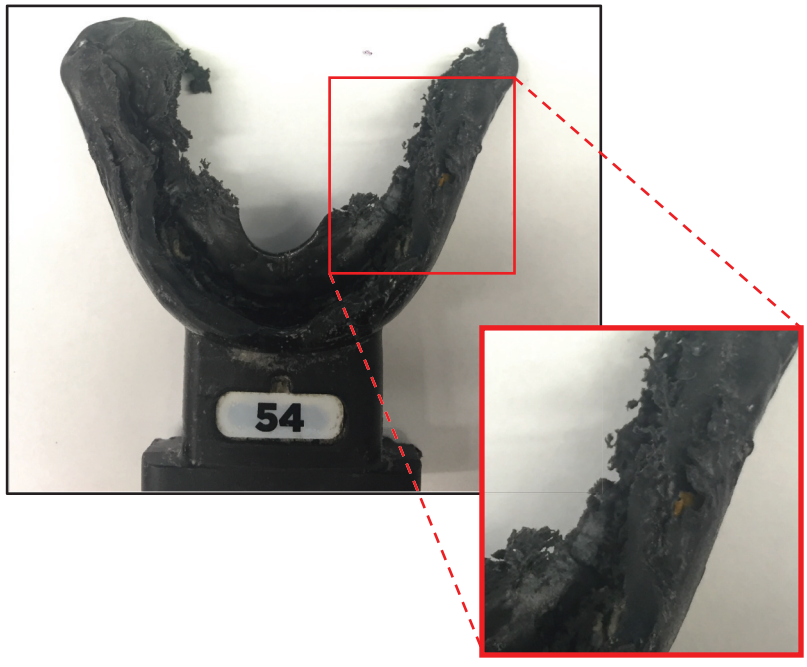

Figure 3

Example of chewing damage to a mouth guard–based sensor used for one season of high school football. Inset reveals exposed wiring from circuitry associated with confirming that the device is in the mouth. Mouth guard devices will require careful placement of batteries and current-bearing electronics to ensure that athletes remain safe, even if they chew through the plastic.

To this end, a variety of technologies have been developed to monitor accelerations experienced by an individual participating in sport, including accelerometers placed in the helmet, on the head, and affixed to the maxilla (via mouth guards). Each technology has advantages and disadvantages (e.g., 48, 50, 88, 89). The earliest implementations relied on helmet-based sensors (49), which offer appreciable ease-of-use with limited required interaction with the athlete. However, such sensor designs are not practical for use in nonhelmeted sports, and it has been well documented that helmet-based sensors may have their signals contaminated by relative displacements between helmet and head, or by flexion of the helmet shell (48, 88). Maxilla-affixed devices represent the conceptual ideal, given that they are expected to move in conjunction with the cranium, but the typical presence of a nonimplantable lithium-polymer battery inside the mouth—often in positions through which athletes might chew (e.g., see **Figure 3**)—raises safety concerns. Circuitry that would limit the risk of high currents in case of damage to the battery might obviate this concern, making this the preferred option for the future. Further, such devices must never allow a battery to be swallowed. Preference for this form factor would be strengthened by the ability to use such a device in nonhelmeted sports that generate HAEs (e.g., soccer, rugby). As of this writing, behind-the-ear designs currently offer the best combination of ease-of-use and safety, as well as sufficient accuracy to permit meaningful prediction of changes in brain health from accumulative exposure data. While there may be some overestimation of accelerations due to the skin possibly being displaced relative to the underlying skull, previous quantification of this error (89) was reported for accelerations in a range (6–13 g) well below those likely to represent meaningful impacts (45). This tested range is also well below thresholds that have thus far been found to be

relevant to predicting changes in brain health (16, 17, 20, 23). Given the consistency of the counts of HAEs across helmet- and head-based systems (48), it would be important to document this error for higher resultant accelerations, because the discrepancies may simply represent a noise floor that averages out over the course of a larger number of higher-magnitude observations.

Regardless of the site used to assess accelerations, current technologies do a poor job of estimating rotational accelerations (48, 50, 88), which are conjectured to be critical in assessing the risk of neural injury (90). Most devices now have embedded gyroscopes or employ machine learning algorithms to classify the most likely rotational acceleration based on the profile of (measured) translational accelerations. The latter technique is suspect, in part because the number of real-world impacts (with accurate classification) required for the training set is almost never acquired and therefore tends to result in a strong (and perhaps erroneous) linear relationship between the reported peak translational and rotational accelerations (45). Even using an embedded gyroscope does not represent a panacea, because these devices more typically report rotational velocity, and the acquired signals must be numerically differentiated to obtain acceleration measurements. The subsequent preservation of high-frequency noise complicates translation of the sensor acceleration to the center-of-mass of the athlete's head. Further, the sampling rate required to achieve high-fidelity translation to the center-of-mass is quite high, complicating the power requirements to achieve the necessary data acquisition, storage, and transmission.

Fortunately, the literature thus far indicates that generic hit counts, particularly those counting only HAEs registering above particular thresholds of translational acceleration, are effective for crude prediction of what is likely the initiation of an underlying neural injury and repair process.

The use of current devices to count HAEs is likely of greatest benefit in providing athletes and coaches evidence of player technique, practice activities, or positional mismatches that warrant examination and possible intervention. Regardless of the technology used, counting HAEs does not yet provide a clear indication of the present brain health for a given athlete. However, these counts are likely to be effective as a proxy for identifying athletes at greater risk of substantive HAEs—and therefore at greater risk of high-energy impacts that would be expected to increase the risk for neural injury.

Future development of technology for monitoring HAEs can likely incorporate information to support enforcement of protective rules. For example, measuring and monitoring orientation of the head of a football athlete may permit automated calling of penalties for spearing or otherwise lowering one's head prior to tackling or blocking. Additional information could be generated by such devices. This includes relative positions of the heads/helmets of multiple players involved in a collision, perhaps alerting coaches and athletic trainers to the individual who struck their head on another athlete's knee or the ground—two causes frequently documented to be associated with subsequent diagnosis of concussion (91–93).

Protective Technology

In 1973, the National Operating Committee on Standards for Athletic Equipment (NOCSAE) adopted a drop-tower test that was subsequently used to certify football helmets. Similar standards were later developed for hockey and lacrosse helmets. These standards dramatically reduced the number of skull fractures and fatalities (94). Using drop-tower-based methods, it was established that current football helmets offer significantly more protection than do lacrosse helmets (95) and that the differences between new and used lacrosse helmets are minor (96). Aftermarket add-on devices, such as the Guardian Cap, demonstrated some improvements, but the effect sizes were small (97). It should be noted, however, that the traditional drop-tower systems and the more modern versions that utilize pneumatic rams employ similar output metrics, which have never

been validated against closed-head trauma. In 2019, Cummiskey et al. (98) reported a system that integrated a modal impulse hammer to record the input force with a Hybrid III Headform adapted to output the translational and angular accelerations. Quantifying both the inputs and outputs makes it possible to obtain a transfer function at each impact location that can be used to evaluate the effects of specific helmet design elements.

Such testing capabilities are crucial because recent studies on high school football and women's soccer have demonstrated that changes in neurovascular coupling (20) and brain chemistry (23) correlate best with the number of head impacts exceeding 50 g in magnitude, while structural changes in the brain, quantified with diffusion-tensor imaging, were found to correlate with lower acceleration levels (16). These data provide the first true design goals for helmets and other protective systems aimed at reducing the cumulative burden of HAEs. Current data on football (98) and lacrosse helmets (99) suggest that helmets can be designed to achieve the 50-g threshold for the 95th percentile head impact observed in high school and collegiate contact sports. It should be noted, however, that the ultimate validation of new helmet features will require the aforementioned MRI gold standard to quantify changes in brain structure, function, and chemistry.

Detection

As we enhance the ability to monitor HAEs, the critical question of confirmation of the development of pathophysiology rises to the fore. Any approach that seeks to reduce exposures, to improve protection, or to monitor and predict pathophysiology merely serves to improve our assessment of the risk of injury in any given individual. Diagnosis and treatment of HAE-associated pathophysiology requires a local, effective means to confirm the presence of that pathophysiology. Methods to detect alterations in brain health represent one frontier upon which depends the scientific pursuit of the consequences of prophylactic interventions intended to prevent repetitive HAE exposure and their translation into future standard-of-care for preventing brain injury.

Several tools have been promoted as potential means to enhance diagnosis of concussion, with an eye toward detection of the more subtle neurological alterations associated with repetitive HAE exposure. Some of these tools are primarily checklist evaluations—such as the Sport Concussion Assessment Tool (SCAT), Concussion Symptom Inventory (CSI), and Glasgow Coma Scale (GCS). Although these have been used as a means to regularize assessment of the most commonly observed symptoms associated with a diagnosed concussion (100–104), at least one (GCS) was never intended or validated for that purpose. Recent tools development has emphasized computer-based versions and/or extensions of traditional neuropsychological tests, such as the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) battery (105, 106). Such tests are intended to evaluate higher-order cognitive function that relies on greater neurological integration and may, therefore, be more likely affected by subtle alterations in the transmission of information in the brain (107–109). However, computer-based neuropsychological testing is sensitive to how it is administered, and interpretation of results is not trivial (110–112). Finally, as a complement to neuropsychological tool extension, there have been efforts to apply neurological function testing to head injury (with or without a diagnosis of concussion), including assessments developed for vestibular function (113–117), oculomotor behavior (118–120), or the integration thereof (121–123).

Nearly all of these tools (or their subcomponents) were originally developed to confirm symptomatic concussion—i.e., used by clinicians in an effort to quantify deficits associated with a suspected or already-diagnosed concussion, allowing some recovery tracking in the acute period following injury. While proving to contribute some value in the multifactorial assessment of nonconcussed populations exposed to HAEs, none of these tools has been found to definitively

suffice as a diagnostic vehicle (e.g., 124–126). Serving in the role of a diagnostic aid, many of these tools offer limited benefit, because they suffer from shortcomings related to reproducibility and subsequent reliability of individual-subject baselines (111, 127–129—but see 130 for a countering view). Perhaps these shortcomings tie back to the fact that few such tools provide direct information about the underlying physiology, and whether it remains intact or is compromised.

The most robust insights into the presence and nature of pathophysiologic alterations associated with exposure to HAEs have been derived from medical imaging research. Noninvasive measures that are capable of quantifying physiology and structure offer the best opportunity to detect presymptomatic changes in body tissues and have been readily adopted by multiple clinical fields (e.g., cardiology). With pathophysiology from HAE exposure being first observed with fMRI (3, 4), it is no surprise that various modalities of MRI have proven effective in detecting and characterizing physiological alterations in collision-sport athletes that lie outside the range of natural variation of peer populations who are not engaging in collision sports. While MRI can justifiably serve as a gold standard for detection of a range of pathophysiologic outcomes, it remains an impractical (size and cost) modality to be deployed for widespread detection (and tracking) of consequences of brain injury. Several neurologically related assessments—largely representing assessment of oculomotor behavior—have been evaluated in conjunction with MRI acquisitions, providing key evidence of their potential as portable and affordable options for injury detection (e.g., 131–133).

Fortunately, other noninvasive imaging modalities that lie outside the traditional standard-of-care (for persons not diagnosed as concussed) may also reveal measurable changes in brain health with HAE exposure. Quantitative EEG (QEEG), which is more portable and affordable than MRI, has been extensively applied for detection of alterations in brain health, proving highly effective for detection of concussion (134–137). However, limited effort has been directed at QEEG categorization of subjects who have been exposed to repetitive HAEs in the absence of symptoms, so there is yet little evidence whether QEEG provides a strong match to the gold standard currently represented by MRI. In contrast, another noninvasive modality that has been used quite frequently in conjunction with MRI to evaluate concussion or other brain injury is functional near-infrared spectroscopy (FNIRS) (138). Encouragingly, investigations have frequently observed similar changes in brain physiology as assessed by MRI and FNIRS, while the brain is at rest (139) and during task performance (140). As researchers seek to overcome the logistical impediments associated with MRI from the evaluation of brain health in concussed and nonconcussed individuals exposed to HAEs, it is likely that one or more alternatives will meet a minimum standard to become widely adopted and enhance the standard of care.

IMPLICATIONS FOR HAE-RELATED BRAIN INJURIES

Failure to diagnose injuries that are (by traditional methodologies) undetectable at the time of acute injury, but are suspected to contribute to catastrophic debilitation later in life, is the most important health issue facing sports today. Lack of coherence across the diversity of neural tissues that are compromised by TBI implies that there is no reason to expect consistency of easily observable symptoms in a population exposed to repetitive HAEs. Such an implication is well supported by literature that documents a high rate of missed or unreported concussions (e.g., 28, 32), and by inconsistent imaging findings in populations exhibiting a common clinical presentation (141). We must accept that in studies of concussion—and perhaps even more typically in other forms of TBI—populations are sampled as a whole across a range of a complex postinjury repair processes despite the fact that these populations are possessed of unique (to each population) patterns of compromised tissues. In other words, deviations from normality induced by repetitive HAEs or

other subconcussive events are fundamentally diffuse and, over time, likely expand and coalesce to impair transmission of information around the brain, at which point symptoms arise and the underlying injury is finally acknowledged (107, 109).

This hypothesis regarding an accumulative origin of symptomatic brain injury does not preclude an individual from exhibiting easily observable symptoms arising de novo from a single event. Should a particular event result in sufficient mechanical strain to compromise a functional unit of tissue (e.g., the lateral geniculate nucleus on one side of the brainstem, leading to inability to see a full field of vision), there is no reason to expect the individual to remain asymptomatic.

Ultimately it may be argued that the only difference between a subconcussive event and a concussive event is one of degree, in terms of the severity and focal nature of the tissue-level injury. Therefore, it is imperative that we continue to investigate and learn about cause and effect in brain health for collision-sport athletes (as a specific test bed), for the sake of current participants and generations to come.

CONCLUSION

HAEs—whether resulting from direct impacts, blast waves, or whiplash movements—have been documented with neuroimaging to produce low-level cellular damage and tissue dysfunction (injury) in the brain. These low-level injuries are poorly connected to readily observable clinical impairments that may be identified as concussion symptoms—an observation not altogether surprising given the complexity and interconnectedness of the brain. Thus, low-level injury can be deemed subconcussive. Better identification of the HAEs that accumulate and thereby contribute to ultimately deleterious clinical outcomes can be achieved through improved modeling of energy transmission and absorption in brain tissues, coupled with enhanced characterization of head movements. Until such time as these characterizations have been achieved, minimization of HAE exposure represents the simplest method to reduce accumulative brain injury, particularly for individuals participating in activities regularly involving collisions (e.g., sports such as football and soccer). In sports, minimization may be effected through changes in the number or nature of collision activities in practices and games, improved training to promulgate more safe techniques, and improvements in protective equipment.

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