

## An overview of the basic science of concussion and subconcussion: where we are and where we are going

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There has been a growing interest in the diagnosis and management of mild traumatic brain injury (TBI), or concussion. Repetitive concussion and subconcussion have been linked to a spectrum of neurological sequelae, including postconcussion syndrome, chronic traumatic encephalopathy, mild cognitive impairment, and dementia pugilistica. A more common risk than chronic traumatic encephalopathy is the season-ending or career-ending effects of concussion or its mismanagement. To effectively prevent and treat the sequelae of concussion, it will be important to understand the basic processes involved. Reviewed in this paper are the forces behind the primary phase of injury in mild TBI, as well as the immediate and delayed cellular events responsible for the secondary phase of injury leading to neuronal dysfunction and possible cell death. Advanced neuroimaging sequences have recently been developed that have the potential to increase the sensitivity of standard MRI to detect both structural and functional abnormalities associated with concussion, and have provided further insight into the potential underlying pathophysiology. Also discussed are the potential long-term effects of repetitive mild TBI, particularly chronic traumatic encephalopathy. Much of the data regarding this syndrome is limited to postmortem analyses, and at present there is no animal model of chronic traumatic encephalopathy described in the literature. As this arena of TBI research continues to evolve, it will be imperative to appropriately model concussive and even subconcussive injuries in an attempt to understand, prevent, and treat the associated chronic neurodegenerative sequelae.

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**T**HERE has been a growing interest in the diagnosis and management of mild TBI, or concussion. With new research initiatives and skyrocketing levels of public awareness, society has gained a better understanding of concussion and mild TBI, while we as a medical community have learned that we have a long way to go. Repetitive concussion and subconcussion have been linked to significant morbidity and death. This paper will review the forces behind the primary phase of injury, as well as the immediate and delayed cellular events responsible for the secondary phase of injury leading to neuronal dysfunction and possible cell death associated with mild TBI. While the cascade of events within the cells and neurons of the CNS are profound, the role of both acute and chronic inflammation is also important to acknowledge.

There has also been increased public awareness regarding the long-term sequelae of repetitive mild head

injuries or even subconcussive injuries. We will review some of the pertinent work on repetitive mild TBI and possible implications in the development of neurodegenerative disease, particularly chronic traumatic encephalopathy. More frequent than posttraumatic chronic neurodegenerative disease, however, is the increased risk for season-ending or career-ending effects of concussion or its mismanagement. Paramount to effective prevention, diagnosis, and management of the vast number of athletes, soldiers, and patients affected by the sequelae of mild TBI is a sound understanding of the forces behind the primary injury and the pathophysiological cascade of events that ensue following the primary injury, when the brain falls victim to a concussive event or multiple events over time.

### The Biophysics of Head Impact

Traumatic brain injury is traditionally believed to involve both primary and secondary injury phases. The primary injury is represented by the moment of impact,

Abbreviations used in this paper: BBB = blood-brain barrier; CBF = cerebral blood flow; TBI = traumatic brain injury.

resulting from the translation of kinetic energy and force vectors in either a linear acceleration-deceleration mechanism, through a rotational mechanism, or a combination of both. Newton's Second Law of Motion enables the visualization of how forces in head impacts result in head, and consequently brain, acceleration:

$$\text{force} = \text{mass} \times \text{acceleration (Newton's Second Law)}$$

While this equation quantifies the linear forces that come into play with head injury, in instances of rotational force or torque, we have the equation:

$$\text{torque} = \text{moment of inertia} \times \text{angular acceleration}$$

In understanding just these two basic physics concepts, a great deal can be appreciated in concussion biomechanics, as linear and angular brain accelerations have been shown to be the most predictive variables of head injury. Most cases of head injury involve both linear and angular forces.

When considering the laws of conservation of energy, the sum of the kinetic energies of the struck patient and the striking object is equal to the total linear and angular energy imparted to the head, plus that energy dissipated from the head. A review of the equation for kinetic energy reveals the importance of velocity on the impacted neural structures:

$$\text{kinetic energy} = 1/2 \text{ mass} \times (\text{velocity})^2$$

When we consider modern day athletics, today's athletes are not only larger (increased mass), but more importantly, the velocities at which impacts occur is also substantially increased. With squaring of the velocity of impact in the kinetic energy rotation, the resulting increase in kinetic energy, and therefore imparted forces, is profound.

Early studies on the biophysics of concussion were performed in nonhuman primate models of concussion.<sup>52,70,71,85,89,107</sup> Analyses of the data at that time led investigators to believe that approximately half of the potential for concussion during impact to the unprotected movable head was related to head rotation, with the remaining brain injury potential of the blow being related to the contact phenomena of the impact.<sup>71</sup> Although the biodynamics in these primate models were likely more similar to human concussion, such studies were limited to small group size. With regard to our modern day athletes and the biophysics of head injury, the mandatory use of helmets in American football has allowed for the systematic analysis of injury biomechanics and real-time measurements of forces, velocities, and accelerations of head impacts by implanted telemetry devices.<sup>33</sup> The US National Football League has organized study of detailed computerized video analysis of actual game film in 182 concussive and subconcussive hits that occurred between 1996 and 2001.<sup>73</sup> Using these data, investigators were then able to remodel these impacts in the laboratory setting by incorporating crash test dummies. The results of the investigation demonstrated that the highest strain forces were imparted to the region corresponding to the deep midbrain level, occurring 10 milliseconds following the impact. It was further inferred that these forces imparted to the mesencephalon, corpus callosum, and fornix may be responsible for concussion symptoms such as loss of consciousness, amnesia, and cognitive dysfunction.

tion.<sup>73</sup> Even in less severe impacts, not resulting in loss of consciousness, there appeared to be significant forces transmitted to deep midbrain and brainstem structures, implying injury in subconcussive impacts as well.<sup>73</sup>

Since that time there has been an explosion in research performed investigating the biomechanics and biophysics of mild TBI.<sup>5,11,12,15,27,28,60,73,82,87,100</sup> Biophysics data gathered through football helmet accelerometer studies at the youth, high school, and college level have shown that players may experience a wide range of head impacts, as well as magnitudes of force. This research has also suggested that it may more likely be that the cumulative number of head impacts best correlates with the potential for concussion occurrence or chronic effects. The athlete's risk of experiencing long-standing effects of repetitive blows is likely measured as a cumulative dose over a lifetime, and could include factors such as age at exposure, type and magnitude of exposure, recovery periods as well as differential rates of recovery, genotype, and others.

Among the numerous factors in understanding the increased risk of head trauma in contact and collision sports, the velocities of the collisions are of particular importance. In actuality it is the change in velocity, through acceleration-deceleration, which relates to the energy transmitted to the player's body and brain. In essence, the brain is suspended within fluid-filled space with a certain degree of movement, relatively tethered at discreet intervals, and housed within a rigid container. The brain is able to accelerate with this reserve volume (filled with CSF) through which the brain can accelerate and collide with the skull. This movement has been referred to as "brain slosh" due to the semisolid properties of neural tissue and its surrounding stromal cytoarchitecture.<sup>96</sup>

### Pathophysiology Underlying Secondary Injury in Mild TBI

Secondary injury is classically described as the indirect result of the trauma and its subsequent pathophysiological processes. These pathophysiological processes involve both immediate and delayed cellular events including ultrastructural damage, ionic shifts, and neurotransmission effects, among other events.<sup>64</sup> There are also remarkable effects on cerebral blood flow dynamics and the BBB contributing to the pathophysiology of secondary brain injury.

The forces imparted to the neural structures discussed above are believed to result in shear stress to neurons, thereby resulting in axonal disruption.<sup>57</sup> Although traumatic axonal injury is best described in more severe models of TBI, it is also believed to play an important role in mild TBI.<sup>97</sup> Neurofilament compaction has been shown to occur as soon as 5 minutes after injury and lasts for approximately 6 hours. It is believed that this event is caused by phosphorylation, leading to instability.<sup>65,68,98</sup> Ultimately, the ultrastructural alterations of neurofilaments and microtubules cause focal swellings at the site of injury and interference of axonal transport.<sup>34,83</sup> Eventually, blebbing of this region occurs, and signs of axonal

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disconnection have been witnessed as early as 4 hours after injury.<sup>75</sup> It has been reported that this detachment persists for days to weeks in humans.<sup>10</sup>

Returning to the more immediate effects of shear injury to neuronal membranes, dysregulation of protein channels within the neuronal plasmalemma then ensues, resulting in uncontrolled ion flux and neurotransmitter effects.<sup>22</sup> Specifically, liberation of potassium, certain neurotransmitters and excitatory amino acids occurs, particularly glutamate.<sup>21,39</sup> Glutamate then acts on several receptors, including *N*-methyl-D-aspartate receptors, causing further depolarization and calcium influx into the neuron. As a result, adenosine triphosphate-dependent pumps are forced to work “on overdrive” to restore ionic homeostasis, which results in a hypermetabolic state beginning approximately 30 minutes after injury.<sup>40,108</sup> It has also been shown that there is a switch from a hypermetabolic state to a hypometabolic state 5–6 hours later, which can last up to 5 days or longer.<sup>7</sup> Consequently, more glycolysis and anaerobic respiration occurs, and local extracellular acidosis follows, possibly contributing to further membrane permeability.<sup>36</sup>

Glutamate-mediated accumulation of intracellular calcium ions also results in mitochondrial oxidative dysfunction.<sup>47,80,102,105</sup> Hovda et al.<sup>34</sup> showed that cytochrome oxidase, a marker of oxidative function, is downregulated after injury in rodent models up to 10 days after mild TBI. This downregulation likely further potentiates the cascade of adverse events in mild TBI, in which a metabolically hyperactive brain, early in injury, has a hindrance in oxidative functioning. Certainly, this is disadvantageous for a brain in a hypermetabolic state with already reduced adenosine triphosphate, and it is believed that this exacerbates the cascade of events in acute concussion.

### Cerebral Blood Flow Dynamics

In the uninjured brain CBF is highly regulated, with the ability to rapidly adjust perfusion levels to meet the brain’s metabolic needs. In TBI, however, CBF has been shown to be decreased immediately after injury.<sup>26,63</sup> This was further shown by Yamakami and McIntosh<sup>106</sup> in a rat model of concussion, in which there was decreased regional CBF in the perilesional area within 15 minutes and that persisted for at least 2 hours after injury.

A study of human CBF in 125 patients with severe TBI by Martin et al.<sup>50</sup> documents 3 phases of blood flow dynamics. Phase I is characterized by an acutely hypoperfused state, lasting for 1 day. Phase II, beginning on the 2nd day, consists of significantly increased CBF. Phase III, which begins on Day 4, is characterized by vasospasm that may last until 15 days after the inciting injury. Angiographic vasospasm has been shown during the time period designated as Phase III in a separate work.<sup>99</sup> Maugans et al.<sup>53</sup> studied pediatric patients ages 11 to 15 years old. They examined 12 athletes at 3 time points after injury (within 3 days, at 14 days, and 30 days or greater after concussion), comparing blood flow using phase-contrast angiography. These investigators found a significant reduction in blood flow compared with controls at the first time point, which continued through the

final time point (compared with controls). In fact, only 27% of the participants had returned to within 10% of control mean CBF by 2-week measurements, and only 64% by the final time point.

### Breakdown of the BBB

The BBB is the highly regulated separation between the intravascular and extravascular content of the CNS. Blood-brain barrier breakdown is well documented in animal models of severe TBI.<sup>90</sup> Furthermore, a study of patients with postconcussion syndrome demonstrated that BBB disruption can be observed weeks to months after the original insult.<sup>42</sup> The events leading to BBB breakdown are likely multiple in nature. The shearing forces of primary injury are believed to damage the BBB endothelium, resulting in increased small vessel permeability and dysregulation.<sup>93</sup> A metabolic imbalance from ischemic zones of tissue hypoxia likely ensues, potentiating localized BBB destruction. Other mechanisms such as vasospasm, CBF alterations, irregularities in nitric oxide secretion, and coagulopathy may also contribute early after injury. At time points further from injury, astrocyte dysfunction, inflammation-mediated disturbances, and metabolic disturbances may further contribute to, or prolong, BBB breakdown.

Breakdown of the BBB has several untoward consequences. First and foremost, fluid exudation from BBB breakdown results in brain edema. This edema may result in increased intracranial pressure, and lower cerebral perfusion pressure can ensue with sufficient fluid accumulation. Excitotoxicity from neuronal membrane damage may be further exacerbated by the loss of ionic flux control from BBB breakdown, resulting in extravasation of excitatory amino acids. Similarly, as other ions and molecules equilibrate in the serum and CSF, a neuronal microenvironment develops that creates a predisposition for focal seizure activity.<sup>42</sup> Numerous *in vitro* studies of isolated brain slices have demonstrated enhanced cortical excitability, hypersynchronicity, and epileptiform-like activity.<sup>3,81,84,88</sup> These numerous studies provide a possible explanation for the seizure activity noted in animal models of mild head trauma<sup>66</sup> and in several reports in humans.<sup>30,55</sup>

### The Role of Neuroinflammation

The role of immunoexcitotoxicity is significant in TBI. In the brain, microglia play a key role in the initiation of inflammatory events following injury.<sup>20,25,32</sup> As microglia become activated, anti- and proinflammatory cytokines, chemokines, nitric oxide, prostaglandins, trophic factors, free radicals, lipid peroxidation products, and excitatory molecules are released into the extraneuronal space within the 1st postinjury hour and may be present for up to 30 days.<sup>9,78</sup> Some of these chemokines attract peripheral macrophages to the brain to transdifferentiate into microglia and further participate in cytokine release.<sup>77,79</sup>

In normal reactions to a single mild TBI, over time microglia eventually enter a reparative phase composed

of phagocytic activity to repair any debris and damaged cells, and ultimately return to their resting state.<sup>8</sup> With repeated brain injury, microglia may enter a constitutively activated state and become neurodestructive, which may translate into risk for chronic traumatic encephalopathy.<sup>8</sup>

### Sequelae of Repetitive Mild TBI

In the past decade, there has been an increased interest in laboratory research focused on repetitive mild TBI.<sup>2,6,13,14,18,23,38,43,48,76,92,101,109</sup> Most studies have used rodent models, although some have investigated repetitive injury in pigs. DeFord et al.<sup>18</sup> showed that compared with a single episode of mild TBI, repeat injury was associated with impairments in complex spatial learning and cognitive impairment, without overt cell death in the cortex or hippocampus, or BBB compromise. In this study, the authors characterized the head injury as mild by neurological assessment. The latency to right itself and latency to orient to a novel object within an open field (orientation to place) following each injury or sham injury was recorded. Mice were considered oriented to place when stable posture and at least 2 of the following criteria were observed: 1) remained alert for 10 seconds without losing consciousness; 2) attended to the novel object within the open field by sniffing or touching it with forepaws; and 3) demonstrated exploratory behavior by standing up steadily on hind legs to investigate outside the open field.<sup>18</sup> Kanayama et al.<sup>37</sup> demonstrated that repetitive mild TBI caused changes in cortical and hippocampal cytoskeletal proteins, whereas single injury did not. The authors in this study defined the magnitude of “sub-threshold brain injury” that did not induce brain tissue damage by a single hit, and used this magnitude of head impact for mild TBI studies. Laurer et al.<sup>43</sup> showed that a second injury induces both local and regional changes in the cerebral cortex. On the basis of their results, the authors suggested that the brain has an increased vulnerability to a second traumatic insult for at least 24 hours following an initial episode of mild brain trauma. From a behavioral standpoint, the magnitude of mild trauma in this study caused a transient motor deficit following a single hit, as measured on motor neurological score, which resolved by 1 week after injury. This motor deficit was much more pronounced and protracted in the repetitive head injury group. Interestingly, in this model of repetitive injury there were no differences in cognitive testing at any time point in both the single and repetitive mild TBI groups.<sup>43</sup> Another study from this same group used microtubule-associated protein-2 staining techniques to demonstrate that local and remote injury were significantly greater if they occurred in a shorter time window following the initial injury in mice that were observed to exhibit minimal behavioral response following head impact.<sup>48</sup> Some of these studies have reported evidence of CNS injury despite no overt behavioral deficits, consistent with subconcussive injury.<sup>94</sup>

A few studies have found increases in cellular markers associated with Alzheimer disease after repeated mild injuries.<sup>13,37,101</sup> For example, Kanayama et al.<sup>37</sup> showed an increase in tau immunoreactivity in neurons following multiple injuries. Uryu et al.<sup>101</sup> and Conte et al.<sup>13</sup> used a transgenic mouse model of Alzheimer disease–like amy-

loidosis, and demonstrated that amyloid levels and deposits increased in the brain after repeated injuries, but not after a single insult. Yoshiyama et al.<sup>109</sup> used the same transgenic mouse model and analyzed the effects of 4 injuries given per day, once a week, for a period of 4 weeks, in an attempt to simulate dementia pugilistica. After 9 months, only 1 mouse demonstrated pathology consistent with this syndrome. Although the findings were not significant and more work is warranted, such studies suggest that repetitive head injury may be implicated in the development of chronic neurodegenerative disease.

There is a spectrum of neurological sequelae that are likely related to repetitive concussive and subconcussive head injury, including postconcussion syndrome, prolonged postconcussion syndrome, posttraumatic stress disorder, mild cognitive impairment, chronic traumatic encephalopathy, and dementia pugilistica. Likely related to recent increased public awareness of the possible untoward effects of repetitive head injury on athletes and soldiers, there has been a recent surge of data in this field, particularly regarding chronic traumatic encephalopathy. Initially described by Omalu et al. in 2005,<sup>69</sup> chronic traumatic encephalopathy is defined as a progressive neurodegenerative syndrome caused by episodic and repetitive blunt force impacts to the head and transfer of acceleration-deceleration forces to the brain. Chronic traumatic encephalopathy usually presents clinically after a prolonged latent period as a composite syndrome of mood disorders, neuropsychiatric disturbance, and cognitive impairment. Gross examination of the brain reveals normal findings and fails to disclose any area of remote injury, infarction, or atrophy. Direct microscopic brain tissue analysis reveals neuronal loss and hyperphosphorylated tau protein deposits in topographic neurofibrillary tangles and neuritic threads, usually without amyloid plaques, involving various areas of the neocortex and subcortical region, basal ganglia, and brainstem. Such emerging necropsy data has highlighted the importance of subconcussion in the development of neurological injury; however, data are limited to postmortem analysis and at present there is no animal model of chronic traumatic encephalopathy that has been described in the literature. Generally, it takes years before the onset of symptoms of neurodegenerative disorders after an individual has experienced a TBI, and therefore it requires an extremely long time to gather this type of epidemiological data from the human population.<sup>104</sup> Thus, an experimental animal model could truly help decipher the mechanisms by which chronic traumatic encephalopathy, as well as any of the other neurological sequelae such as postconcussion syndrome or mild cognitive impairment, may be triggered by repetitive brain injury.

### Future Directions

Much of what we know regarding the pathophysiology of concussion is gleaned from animal work in more moderate and severe models of TBI. There has been concern over how well prior animal studies have modeled concussion. Injury models such as controlled cortical impact and fluid percussion injury have traditionally involved surgery and injury directly upon the exposed

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brain. Animal choice also presents its challenges. Rodent models allow for genetic manipulation and are typically used in most animal studies for ease and cost; however, the brain anatomy of rodents is quite different than the anatomy studied in larger animal models such as the rabbit, sheep, pig, or nonhuman primate models, and this may affect the injury patterns observed. Additionally, these models have used anesthesia during the delivery of injury, which could confound the observed pathophysiology as well as make it difficult to ascertain any subsequent periods of unconsciousness. Newer models have been developed however, that have adapted these other methods in an attempt to lessen the injury and model mild TBI more effectively.<sup>41,58,61,62,101,109</sup> Another difficult challenge in modeling concussion has been defining and quantifying “mild TBI” for the purposes of animal modeling. The definition and perception of concussion has changed significantly over the last few years, let alone the last decade. In addition, the variable clinical nature with which each concussion presents makes 1 exact animal model not likely feasible.

In an effort to remain clinically applicable, experimental models should likely continue to use minimally invasive methods and those that do not require a craniotomy, such as weight drop models. Models must also be administered at a level that produces minimal, or preferably no fatality. Studies should be careful to clearly characterize how they define concussion within the context of their animal model with regard to behavioral response to injury. Research should also begin to focus on the emerging concept of subconcussion and its potential neurological effects. In addition to varying the injury severity, further research will be needed to investigate the effect of different inter-injury intervals. Consideration will need to be given to the animal of study, as well as choosing appropriate comparison groups and proper end points for analysis. In addition, studies investigating the long-term effects (many months) following injury will be necessary to further elucidate the process of posttraumatic neurodegeneration.

As we further investigate the pathophysiological cascades underlying concussion, particularly repetitive head injury, several points are worth considering. Repetitive injury studies should attempt to evaluate cognitive function, for example using the Morris water maze test, as well as other measures of behavior observed clinically in the postconcussive setting. Pathophysiological mechanisms underlying these behavioral deficits should be pursued, as correlates could pave the way for novel translational treatment approaches. Toward the pursuit of translational treatments, in addition to trying to prevent cells from dying following repetitive injuries, it will be important to learn how to restore normal cellular physiology after head impacts. Combining studies at the cellular and behavioral levels is essential, and one area of interest will be the evaluation of the effects of repetitive TBI on both cortical and hippocampal synaptic plasticity.<sup>104</sup>

Shear strain and tissue deformation caused by rotational acceleration after a closed head injury can result in diffuse axonal damage, and concussion can be viewed as residing at the very mild end of the diffuse axonal injury spectrum.<sup>4,44,51</sup> Typically, diffuse axonal injury presents

histologically with microscopic axonal damage including myelin loss, axonal degeneration, and/or axonal swellings, as observed in much of the bench work previously discussed. These changes, however, are difficult to detect with traditional neuroimaging techniques.<sup>1,24,51,72,74,95</sup> Although there are a number of publications evaluating the sensitivity of MRI in mild TBI,<sup>19,31,35,46,103</sup> no study has addressed the role of MRI in the management of sports-related concussion, which may partly explain the absence of guidelines for the use of MRI as a routine tool in the investigation of concussion.<sup>17</sup> Additionally, the overall availability of MRI machines and costs may limit its routine use. Another important point of consideration that has been raised in several recent reviews<sup>51,59</sup> is that standard structural MRI does not correlate well with the number of self-reported postconcussive symptoms, performance on neuropsychological tests, or long-term outcome.<sup>35,45,67,86</sup>

Yet MRI may still play a role in the workup of the athlete with a head injury, and more importantly, could provide additional insight regarding the structural injury underlying concussion and subconcussion. Newer advanced structural MRI techniques include susceptibility-weighted imaging, diffusion-weighted imaging/apparent diffusion coefficient mapping, quantitative MRI techniques (such as voxel-based morphometry and brain segmentation), diffusion tensor imaging, and high-density fiber tracking. Additionally, advanced functional imaging can possibly supplement behavioral and structural imaging techniques by aiding in the evaluation of the pathophysiological and functional sequelae of concussion;<sup>51</sup> such methods include functional MRI and magnetic resonance spectroscopy. At present, most of these advanced imaging modalities are used primarily as research tools in the area of concussion and TBI in general. The analysis of these advanced neuroimaging techniques requires considerable expertise, both in the reconstruction and in the interpretation of the data. There is also a need for standardization from one study to another.

Although imaging sequences such as diffusion tensor imaging and functional MRI are being used more commonly, their use as a regular tool in the diagnosis and management of concussion in adults and children remains to be seen. Some of the emerging data appear to corroborate some of the laboratory evidence suggesting that there may be a structural component to the injury (axonal injury observed in diffusion tensor imaging studies),<sup>5,29,67</sup> as well as a functional/metabolic component (observed in functional MRI studies).<sup>11,100</sup> The studies thus far have suggested that these two modalities in particular could be used in future research to evaluate treatment efficacy, given their enhanced sensitivity to alterations in the brain.<sup>5,11,16,29,49,67,91,100,110</sup> Future studies may demonstrate that such advanced imaging modalities could potentially direct rehabilitation after concussion and possibly aid in the decision of determining when it is safe for an athlete to return to play,<sup>56</sup> although there is no evidence at the present time to support those conclusions.

## Conclusions

Most scientific studies have focused on moderate

and severe TBI, but concussive and subconcussive head injuries affect more people, occur more frequently, and are an increasingly important silent epidemic because younger patients suffer more mild TBI as a consequence of sports activities and military experience. The science behind concussion continues to evolve at a rapid pace. As we learn more about the pathophysiology and biophysics underlying concussion and repetitive head injury, further questions arise. As this arena of TBI research continues to evolve, it will be imperative that models of repetitive injury replicate injuries in humans as closely as possible. It will also be important to appropriately model concussive episodes and even lower-level injuries (such as subconcussion) as we search for translational treatment approaches as well as answers to how mild TBI results in the observed spectrum of neurological sequelae, particularly chronic neurodegenerative disease.

#### Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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