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Translational models of mild traumatic brain injury tissue biomechanics

Xianghao Zhan[1], Anna Oeur[2], Yuzhe Liu[1], Michael M. Zeineh[3], Gerald A. Grant[4], Susan S. Margulies[2] and David B. Camarillo[1]

Abstract

Traumatic brain injury (TBI) is a global health concern. Mild TBI (mTBI) which accounts for the majority of TBI cases, is hard to detect since often the imaging is normal but can still cause brain damage and long-term sequelae. Physiologically, acute primary damage to the brain is thought to be caused by tissue deformation from the inertial movement of the brain after rapid head rotation. Respecting tissue biomechanics, animal models are often used to understand the pathophysiology of mTBI. We have reviewed the literature focusing on connecting biomechanics with mTBI pathologies at the tissue scale using neuroimaging, neurobehavioral tests, and pathologies across species, particularly studies using strain and strain rate. These studies have found strain and strain rate predict mTBI pathology and strain is generalizable across species, including small animals, large animals, and humans. We propose that researchers can leverage tissue-level strain and strain rate to bridge biomechanics and mTBI pathology.

Addresses

[1] Department of Bioengineering, Stanford University, Stanford, CA, USA

[2] Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, USA

[3] Department of Radiology, Stanford University, Stanford, CA, USA

[4] Department of Neurosurgery, Duke University, Durham, NC, USA

Corresponding author: Zhan, Xianghao (xzhan96@stanford.edu)

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Introduction

TBI is one of the leading causes of disability and death worldwide, particularly for children and young adults [1,2]. The onset of TBI can be attributed to head impacts or rapid head rotation from multiple sources, including but not limited to accidental falls, traffic accidents, various contact sports, and domestic abuse [3–7]. Repetitive mild TBI (mTBI) may cause cumulative brain injury over time and lead to long-term cognitive deficits [8]. It has been postulated that repetitive TBI can lead to neurodegenerative diseases and chronic traumatic encephalopathy in some cases [9,10].

Human patients with a Glasgow Coma Scale (GCS) score of greater than 12 (13–15) are classified as having mTBI. Because of the variability of the outcomes in mTBI in human patients, animal mTBI models have been developed to study mTBI more rigorously [11,12]. In large animal models, in the absence of capturing clinical signs, researchers often define mTBI by the postmortem neuropathological examination of axonal injury [12,13], such that animals with axonal injury volume levels $<0.26\%$ of cerebral volume are classified as below a clinical radiologically detectable level, with no observable cognitive or behavioral deficits [14].

When the head suddenly starts or stops (with or without impact), the resulting brain tissue deformation may lead to mTBI pathology, including blood-brain barrier (BBB) disruption [15] and diffuse axonal injury (DAI) [12,13]. The strain and strain rate (as metrics of tissue-level deformation) are thought to be the key parameters that indicate mTBI risk. The state-of-the-art method to compute the strain-based injury metrics is finite element modeling (FEM) [16–22], which takes the material properties of different animals' brains into consideration [13,23], as well as machine learning head models [24–27]. Different from kinematics-based parameters, the strain-based metrics, which reflect the tissue-level biomechanical loading, may better translate across different species. Therefore, in this study, we will focus on the publications which have investigated the connection between biomechanics, particularly the strain and strain rate, and the mTBI findings as shown by neuroimaging, histopathology, and neurobehavioral tests. We performed a literature search on papers across various species with keywords including "biomechanics," "traumatic brain injury," "strain," "strain rate," "injury threshold." All abbreviations in this review are shown in Table 1. Compared with some newly published review article on the concussion biomechanics in

Table 1

Abbreviations used in this study.

Abbreviation	Meaning
mTBI	Mild traumatic brain injury
GCS	Glasgow Coma Scale
BBB	Blood-brain barrier
FEM	Finite element modeling
FE	Finite element
MPS	Maximum principal strain
MPSR	Maximum principal strain rate
MAS	Maximum axonal strain
MASR	Maximum axonal strain rate
CSDM	Cumulative strain damage: percentage of brain elements with MPS larger than a threshold
CCI	Controlled cortical impact
FP	Fluid percussion
FA	Fractional anisotropy
MD	Mean diffusivity
DTI	Diffusion tensor imaging
CHIMERA	Closed-head impact model of engineered rotational acceleration
AIV	Axonal injury volume
EEG	Electroencephalograph
MMA	Mixed martial arts

contact sports and protective gears [18,19], in this review, we show the mTBI biomechanics across different species with a clear focus on the preclinical studies and translation, which extends beyond human studies. The injury thresholds on tissue-level strain and strain rate have been summarized in Table 2. Readers should take caution when interpreting the injury risk thresholds due to: 1) the models have selection bias caused by under-sampled non-injury cases; 2) the models do not account for the reduced injury tolerance after previous brain trauma; 3) the different FE models used by different researchers (Table 4).

Connecting biomechanics with mTBI pathologies in small animal models

Animal models are crucial translational tools to investigate pathology, diagnostics and therapeutics of many diseases, including TBI and mild TBI (example animal models are listed in Table 3) [36]. Although the brains of the large animal models such as non-human primates, pigs, and sheep are more similar to human brains with a thick skull and gyrencephalic properties, small animal models have much lower cost, and the animal logistics are more feasible.

Small animal models typically involve rodents, and the models can be generally categorized into open-head injury and closed-head injury [36]. The open-head injury typically involves direct brain deformation. Typical examples of open-head injury models include the controlled cortical impact (CCI) [37,38] models and fluid percussion (FP) models [39,40]. In the open-head models, to link biomechanics with mTBI pathologies, Donat et al. [23] developed an FE model for a CCI rat model. Neuroimaging and histopathology were used to quantify TBI pathology. The authors found the maximum principal strain (MPS) threshold of 0.3 and the MPS rate (MPSR) threshold of 2500/s to accurately predict the volume fraction of contusion. Based on the marginal R^2 in linear models, the strain and strain rate explain 33% and 28% variance in the changes in fractional anisotropy, 22% and 16% variance in the changes in orientation dispersion in diffusion tensor imaging (DTI). In another study, Farajzadeh Khosroshahi et al. [41] leveraged the CCI model on 9-week-old rats and developed a multiscale model of cerebrovascular injury. The researchers find large axial stress in the vessels at the locations of fibrinogen extravasation and quantitatively, the multiscale model can accurately predict the location of fibrinogen extravasation with a R^2 of 0.72 when thresholding the stress with a critical value of 200 kPa. This study also found strong correlation between the area of fibrinogen extravasation and the brain area where axial strain in vessels exceeds 0.14. Mao et al. [42] developed an FE model with more than 250,000 hexahedral elements for the rat CCI model and showed that the high strains estimated by the FE model correlated with the experimentally reported contusions, hippocampal cell injury and cortex axonal dysfunction several days post injury.

Closed-head injury models typically involve the impact onto the animal or the rapid rotation of the head movement (inertial loading), and restrained or unrestrained head movement. Examples are weight-drop models [43], the inertial loading model [44,45] and the blast-wave model [46]. In the closed-head injury models, FE models has also been developed and applied. Unnikrishnan et al. [47] developed a high-fidelity 3-D rat brain FE model for blast-wave exposure and validated the model with blast simulation. Zhu et al. [48] developed an FE model with 530,000 hexahedral elements of rat heads subjected to air shock loading. Namjoshi et al. [49] leveraged the closed-head impact model of engineered rotational acceleration (CHIMERA) to induce injury on rats aging from 4 to 5 months (approximately 17 years in humans). This study quantifies the biomechanics loading in the term of impact energy and tested the loading ranging from 0.1 to 0.7 J on inducing neurological deficits, axonal damage, white matter tract microgliosis and astrogliosis. This study shows that 0.5 J is the injury threshold that led to one or more phenotypes and 0.6 and 0.7 J resulted in significant changes in all mTBI outcomes assessed.

Connecting biomechanics with mTBI pathologies in large animal models

In the 1940–60s, large animal models delivered direct, and often multiple head impacts to dogs, cats, and

Table 2

The injury thresholds of mTBI pathology on strain-based injury metrics across different species. It should be noted that the FE models for different species were validated differently.

Species	mTBI	Metric	Threshold	Model Validation	Reference
Human	Concussion[a] (50%)	MPS95	0.271	Profiles of displacement, *in situ* [16]	[16]
Human	Concussion[a] (50%)	MAS95	0.127		
Human	Concussion[a] (50%)	MPS x SR95	6.2/s		
Human	Concussion[a] (50%)	MAS x SR95	1.4/s		
Human	Concussion[a] (50%)	MPS95 (Gray Matter, Corpus Callosum)	0.26, 0.21	Profiles of displacement, *in situ* [28]	[28]
Human	Concussion[a] (50%)	MPSR95 (Gray Matter)	48.5/s		
Human	Concussion[a] (50%)	MPS x SR95 (Gray Matter)	10.1/s		
Human	Concussion[a] (50%)	CSDM10(White Matter)	0.47		
Human	Concussion[a] (50%)	Von Mises Stress(White Matter)	8.4 kPa		
Human	Concussion[a]	CSDM10	0.182	Profiles of displacement, *in situ* [29]	[30]
Human	DAI	CSDM10	0.85	Profiles of displacement, *in situ* [31]	[31]
Human	DAI	CSDM15	0.59		
Human	DAI	CSDM25	0.27		
Human	DAI	MAS	0.1465		
Human	DAI	MASR	80		
Human	Concussion[a] (50%)	Peak MPS	0.20,0.21	Profiles of displacement, *in situ* [32]	[33]
Human	Concussion[a] (50%)	Peak MAS	0.09, 0.1		[33]
Pig	Axonal injury	MPS95	0.286	Strain distribution, *Ex vivo* [16]	[16]
Pig	Axonal injury	MPSR95	140.86		[12]
Pig	Axonal injury	MAS95	0.121		[16]
Pig	Axonal injury	MPS x SR95	24.91/s		[12]
Pig	Axonal injury	MAS x SR95	4.87/s		[12]
Pig	Axonal injury	MASR95	66.45		[12]
Rat	Focal Contusion	Maximum Axial Strain	0.14[b]	No direct validation	[23]
Rat	Focal Contusion	MPS	0.3		
Rat	Focal Contusion	MPSR	2500/s		
Rat	BBBD	MPS	0.18	Cortical displacement, *in vivo* [34]	[34]
Rat	BBBD	Maximal Principal Stress	5.6 kPa		
Multiple Species	Concussion[a] (50%)	MPS95	0.270	-	[16]
Multiple Species	Concussion[a] (50%)	MAS95	0.123		
Multiple Species	Concussion[a] (50%)	MPS x SR95	12.21		
Multiple Species	Concussion[a] (50%)	MAS x SR95	2.622		
Multiple Species	Concussion[a] (50%)	MPS95	0.360		[35]
Multiple Species	Concussion[a] (50%)	MPS99	0.463		
Multiple Species	Concussion[a] (50%)	CSDM15	0.477		
Multiple Species	Concussion[a] (50%)	CSDM25	0.139		

Abbreviations: BBBD: blood-brain-barrier disruption; MPS95: 95th percentile maximum principal strain; MPSR95: 95th percentile maximum principal strain rate; MAS95: 95th percentile maximum axonal strain; MASR95: 95th percentile axonal strain rate; CSDM10: cumulative strain damage (percentage of brain elements with MPS larger than 0.1).

[a] Concussion (clinically defined mTBI) is not strictly recognized as a pathology but a symptom.

[b] No classification models have been developed. Strong correlation between the area of fibrinogen extravasation and the brain area where axial strain in vessels exceeded 0.14 was found.

non-human primates [50–52]. Concussion was defined as a loss of voluntary movement and consciousness because of local tissue response to trauma [52]. Brain deformation was identified as the key contributor to injury, however due to the lack of sophisticated computational models and sensitive measurement tools, head kinematics and physiological responses (heart rate, blood and intracranial pressure, EEG) were correlated with graded concussion [53]. Severity of concussion was correlated to the magnitude and duration of the applied mechanical input to the head [54], with key findings from this research highlighting the importance of rotational kinematics on shear strain deformations linked to diffuse axonal injuries, including mTBI [55].

Current large animal models of mTBI have employed ferrets [56], sheep [57], and swine [58]. Neuroanatomical characteristics such as the skull, falx, and tentorium, gyri, sulci, gray and white matter distinctions are important determinants of the distribution of deformations from head loading as they play an important role in modeling the biomechanics and patterns of human TBI [54,59]. Sheep have been used to model closed head injuries from high-velocity head impacts using a cap gun where the early version of this model

Table 3

Some example animal models for mild traumatic brain injury.

Animal	Model	Biomechanics loading	Characteristics
Rat	CCI	Impact	Can induce graded injury severity, high controllability, no rebound injury, induce focal injury
Rat	FP	Impact	Can induce graded injury severity, high controllability, may induce focal injury
Rat	Blast	Blast wave	More related to military TBI, waves induce ICP changes
Rat	Weight Drop	Rotation	Simple, inexpensive, may lead to highly variable results
Rat	CHIMERA	Rotation	Induce less focal injury, better simulates human mTBI
Ferrets	CHIMERA	Rotation	Induce less focal injury, better simulates human mTBI
Pig	Rapid Rotation	Rotation	Induce less focal injury, better simulates human mTBI
Pig	CCI	Impact	High controllability, no rebound injury
Sheep	Impact Acceleration	Impact	High velocity, rubber bolt reduces skull fracture, can induce graded injury severity

produced axonal injuries similar to human TBI [60]. The latest developments of this model employed a modified bolt with a rubber tip that produced a range of TBI from mild to severe as confirmed using MRI [57]. More recently, CHIMERA was designed to deliver direct and unrestricted head impacts to ferrets. In a study of three 5–6-month-old ferrets sustaining 6–10 head impacts, radio-opaque markers and high-speed cameras tracked dynamic brain motion, confirming the lag in brain motion after the skull started to move [56]. Both the sheep and ferret animal models are under continued development for applications for mTBI, and these studies have demonstrated feasibility of the impact methods employed.

Swine models of TBI have been involved in extensive experimental and advanced computational work because of similarities in anatomy and physiology [61] including the study of diffuse axonal injuries from mild to severe, in addition to focal types of brain injuries [62]. Different ages of swine have been used to capture human infants to adults [63,64]. In regard to mTBI, swine have undergone head rapid non-impact head rotation loading conditions scaled from human levels producing neuropathology (or lack thereof) consistent with mTBI [65], disruption of the blood-brain barrier with a leakage of fibrinogen at regions consistent with axonal injury and gray matter regions as early as 6 h post head rotation in swine [66]. Additionally, neuroinflammation after single and repetitive head rotations were observed in adult swine subject to mild and moderate rotational velocities [67]. In summary, mTBI affects axons, neurons, neurovascular tissues, and microglia.

To model the biomechanics of diffuse brain injury, a finite element model of the swine brain was first developed by [68] to study intracranial hemorrhage associated with rapid head rotation. Later [69], improved the model by adding axonal fiber tractography illustrating that white matter axonal strain is an important correlative to diffuse axonal injury pathology. This model has been recently modified to include anatomical features such as the lateral ventricles, corpus callosum, white matter and axonal structures [12] and was combined with experimental results of piglets experiencing DAI as determined by pathology. The axonal injury volume (AIV) was calculated using these maps for the whole brain and was found to be between 0.02 and 1.65% of cerebral volume [12]. Results of the FE simulations revealed that axonal strain and strain rate were better predictors for DAI in pigs [12], strain response metrics are more related to angular velocity, and that angular acceleration is more related to strain rate measures for rapid head rotations lasting between 12 and 20 ms [65,70]. Additionally, the axonal deformation measured in this piglet FE model was able to predict the location of DAI confirmed from neuropathology within 2.5 mm (brain size: 42–66 mm, number of 3-mm brain slices: 14–22, [13]. Further, this model was used in a study comparing inter-species brain injury metrics employing a baboon and a human FE model. These models were simulated using reconstructions of head acceleration events of no-injury, mTBI, or severe TBI [16]. Finite element simulations of species-specific models yielded stress and strain responses associated with the severity of the different brain injury levels, which were then employed in predictive analyses to establish TBI risk functions (Table 2). Overlapping strain levels across different studies support that strain and strain rate measures may be robust predictors of mTBI and these findings show promise of translatability of pre-clinical animal models to human levels of mTBI.

Connecting biomechanics with mTBI pathologies in human studies

In humans, brain tissue deformation has been linked to the risk of concussion and brain imaging changes. To calculate the brain tissue deformation, real head kinematics during the impacts were measured, which were then given as input to the FE head model [71–73]. In parallel, concussion or non-concussion of patients were diagnosed and recorded to develop logistic risk models

of concussion. The correlations between the changes in MRI scans in specific brain regions and the brain strain and strain rate were tested [74–77].

Kleiven et al. [28] developed the KTH model and simulated brain deformation of 58 reconstructed NFL head impacts with 25 concussions [78]. Instead of brain strain, the maximum pressure over the entire gray matter showed a higher correlation with injury (concussion). Merging the on-field head impacts [79] and a reconstructed NFL dataset [78], Kimpara et al. [30] simulated head impacts and found that 50% risk of concussion corresponded to CSDM of 18.2% for the strain of 0.1. It should be noticed that the NFL dataset was updated because of the sensor issue, and the updated kinematics resulted in an average error of 20% in MPS [80]. Hernandez et al. [81] calculated brain strain and strain rate of head impacts in collegiate football, boxing, and mixed martial arts (MMA) (caveat: only two concussions were in the dataset used to fit the logistic regression model) and found that the peak principal strain in the corpus callosum was the strongest predictor of concussions based on logistic regression. Based on the on-field and reconstructed football head impact datasets, Wu et al. [82] developed a network-based response feature matrix of brain strain, which could predict the concussion cases with high accuracy. Using helmet-mounted sensors, Beckwith et al. [83] collected kinematics from 105 diagnosed concussions and 532 control impacts and calculated the brain strain and strain rate from computational models. Unlike previous studies, the brain strain and strain rate did not improve the estimation of injury risk compared with kinematics.

Besides binary prediction of concussion, researchers have also pursued correlating the brain strain and strain rate with results of MRI scans. Using subject-specific head models McAllister et al. [84] investigated the variations of DTI results along with the brain strain and strain rate in 10 collegiate players who were diagnosed with concussions, and found that brain strain and strain rate at corpus callosum were positively correlated with the change of fractional anisotropy (FA), and negatively correlated with the change of mean diffusivity (MD). Based on a dataset collected from youth football players, Miller et al. [77] examined the correlation between DTI changes and kinematics-based and strain-based injury metrics. Similar to [84], a positive correlation was found between injury metrics and FA, and the strain-based injury metrics were found to outperform kinematics-based metrics. Ghajari et al. [85] developed a high-fidelity head model with modeling the sulci and gyri and predicted large strain most prominent at the depth of sulci, which was consistent with the finding of the distribution of tau pathology in CTE. O'Keeffe et al. [76] instrumented 5 MMA fighters and measured blood-brain barrier (BBB) disruptions after fights. The largest brain strain and strain rate as well as the number of impacts that fighters experienced were found to correlate with the volume ratio of BBB disruption, as estimated from imaging changes, rather than the "gold standard" of neuropathology.

Discussion

Based on the previous publications, the mTBI injury thresholds found across different species can be summarized in Table 2 and the thresholds were compared across different species in Table 4. Across different animal models, there has been generalizability in the relationship between strain-based injury metrics and mTBI pathology. The MPS95 threshold on mTBI was generally within the range between 0.2 and 0.4 and the MAS95 threshold on mTBI was generally within the range between 0.12 and 0.15. On the other hand, the injury thresholds on strain rate vary largely across different species. These findings indicate that strain can be a biomechanics loading metric that can be translated across species. However, one caveat in the translational study is that there is no generalizable definition of mild traumatic brain injury across different species on which researchers widely agree. The definition of mTBI in human beings based on GCS cannot be directly matched with mTBI definitions in animals. Studies on more accurate and generalizable mTBI definitions should be investigated.

With previous studies showing the generalizability of strain as an mTBI predictor, the time scaling effect (e.g., what age in an animal species is equivalent to what age

Table 4

Comparison of the injury thresholds of mTBI pathologies across species based on the injury risk functions fitted on the datasets of different species.

Metric	Human	Pig	Rat	Multiple species[a]
MPS95	0.20–0.271	0.286	0.18–0.3	0.27–0.36
MAS95	0.09–0.1465	0.121	0.14[b]	0.123
MPSR95 (/s)	48.5	140.86	2500	–
MASR95 (/s)	80	66.45	–	–
MPS x SR95 (/s)	6.31–10.1	24.94	–	12.21
MAS x SR95 (/s)	1.4	4.87	–	2.622
CSDM10	0.47–0.85	–	–	–
CSDM15	0.59	–	–	0.477
CSDM25	0.27	–	–	0.139

Multiple thresholds can be found for some metrics because of different pathologies and different studies, and the thresholds of some metrics cannot be found and marked as "-"

[a] The numbers in this column are the injury thresholds found on multi-species datasets, not those calculated from the previous three columns.

[b] No classification models have been developed. Strong correlation between the area of fibrinogen extravasation and the brain area where axial strain in vessels exceeded 0.14 was found.

in humans; and how do days or weeks after injury in rats of pigs translate to post-injury timepoints in humans) when translating from species to species should be elucidated. The time scaling effect has been under investigation over the past years [86], but lacks the sophistication of these more nuanced time course issues. Firstly, in previous studies, animal models with different ages were used by researchers to reflect the TBI effects on humans of different age groups [12,23]. Secondly, the time scaling effect can also affect the injury thresholds because the thresholds associated with acute neuropathological presentation may differ from thresholds associated with persistent neuropathologic features (of note, Tables 2 and 4 combined all the data available without distinguishing acute versus persistent thresholds). Thirdly, the time window in which significant changes in the metrics of DTI can be detected on an animal model may not reflect the actual time window in which such changes can be observed in humans. Lastly, typical animal studies sacrifice subjects within a week after the exposure to the impact or rotational load. In the future, in addition to selecting animals to represent the human age group of interest, we propose investigating neuroradiological and pathological evidence of mTBI to determine injury thresholds in animal models at specified acute and longer-term post-injury timepoints that are relevant to humans and scaled to animals. Given the attention to mTBI effects in humans lasting months and years, we recommend animal studies that capture the long-term neuroimaging, behavioral and histopathology evidence, to distinguish persistent from transient features.

It should be mentioned that in this study, the focus has been placed on the tissue-level mechanical properties in cross-species mTBI predictions, which is limited in the information for the predictions. In the future, the cross-species differences in the brain-skull interface conditions and cellular-level tolerance criteria and their influence on the predictions of mTBI should be further investigated. In addition, most of the injury thresholds in animal models are defined by the structural damage, consistent hallmarks of more severe brain injury, and less consistent fingerprints in mTBI, which is more typically diagnosed by symptoms and neurodysfunction. However, mTBI should be defined by brain functional damage. In the future, more studies relating the biomechanics with the neurobehavioral test results and brain functional damage should be done.

As more mTBI diagnostics approaches and modalities are developed, more studies will investigate the relationship among the biomechanics loading, neuroimaging biomarkers, neurobehavioral tests, blood biomarkers, cerebral spinal fluid biomarkers, and histopathology. Therefore, it is also worthwhile to comprehensively test the effectiveness and generalizability of the biomarkers in different animal models and loading conditions. For example, in small animal models, diffusion MRI has been recently combined with FEM and histopathology in CCI models [23]. In large animal studies, neurobehavioural tests have been combined with FEM and histopathology in swine models [87]. In clinical studies with TBI patients, microdialysis of interstitial fluid in the brain has been used to investigate various biomarkers in characterizing TBI [88]. Whether the biomarkers associated with specific species can be translated across different species is still open to investigation and these studies can be significant in proving that the biomarkers can be translated to clinical studies.

In the term of correlating biomechanics with pathologies, the studies which focus on the spatial distribution are still limited. Although there have been researchers investigating the prediction of traumatic axonal injury locations with whole-brain MPS and MAS [13], most previous studies leverage scaler metrics (e.g., MPS95, MPSR95, CSDM) to predict the binary outcome of mTBI. These metrics are deemed as limited without the consideration of spatial distribution and there have been studies showing the concern regarding the facts that the injury tolerance can be spatially different, and the variance and sensitivity of different metrics such as MPS, MPSR, MPSxSR can be spatially different [18,89]. Considering the neuroimaging results (e.g., DTI metrics) are generally spatially distributed, the correlation between biomechanics metrics and the pathologies should be further investigated beyond the scaler metrics.

The validation of FE models are important to interpret the brain strain and strain rate results. Human brain deformation during head impact of cadaver were measured by high-speed x-ray and sonomicrometry [90–92], and the human FE head models were validated by comparing the displacement–time profiles of the trackers. Different from humans, the only available brain deformation data for pigs is ex-vivo: the pig brain was placed into a cylindrical canister and the brain strain was measured by tracking ink marks on brain tissue using high-speed cameras [12]. The brain deformation data for rats is missing except the study where the brain was injured by vacuum pulse [34]. Considering the different validations of the FE models for different specifies, we think the specific values listed in Tables 2 and 4 may vary when the animal FE head models are validated against more accurate measurement of brain deformation. In order to translate the preclinical results, we also think measuring brain deformation of animals using the methods for humans is necessary.

Several concerns associated with the broad idea of injury risk models also worth discussion: as pointed out by a newly published review article [18], firstly, the injury risk models are generally affected by the selection bias because of the severe under-sampling of non-injury

cases; secondly, the injury risk models do not account for the reduction in the injury tolerance caused by the accumulation of previous brain injury; furthermore, the comparison across different injury risk models can be hard due to the different datasets and FE models used by different researchers as well as the different approaches to validate these FE models. Because Therefore, the readers should interpret the thresholds with caution. In the future, more studies that seek to address these concerns should be done to validate the injury threshold values.

Additionally, different researchers tend to use different metrics to quantify the biomechanics loading of mTBI and investigate the relationship between the metrics and mTBI pathology. Strain-based metrics, kinematics-based metrics, the height and weight of dropping weights and the impact energy have all been used in previous studies to describe biomechanics loading. As the brain is damaged due to tissue-level deformation, strain-based metrics may better represent the proximal causal biomechanical mechanism of mTBI. Therefore, in the future, we recommend standardizing the use of strain-based metrics for injury thresholds and target loading conditions for animal studies instead of head kinematics or weight drop heights, as strain-based metrics offer more relevant loading conditions that are independent of species.

Declaration of competing interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: David Camarillo reports a relationship with Savior Brain Inc. that includes: board membership, consulting or advisory, equity or stocks, and funding grants.

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Brief description: The authors modified a previously developed pig FE model to include anatomical features such as the lateral ventricles, corpus callosum, white matter and axonal structures and was combined with experimental results of piglets experiencing traumatic axonal injury (TAI) as determined from pathology maps. The axonal injury volume (AIV) was calculated using these maps for the whole brain and was found to be between 0.02 and 1.65% (Hajiaghamemar et al., 2020). Results of the FE simulations revealed that axonal strain and strain rate were better predictors for TAI in pigs.

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Brief description: In this study, the authors created a multi-scale FEM of the pig brain with embedded axonal tracts to estimate the sites of traumatic axonal injury. The authors showed that firstly, the distributions of the FEM-derived brain/axonal deformations spatially correlate with the locations of acute DAI. Secondly, the axonal deformation measured in this piglet FE model was able to predict the location of DAI confirmed from neuropathology within 2.5 mm

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Brief description: This pig FE model with embedded axonal fiber was used in a study comparing inter-species brain injury metrics employing a baboon and a human FE model. These models were simulated using reconstructions of head acceleration events of no-injury, mTBI, or severe TBI. Finite element simulations of species-specific models yielded stress and strain responses associated with the severity of the different brain injury levels which were then employed in predictive analyses to establish TBI risk functions. The authors showed that when the human and animal datasets were combined, the injury analysis was able to delineate maximum axonal strain (MAS) as the best predictor of injury for all species and TBI severities, with maximum principal strain (MPS) as a suitable alternative metric. Overlapping strain levels supports that strain and strain rate measures may be robust predictors of mTBI and these findings show promise of translatability of pre-clinical animal models to human levels of mTBI.

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Brief description: This newly published review article reviews the studies investigating the relationship between biomechanics and mTBI in contact sports. Multiple finite element (FE) models have been investigated, in which the head impact kinematics are translated into brain mechanical responses through physics-based computational simulations. This review also presented lots of perspicacious ideas on the validation of the FE models in investigating the injury biomechanics of mTBI and the data-science approaches in this research field to facilitate the injury risk monitoring and prevention in contact sports.

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Brief description: The relationship between biomechanical forces and neuropathology is key to understanding traumatic brain injury. The authors developed a finite element (FE) model for the mouse and delivered injury on the rats aging from 8 to 9 weeks with controlled cortical impact (CCI). Neuroimaging with *in vivo* MRI and histopathology were used to quantify the TBI pathologies, which showed that the strain and strain rate predict the location of focal contusions, moderate CCI impact causes a marked thinning of the corpus callosum segments subjected to the highest strain, strain and strain rate are the predictors of the white matter imaging abnormalities and glia activation. The authors found the maximum principal strain (MPS) threshold of 0.3 and the MPS rate (MPSR) threshold of 2500/s to accurately predict the volume fraction of contusion. Based on the marginal R^2 in linear models, the strain and strain rate explain 33% and 28% variance in the changes in fractional anisotropy, 22% and 16% variance in the changes in orientation dispersion in diffusion tensor imaging (DTI). Additionally, 35% and 26% variance in the change of thickness of corpus callosum, 51% and 73% variance in the change of IBA1+ cells, 52% and 23% variance in the change of GFAP + cells are explained by strain and strain rate, respectively. The results provide support for the use of this model in understanding the relationship of biomechanics and neuropathology

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Brief description: The authors leveraged the CCI model on 9-week-old rats and developed a high-fidelity multiscale model of cerebrovascular injury. The researchers find large axial stress in the vessels at the locations of fibrinogen extravasation and quantitatively, the multiscale model can accurately predict the location of fibrinogen extravasation with a R^2 of 0.72 when thresholding the stress with a critical value of 200 kPa. This study also found strong correlation between the area of fibrinogen extravasation and the brain area where axial strain in vessels exceeds 0.14.

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Brief description: In this study, a pig model of traumatic axonal injury (TAI) was used to examine a wide range of the biomechanics loading on the head in two directions. The correlation between either the FEM-derived tissue deformations or the head rotational kinematics and the pathology-evidence TAI was examined. Peak angular acceleration and maximum strain rate of axonal fiber and brain tissue showed good correlation to the volume of TAI, with similar correlation trends for both directions separately or combined. These rotational kinematics and tissue deformations can estimate the TAI volume. The relationships between the head kinematics and the tissue strain, strain rate, and strain times strain rate demonstrate that peak angular velocity and acceleration affect the underlying tissue deformations and the knowledge of both help to predict TAI risk. These relationships were combined with the injury thresholds, extracted from the TAI risk curves, and the kinematic-based risk curves representing overall axonal and brain tissue strain and strain rate were determined for predicting TAI.

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