Clinical Biomechanics 64 (2019) 114–121

Contents lists available at ScienceDirect

Clinical Biomechanics

journal homepage: www.elsevier.com/locate/clinbiomech

Biomechanical simulation of traumatic brain injury in the rat

John D. Finan

NorthShore University Health System Research Institute, 1001 University Place, Evanston, IL 60201, United States

ARTICLE INFO

Keywords:
Traumatic brain injury
Rat
Biomechanics
Finite element modeling

ABSTRACT

Background: Traumatic brain injury poses an enormous clinical challenge. Rats are the animals most widely used in pre-clinical experiments. Biomechanical simulations of these experiments predict the distribution of mechanical stress and strain across key tissues. It is in theory possible to dramatically increase our understanding of traumatic brain injury pathophysiology by correlating stress and strain with histological and functional injury outcomes. This review summarizes the state of the art in biomechanical simulation of traumatic brain injury in the rat. It also places this body of knowledge in the context of the wider effort to understand traumatic brain injury in rats and in humans.

Methods: Peer-reviewed research articles on biomechanical simulation of traumatic brain injury in the rat were reviewed and summarized.

Findings: When mathematical models of traumatic brain injury in the rat first emerged, they relied on scant data regarding biomechanical properties. The data on relevant biomechanical properties has increased recently. However, experimental models of traumatic brain injury in the rat have also become less homogeneous. New and modified models have emerged that are biomechanically distinct from traditional models.

Interpretation: Important progress in mathematical modeling and measurement of biomechanical properties has led to credible, predictive simulations of traditional, experimental models of traumatic brain injury in the rat, such as controlled cortical impact. However, recent trends such as the increasing popularity of closed head models and blast models create new biomechanical challenges. Investigators studying rat brain biomechanics must continue to innovate to keep pace with these developments.

1. Introduction

Traumatic brain injury (TBI) remains a devastating and intractable cause of morbidity and mortality around the world. The Centers for Disease Control defined TBI as 'injury to the head (arising from blunt or penetrating trauma or from acceleration–deceleration forces) that is associated with symptoms or signs attributable to the injury: decreased level of consciousness, amnesia, other neurological or neuropsychological abnormalities, skull fracture, diagnosed intracranial lesions—or death' (Thurman et al., 1999). Mild TBI, also known as concussion, was once considered a temporary phenomenon. However, recent investigations show that mild TBI increases the risk of Parkinson's disease (Crane et al., 2016; Gardner et al., 2015) and can also cause chronic traumatic encephalopathy (CTE) (McKee et al., 2015). Disability due to TBI is sometimes permanent and severe (Roozenbeek et al., 2013). 52,000 deaths due to TBI occur in the United States every year in addition to 275,000 hospitalizations (Faul et al., 2010). The enormous burden of TBI has motivated concerted efforts to understand and treat the condition. Recently, exciting investigations have brought us closer to fully understanding how physics and biology interact to cause morbidity after a head impact. Rat models are vital to this work because they are the most commonly used pre-clinical models of traumatic brain injury.

2. Historical perspective on pre-clinical models of traumatic brain injury

World War II motivated the pioneering work (Denny-Brown and Russell, 1941) that launched the modern era of pre-clinical TBI research (Gennarelli, 1994). Previously, head impact was thought to cause unconsciousness by compressing the skull and squeezing blood out of the brain. Denny-Brown and Russell argued that head acceleration, not compression, was the primary mechanism of closed head injury in humans. The dogma of acceleration-induced head injury became widely accepted during World War II (Stone et al., 2016). Cairns (a neurosurgeon) and Holbourn (a physicist) concluded that rotational acceleration of the head was the mechanical cause of TBI (Holbourn, 1943). Gurdjian and Lissner, a similar team of a neurosurgeon and an engineer, argued that linear acceleration was at least as important as rotational acceleration (Gurdjian and Lissner, 1944). They produced the Wayne

E-mail address: jfinan@northshore.org.

https://doi.org/10.1016/j.clinbiomech.2018.01.015
Received 15 September 2017; Accepted 18 January 2018

State Tolerance Curve (WSTC), which estimated the injury risk using the magnitude and duration of linear acceleration. The WSTC was based on experimental measurement of the acceleration pulses required to cause skull fracture in impact testing of human cadaver heads (Gurdjian et al., 1966). This curve evolved into the foundation of most modern safety standards (D.O.T., 2017a, b; UNECE, 2017a, 2017b). Today, acceleration is considered the primary cause of closed head injury in humans. This consensus is based on animal studies showing that acceleration without impact can induce TBI (Meaney et al., 1995). Despite this consensus, the compression mode of injury remains popular in pre-clinical models, including rat models. The human brain is more vulnerable to acceleration loads than compression loads in a blunt impact but for the rat, the opposite is true. This difference is the reason why biomechanical simulations are so important: they allow rat experiments to be related to human injuries at the level of stress and strain – which may act on neurons in similar ways across species – rather than at the level of force and acceleration – which certainly act on the head in different ways across species.

2.1. Acceleration models of TBI

Humans are more vulnerable to acceleration-driven TBI than almost any other species because their brains are bigger than those of any practical model animal. The force due to acceleration is proportional to mass and therefore to volume. Stress is force divided by cross-sectional area. Therefore, stress due to acceleration is proportional to volume and inversely proportional to cross-sectional area. The square-cube law states that volume increases with size more rapidly than area because volume scales with the cube of length while area scales with the square of length. Therefore, the bigger the brain, the more stress it bears when accelerated. The acceleration applied to the smaller brain of an animal must be scaled up to truly replicate the stress in the human brain (Ommaya et al., 1968). Unfortunately, in addition to having smaller brains, model animals, particularly rodents, have thinner, weaker skulls than humans. It is difficult to apply enough impact force to the rat head to induce an injurious acceleration without deforming the skull on contact and compressing the underlying brain tissue. Marmarou et al. bonded a metal disk to the skull at the point of impact to spread impact forces across the skull while inducing large accelerations (Marmarou et al., 1994). Other investigators have gone to even greater lengths to spread forces imparting acceleration across as much of the rat skull as possible (Davidsson and Risling, 2011; Fijalkowski et al., 2007; Namjoshi et al., 2014). The challenge of repeatably generating these large accelerations without deforming the skull deters some from adopting acceleration-based models.

2.2. Compression models of TBI

Compression injury has evolved into two main forms, controlled cortical impact injury (CCI) (Dixon et al., 1991) and fluid percussion injury (FPI) (Dixon et al., 1987). Both require a craniotomy to expose the brain. In CCI, a rigid, mechanical piston is indented rapidly into the cortex to a prescribed depth for a prescribed time and then retracted. In FPI, the brain is loaded with a pressure pulse in a column of fluid. CCI induces a focal contusion while FPI induces diffuse injury. These insults differ biomechanically from clinical closed head injury because the brain is loaded directly through an open skull. Nevertheless, the experimental pathology reproduces some aspects of clinical pathology in a repeatable fashion and these models are widely used. For most of the twentieth century, almost all animal models in TBI could be categorized as either compression or acceleration-type models. However, recently, armed conflict has again changed the direction of the field, introducing new models and new biomechanical challenges.

2.3. Blast models of TBI

The nature of combat has changed during recent conflicts in Afghanistan and Iraq. Improvised explosive devices (IEDs) are now used more frequently (DePalma and Hoffman, 2018). IEDs caused almost 80% of U.S. casualties between 2001 and 2005 (Owens et al., 2008). The sudden challenge of coping with many blast injured veterans has triggered determined efforts to understand blast-induced TBI. Postulated mechanisms of blast-induced TBI include head acceleration, direct transmission of the pressure wave into the brain and indirect transmission of the pressure wave into the brain via the thorax. However, the relative contributions of these mechanisms are currently unclear (Courtney and Courtney, 2015). Most pre-clinical models employ shock tube devices that reproduce the blast overpressure wave (Effgen et al., 2012; Panzer et al., 2012a). Blast models are difficult to categorize into the scheme of acceleration and compression models presented above. Some are designed to eliminate head acceleration while others allow substantial head acceleration. The blast wind may cause the skull to flex inwards, compressing the brain (Bolander et al., 2011). The blast wave induces deviatoric strains of small magnitude but high rate as it traverses the brain (Panzer et al., 2012b). In short, blast injury can be described as part acceleration injury, part compression injury and part neither, depending on the details of the particular blast model.

2.4. Repetitive models of mild TBI

Interest in repetitive mild TBI has increased in recent years. This interest stems from evidence that repeated mild TBI among military veterans, athletes and other highly exposed individuals leads to a form of neurodegeneration called chronic traumatic encephalopathy (McKee et al., 2016). This trend has motivated modifications of popular models. CCI and FPI require a craniotomy and the Marmarou drop weight model requires attachment of a steel disk to the exposed skull. Maintaining or repeating these modifications for repeated injuries is not trivial. Different labs have adapted these models for repetition in different ways so models have proliferated and diverged. Several groups strike the intact skull of the rat with a piston. Some strike the intact scalp with a steel indenter (Prins et al., 2010; Thomsen et al., 2016) while others use a rubber-tipped indenter (Petraglia et al., 2014). All these adaptations change the biomechanical insult and create new simulation challenges.

2.5. Comparison of rat models to other pre-clinical models

In most neurological disorders, rodent models are used for proof-of-concept, large animal models are used for translational studies and non-human primate models are used for final validation before clinical trial. Important TBI work has been done with non-human primate models (Ommaya et al., 1966; Ommaya and Hirsch, 1971) but recently, animal welfare controversies have reduced activity in this area. The most popular large animal model in TBI today is the pig, which has been applied in controlled cortical impact (Dekker et al., 2014; Sindelar et al., 2017), fluid percussion (Kim et al., 2014) and non-impact inertial loading (Margulies et al., 2015; Meaney et al., 1995). Large animals such as pigs and sheep are useful for studies of severe injury because they can receive respiratory support and vital signs monitoring like a human patient in intensive care (Manley et al., 2006; Vink et al., 2008). These animals also have human-like, gyrencephalic (i.e. folded) neuroanatomy. Ferrets are a cheaper large animal model with gyrencephalic anatomy (Schwerin et al., 2017). Rats have simpler, unfolded neuroanatomy and are more phylogenetically remote from humans than larger animals. The chief reason for their popularity is cost. Rat models also benefit from the large body of knowledge accumulated through the use of rats across neuroscience. Behavioral protocols for measuring cognitive function in the rat are more refined than in larger animal models. Mouse models have also recently become popular (Zhang et al., 2014). The mouse head is biomechanically even

less human-like than the rat, with a smaller brain and a thinner skull. Nevertheless, the genetic tractability of the mouse is advantageous for certain, experimental questions.

2.6. The role of biomechanical simulation in pre-clinical TBI research

More than 30 clinical trials have been conducted in TBI without a single success (Kabadi and Faden, 2014). The most recent phase III trial, which addressed progesterone therapy, failed after > 300 positive animal studies (Stein, 2015). Clearly, the pathophysiology and treatment of TBI differ between humans and model animals. These differences must be understood so they can be accounted for when interpreting results. These differences exist on several levels: genomic, transcriptomic, proteomic, functional and biomechanical. The distribution of stress and strain across key tissues during head impact differs widely between the rat and the human. This difference can in theory be accounted for using biomechanical simulations of each event. There is therefore an urgent need for biomechanical simulations of TBI in the rat that can provide the credible, quantitative predictions required to compare human and rat TBI at the level of mechanical strain.

3. Experimental measurement of rat brain biomechanical properties

3.1. Selecting a constitutive law

The biomechanical properties of brain tissue are constants relating stress to strain in a constitutive law. There are many important phenomena to consider in selecting a constitutive law. Severe injury events occur at large strains (Morrison 3rd et al., 2003), creating both geometric and material non-linearity (Miller and Chinzei, 1997). Properties differ in tension and compression (Miller and Chinzei, 2002) and are rate-dependent (Galford and McElhaney, 1970). Some brain regions are anisotropic because they have directed microstructure (Prange and Margulies, 2002). In magnetic resonance elastography (MRE) studies, blood perfusion influenced brain stiffness (Chatelin et al., 2016; Hetzer et al., 2018) but in an indentation study applying larger strains, it did not (Gefen and Margulies, 2004). Brain tissue can be modeled as a triphasic material consisting of a porous solid, a permeating fluid and an ionic phase (Lai et al., 1991). Ions accumulate near fixed charges in the solid and create osmotic pressure in the fluid. This theory explains brain edema due to failed fluid regulation after trauma (Elkin et al., 2010b) and suggests novel therapeutic countermeasures (Elkin et al., 2011b; Finan et al., 2016). Careful judgements must be made about which of these phenomena to incorporate into the constitutive law.

3.2. Executing experimental measurements

Measuring the mechanical properties of the brain presents challenges in any species. The tissue is soft so forces associated with deformation are low and therefore vulnerable to signal-to-noise problems. Conventional material testing relies on homogenous loading modes. A sample of material is fixed between two platens and subject to a load or displacement boundary condition that induces homogeneous deformation (Jin et al., 2013). Cutting these sample shapes out of the brain in a reproducible fashion is non-trivial. Furthermore, the brain consists of several distinct anatomical structures with different biomechanical properties (Elkin and Morrison, 2013). These differences affect how strain distributes across structures (Mao et al., 2013). Different structures have different functional roles. Therefore, the distribution of damage determines functional outcome. Measurements of structure-specific properties require small samples from each structure which are even more difficult to prepare. All of these challenges are compounded when the brain in question is small so biomechanical investigation of the brain began in humans and large animal models (Ommaya, 1968).

3.3. Brain stiffness measurement in humans and large animals

Experimental investigations of the stiffness of human brain date back over fifty years and reported values vary across a wide range (Chatelin et al., 2010). Some of this variability arises from inconsistent methods. Brain tissue degrades and stiffens quickly post-mortem (Garo et al., 2007). Early studies used tissue from autopsy (Fallenstein et al., 1969; Galford and McElhaney, 1970; Shuck and Advani, 1972) and so were delayed by the autopsy process. They reported short term moduli between 5 and 10 kPa. The first values not influenced by these delays were substantially lower (Prange and Margulies, 2002). Important lessons have been learned over time and, as a result, more recent investigations report softer, more consistent, mechanical properties for the human brain (Budday et al., 2017). Conventional homogeneous loading modes have been widely used in human brain biomechanics (Jin et al., 2013) but they are difficult to apply to small structures. Indentation loading is a convenient way to test small structures because the results depend on the stiffness of a small volume close to the tip of the indenter. The Hertz contact theory relates load to stiffness during indentation. The associated assumptions can be difficult to satisfy experimentally, although finite element modeling can address this (Finan et al., 2014; Pierrat et al., 2018). Indentation has been used to measure human brain stiffness in small tissue specimens resected during surgery (Finan et al., 2017). Slices of pig tissue were indented to measure the regional variation of stiffness (Chen et al., 2015; Kaster et al., 2011).

3.4. Indentation studies in rats

The first direct measurements of the biomechanical properties of the rat brain employed indentation (Gefen et al., 2003). Whole rat brains were hemispherically indented either directly via a craniotomy or through the intact skull. For direct brain indentation experiments, the shear modulus was computed from the indentation load using the Lee and Radok solution for indentation of a viscoelastic half space (Lee and Radok, 1960). This solution assumes quasi-linear viscoelasticity (QLV) i.e. that stress is a separable function of strain and time. This allows an elastic solution (the Hertz contact solution in this case) to be converted to a viscoelastic solution by replacing the constant modulus with a function of time. The Lee and Radok solution inherits the assumptions of the Hertz contact solution. The brain is modeled as a homogeneous, infinite half space. The mechanical properties of the 'brain case' (i.e. the skull, sutures and meninges) were determined using inverse finite element analysis. The brain softened as the animal aged without any changes in the stiffness of the brain case. Shear modulus values for brain were rate-dependent and varied between 0.4 and 3.4 kPa depending on experimental conditions, age and timing. The brain case had an effective elastic modulus of 6.3 MPa.

In 2009, thin slices of rat brain stem tissue were cylindrically indented to measure their stiffness (Shafieian et al., 2009). The tissue slices were too thin to be approximated as an infinite half space so a correction factor to account for finite thickness effects was introduced (Hayes et al., 1972). The QLV model employed a hereditary integral. The hereditary integral eliminates the assumption of an infinitesimal, indentation, ramp time. It therefore allows the model to describe more rapid events. Instantaneous shear moduli were between 5 and 9 kPa depending on preconditioning, history of injury (injury softened tissue) and location. These values are somewhat higher than other reports (Elkin and Morrison, 2013; Finan et al., 2012a, 2012b) and may reflect application of infinitesimal strain theory to large strain experiments. Cylindrical indentation was later applied systematically across multiple regions on three orthogonal planes in the rat (Elkin and Morrison, 2013; Finan et al., 2012a, 2012b). These studies reported short term shear moduli of 0.7–3.6 kPa depending on the structure, age and orientation of the cut plane.

3.5. Atomic force microscopy studies in rats

The atomic force microscope (AFM) indents surfaces with exquisite spatial resolution, making it well-suited to measuring very local mechanical properties. AFM indentation was used to measure strain-dependent moduli at various locations in slices of the rat hippocampus (Elkin et al., 2007). Apparent elastic moduli were 100–300 Pa, depending on location and indentation depth. Cortex was stiffer than hippocampus in juvenile rats but this trend reversed in adults (Elkin et al., 2010a). Slices of rat cerebellum were indented with AFM (Christ et al., 2010). The effective elastic modulus was 100–600 Pa, depending on the location and indentation depth, and grey matter was stiffer than white mater. More recently, AFM indentation showed that injury softens the brain and spinal cord (Moeendarbary et al., 2017), in agreement with previous investigations (Alfasi et al., 2013; Shafieian et al., 2009). Elastic moduli of the intact cortex were 200–300 Pa. All AFM studies of the rodent brain to date have neglected viscoelastic effects.

3.6. Magnetic resonance elastography

In magnetic resonance elastography (MRE), vibration is applied to the brain while it is being imaged and the phase and amplitude of the resulting motion are analyzed to determine viscoelastic properties (Bayly et al., 2012). MRE has important advantages. It is non-destructive so it can be applied repeatedly to the same animal (Pong et al., 2016) or human subject (Klatt et al., 2015) and it provides a high resolution, three dimensional map of viscoelastic properties. Its primary disadvantage is that it is confined to small strains (Clarke et al., 2011) so data must be extrapolated to model large strain events associated with injury. This issue can be addressed by inducing a large, static strain in a sample and then characterizing the compressed sample using MRE (Clarke et al., 2011).

4. Mathematical modeling of TBI in the rat

Mathematical modeling of rat TBI has historically been hampered by the paucity of available data on the mechanical properties of the rat head. Early investigators often resorted to using properties measured in other species. As described above, many of these properties have recently been measured in the rat. However, mathematical models continue to advance, adding new deformable components that require new biomechanical property data. Mathematical models must also be validated against experimental data. It is difficult to collect experimental data that approaches the level of detail in model output. Therefore, progress in mathematical modeling depends directly on experimental progress in TBI biomechanics (see Fig. 1).

4.1. Simulation of dynamic cortical deformation

The first FEM of rat TBI addressed a novel injury model called dynamic cortical deformation (DCD) (Shreiber et al., 1997). DCD involved applying a known vacuum pressure to a craniomtomy and measuring the resulting displacement of the brain surface. A finite element mesh of the rat brain was created using an atlas. The skull was rigid, the ventricles were omitted and the brain was homogeneous and viscohyperelastic. Human brain stiffness data was used because no relevant rat data was available. The selected shear modulus, 20,684 Pa, exceeded values reported in subsequent, experimental studies (Finan et al., 2012a, 2012b). The model was validated by comparison of the predicted displacement of the cortical surface to experimental measurements. Evans Blue was used to measure blood brain barrier (BBB) breakdown in experimental animals. Correlation of these images with model output suggested that strain > 19% compromised the BBB.

4.2. Simulation of CCI

The first FEM of rat TBI to assign different mechanical properties to different anatomical structures was published in 2006 (Mao et al., 2006; Mao et al., 2010a; Mao et al., 2010b). The skull was rigid and the grey matter, white matter, ventricles, spinal cord, dura and pia arachnoid tissues had independent mechanical properties. The geometry was extracted from an atlas. Viscoelastic shear moduli for brain grey matter were taken from experimental measurements in rats (Gefen et al., 2003). White matter structures were assigned a modulus equal to 70% that of grey matter, based on porcine studies (Prange and Margulies, 2002). The modulus of the dura matter was assumed to be 31.5 MPa based on a prior human FEM (Zhang et al., 2001). The elastic modulus of the pia arachnoid complex was assumed to be 12.5 MPa based on bovine studies. A time constant of 20 ms was applied to model viscoelastic effects for consistency with human FEMs (Zhang et al., 2001). The model was validated against DCD data (see Section 4.1). CCI studies in the literature were simulated and output strain fields compared to neuronal damage in histology. The strain threshold for damage was 0.3. This model was updated (Mao et al., 2013) after the publication of structure-specific rat brain properties (Elkin et al., 2011a). This study concluded that CA3 sustained more cell death than CA1 during CCI because it underwent more tensile strain.

4.3. Simulation of rotational acceleration models

The group at Strasbourg University first published their FEM of rat TBI in 2009 (Baumgartner et al., 2009). The geometry of the head was taken from MRI and micro-computed tomography (microCT) images. This model included a mechanically homogeneous, viscoelastic brain, a deformable skull, and a ‘brain skull interface’ structure representing the CSF and meninges. The properties of the skull and the brain skull interface were taken from human FEMs (Baumgartner and Willinger, 2004; Zhang et al., 2001). The viscoelastic properties of the brain tissue were taken from rat experiments (Gefen et al., 2003). This FEM was used to simulate a rotational acceleration rat injury model (Davidsson and Risling, 2011). These authors noted the paucity of experimental data for mechanical properties and output validation at the time. Another FEM of rotation-induced closed head injury was also presented in 2009 (Fijalkowski et al., 2009). Mechanical properties were iteratively adjusted from initial values until the model successfully distinguished injurious and non-injurious events scaled from primate experiments. A subsequent iteration of the Strasbourg FEM (Lamy et al., 2013) cited Fijalkowski et al.'s study and used its initial values for brain material properties. Experimental rat TBI histology due to rotational acceleration was compared to the output of the model to determine that both the magnitude and duration of stress influenced the severity of injury.

Koshiro Ono developed a simulation of rotational acceleration injury in collaboration with a group of Swedish investigators (Antona-Makoshi et al., 2014). This simulation also used the rotational head injury model by Davidsson et al. as its experimental reference (Davidsson and Risling, 2011). The rotational experiments were repeated with a 0.5 mm pin projecting from the skull into the brain. During the insult, the brain moved relative to the skull, generating a scar in the tissue. The length of this scar quantified relative motion between the brain and the skull. This value was compared to model output to validate it. Anatomical regions of the brain were assigned distinct mechanical properties from rat experiments (Elkin and Morrison, 2013). The skull was rigid and the dura mater and pia arachnoid were elastic membranes with a Young's modulus of 40 MPa based on prior human FEMs (Zhang et al., 2004). This study found that shear strains peaked in the hippocampus, potentially explaining its vulnerability to TBI. A subsequent iteration of the model addressed the changes in brain stiffness and volume with age (Antona-Makoshi et al., 2015). In this iteration, the pia mater was assigned a stiffness of 30 MPa, based on a prior experimental study of porcine pia mater

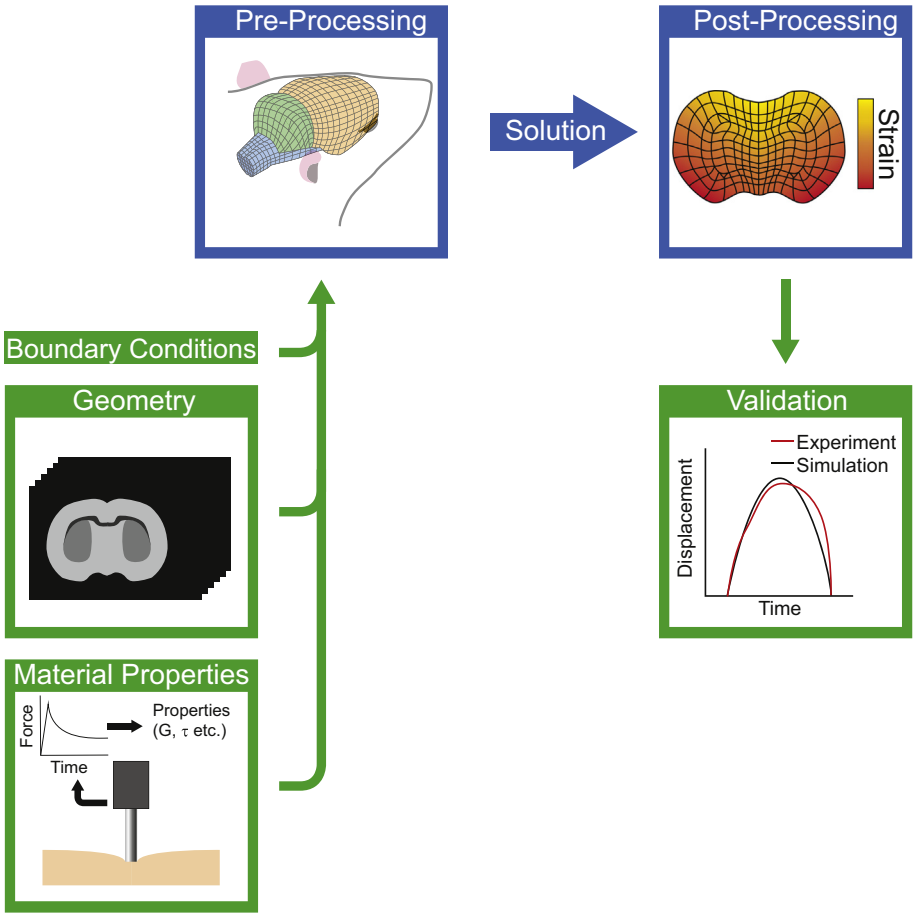

Fig. 1. The ideal workflow for biomechanical simulation of TBI in the rat integrates experimental (green boxes) and computational (blue boxes) tasks. Starting from the bottom left, the material properties (e.g. the shear modulus, G, and the viscoelastic time constant, τ) are measured, the geometry is determined from MRI data or an atlas, and the boundary conditions are identified. This data informs creation of the finite element model during pre-processing. The model is solved and then output is extracted during post-processing. Then, some subset of the model output is compared to experimental data for validation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Kimpara et al., 2006). Stiffness properties for young and middle-aged rats were taken from rat experiments (Elkin and Morrison, 2013). Since similar data was not available for elderly rats, these properties were scaled based on MRE data from human volunteers (Sack et al., 2009). Brain volume changes with age were based on experimental observations in mice (Timaru-Kast et al., 2012). Simulations predicted that older animals were more vulnerable to diffuse axonal injury because the brain was softer and also more vulnerable to rupture of bridging veins because the brain was smaller.

4.4. Simulation of closed head impact

Closed head impact experiments have also been simulated with FEMs. The Gefen group created an FEM of a rigid indenter striking a brain case structure enclosing a homogeneous brain (Levchakov et al., 2006). Simulations predicted that age affected strain distribution in the brain. A more complex model of closed head impact injury in the rat was presented in 2015 (Hua et al., 2015). The geometry was extracted from MRI data. The cerebrum, hippocampus and cerebellum were assigned independent mechanical properties. The brain and skull moduli were taken from rat experiments (Finan et al., 2012a, 2012b; Gefen et al., 2003; Mao et al., 2011). For validation, the mechanical output of the model was compared to the mechanical output of a prior model that had been validated against histological data from animal studies (Mao et al., 2010a). Tu et al. developed an FEM of rat TBI that included the whole rat body (Tu et al., 2016). The white matter, grey matter and dura were assigned independent viscoelastic properties taken from rat experiments. The model was validated by comparing the experimental trajectory of the head upon impact with the model's prediction. This validation addresses the kinematics of the head relative to the body but not the intracranial distribution of strain. Strain distributions predicted by this FEM were used to assess various types of MRI as biomarkers of TBI.

5. Conclusions and recommendations

The lack of data on mechanical properties has historically frustrated biomechanical simulation of TBI in the rat but great progress has recently been made on this front. Early simulations relied almost entirely on properties measured in other species. However, rapid progress with direct mechanical measurement of rat tissues means there are now published values for the stiffness of the dura (Maikos et al., 2008), skull (Mao et al., 2011) and multiple brain regions(Elkin et al., 2011a). Recent models have been populated entirely with data from rat experiments (Tu et al., 2016). However, there remains a critical gap in knowledge related to experimental data against which to validate model output. FEMs of human TBI are frequently validated against important data collected by Hardy et al. (2001) that tracked displacement of the brain at multiple points during head impact. Unfortunately, there is currently no analogous data set in the rat, possibly because a similar study in rat would require higher spatial resolution. Existing validation data (Antona-Makoshi et al., 2015; Shreiber et al., 1997) validate predictions about motion of the brain surface but there is an urgent need for data that can validate predictions about motion of the brain interior.

Building a credible FEM of rat TBI is a formidable undertaking and it is rational to draw mechanical properties from prior publications. However, it is best if the cited sources for mechanical properties are the experimental studies in which they were actually measured, as opposed to other FEM papers. When an FEM paper is cited as the source for a mechanical property, it is unclear if the value was originally determined using experimental testing or if it was estimated in some other

way. Also, each FEM study seeks to address different questions and therefore, the approximations appropriate to one study may not be appropriate to another. Finally, stiffness values influence the stability of FEMs and properties in FEM papers may be adjusted to account for this.

While the study of TBI biomechanics in the rat has progressed significantly in recent years, there is still much to learn. Brain tissue is known to be anisotropic (Prange and Margulies, 2002) but all data reported to date assume isotropy. The stiffness of the brain evolves during the course of life (Elkin et al., 2010a) but associated mechanical properties data is incomplete. The relationship between brain tissue strain and subsequent loss of function is only partially understood (Kang and Morrison 3rd, 2015). The opportunity now exists to compare rat neuron strain tolerance to the strain tolerance of human induced pluripotent stem cell-derived neurons (Sherman et al., 2016). Also, estimating the strain field associated with an experimental insult is becoming more challenging as those insults become more complex. The strain field induced by a CCI injury depends almost entirely on the properties of the brain. However, simulations of closed head injury need to consider deformation of the skull, cerebrospinal fluid and meninges as forces pass through them to the brain. A particularly challenging case of closed head injury is blast injury. In some respects, the state of modern blast injury research resembles the state of impact injury research at the start of the 21st century: many mathematical models have been presented in humans (Cotton et al., 2016; Panzer et al., 2012b), many pre-clinical experiments have been done in animals (reviewed in (Panzer et al., 2014)) but mathematical models describing those pre-clinical experiments are just starting to emerge (Mao et al., 2015; Sundaramurthy et al., 2012; Zhu et al., 2010)and the required mechanical properties are poorly defined. Blast induces lower strain amplitudes and higher strains rates than impact. MRE data (Vappou et al., 2008) may prove very relevant to this type of injury. Mouse models have recently gained popularity in TBI. This trend will inevitably generate demand for FEMs of mouse TBI and associated biomechanical properties. Such an FEM has already been presented, albeit as a modified version of a rat model (Pleasant et al., 2011) and direct experimental measurements of mouse brain biomechanics are available (MacManus et al., 2015, 2016, 2017). As FEMs of the rodent brain become more sophisticated, their potential to contribute to our understanding of brain injury pathology increases. The key to realizing this potential is to perform the difficult experiments necessary to supply accurate inputs and rigorous validation data for these FEMs.

Acknowledgements

This work was supported in part by funding from the National Institutes of Health (grant number R21NS098129-01).

References

Alfasi, A.M., Shulyakov, A.V., Del Bigio, M.R., 2013. Intracranial biomechanics following cortical contusion in live rats. J. Neurosurg. 119, 1255–1262.
Antona-Makoshi, J., Davidson, J., Risling, M., Ejima, S., Ono, K., 2014. Validation of local brain kinematics of a novel rat brain finite element model under rotational acceleration. International journal of automotive. Engineering 31–37.
Antona-Makoshi, J., Eliasson, E., Davidsson, J., Ejima, S., Ono, K., 2015. Effect of aging on brain injury prediction in rotational head trauma–a parameter study with a rat finite element model. Traffic Inj. Prev. 16 (Suppl. 1), S91–99.
Baumgartner, D., Willinger, R., 2004. Human head tolerance limits to specific injury mechanisms inferred from real world accident numerical reconstruction. Revue Europeenne des Elements Finis 14, 421–444.
Baumgartner, D., Lamy, M., Willinger, R., 2009. Finite Element Analysis of Traumatic Brain Injuries Mechanisms in the Rat. IRCOBI, York, UK, pp. 97–108.
Bayly, P.V., Clayton, E.H., Genin, G.M., 2012. Quantitative imaging methods for the development and validation of brain biomechanics models. Annu. Rev. Biomed. Eng. 14, 369–396.
Bolander, R., Mathie, B., Bir, C., Ritzel, D., VandeVord, P., 2011. Skull flexure as a contributing factor in the mechanism of injury in the rat when exposed to a shock wave. Ann. Biomed. Eng. 39, 2550–2559.
Budday, S., Sommer, G., Birkl, C., Langkammer, C., Haybaeck, J., Kohnert, J., Bauer, M., Paulsen, F., Steinmann, P., Kuhl, E., Holzapfel, G.A., 2017. Mechanical characterization of human brain tissue. Acta Biomater. 48, 319–340.
Chatelin, S., Constantinesco, A., Willinger, R., 2010. Fifty years of brain tissue mechanical testing: from in vitro to in vivo investigations. Biorheology 47, 255–276.
Chatelin, S., Humbert-Claude, M., Garteiser, P., Ricobaraza, A., Vilgrain, V., Van Beers, B.E., Sinkus, R., Lenkei, Z., 2016 May. Cannabinoid receptor activation in the juvenile rat brain results in rapid biomechanical alterations: neurovascular mechanism as a putative confounding factor. J. Cereb. Blood Flow Metab. 36 (5), 954–964.
Chen, F., Zhou, J., Li, Y., Wang, Y., Li, L., Yue, H., 2015. Mechanical properties of porcine brain tissue in the coronal plane: interregional variations of the corona radiata. Ann. Biomed. Eng. 43 (12), 2903–2910.
Christ, A.F., Franze, K., Gautier, H., Moshayedi, P., Fawcett, J., Franklin, R.J., Karadottir, R.T., Guck, J., 2010. Mechanical difference between white and gray matter in the rat cerebellum measured by scanning force microscopy. J. Biomech. 43, 2986–2992.
Clarke, E.C., Cheng, S., Green, M., Sinkus, R., Bilston, L.E., 2011. Using static preload with magnetic resonance elastography to estimate large strain viscoelastic properties of bovine liver. J. Biomech. 44, 2461–2465.
Cotton, R.T., Pearce, C.W., Young, P.G., Kota, N., Leung, A.C., Bagchi, A., Qidwai, S.M., 2016. Development of a geometrically accurate and adaptable finite element head model for impact simulation: the naval research laboratory-simpleware head model. Comput. Methods Biomech. Biomed. Engin. 19, 101–113.
Courtney, A., Courtney, M., 2015. The complexity of biomechanics causing primary blast-induced traumatic brain injury: a review of potential mechanisms. Front. Neurol. 6, 221.
Crane, P.K., Gibbons, L.E., Dams-O'Connor, K., Trittschuh, E., Leverenz, J.B., Keene, C.D., Sonnen, J., Montine, T.J., Bennett, D.A., Leurgans, S., Schneider, J.A., Larson, E.B., 2016. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. JAMA Neurol. 73, 1062–1069.
D.O.T., U.S, 2017a. Federal Motor Vehicle Safety Standards. 208 Title 49: Chapter V, Part 571, Subpart B.
D.O.T., U.S, 2017b. Federal Motor Vehicle Safety Standards. 218 Title 49: Chapter V, Part 571, Subpart B.
Davidsson, J., Risling, M., 2011. A new model to produce sagittal plane rotational induced diffuse axonal injuries. Front. Neurol. 2, 41.
Dekker, S.E., Sillesen, M., Bambakidis, T., Jin, G., Liu, B., Boer, C., Johansson, P.I., Halaweish, I., Maxwell, J., Alam, H.B., 2014. Normal saline influences coagulation and endothelial function after traumatic brain injury and hemorrhagic shock in pigs. Surgery 156, 556–563.
Denny-Brown, D., Russell, R., 1941. Experimental cerebral concussion. Brain J. Neurol. 64, 93–164.
DePalma, R.G., Hoffman, S.W., 2018 Mar 15. Combat blast related traumatic brain injury (TBI): decade of recognition; promise of progress. Behav. Brain Res. 340, 102–105.
Dixon, C.E., Lyeth, B.G., Povlishock, J.T., Findling, R.L., Hamm, R.J., Marmarou, A., Young, H.F., Hayes, R.L., 1987. A fluid percussion model of experimental brain injury in the rat. J. Neurosurg. 67, 110–119.
Dixon, C.E., Clifton, G.L., Lighthall, J.W., Yaghmai, A.A., Hayes, R.L., 1991. A controlled cortical impact model of traumatic brain injury in the rat. J. Neurosci. Methods 39, 253–262.
Effgen, G.B., Hue, C.D., Vogel 3rd, E., Panzer, M.B., Meaney, D.F., Bass, C.R., Morrison 3rd, B., 2012. A multiscale approach to blast neurotrauma modeling: part II: methodology for inducing blast injury to in vitro models. Front. Neurol. 3, 23.
Elkin, B.S., Ilankovan, A., Morrison 3rd, B., 2010a. Age-dependent regional mechanical properties of the rat hippocampus and cortex. J. Biomech. Eng. 132, 011010.
Elkin, B.S., Morrison, B., 2013. Viscoelastic properties of the P17 and adult rat brain from indentation in the coronal plane. J. Biomech. Eng. 135, 114507.
Elkin, B.S., Azeloglu, E.U., Costa, K.D., Morrison 3rd, B., 2007. Mechanical heterogeneity of the rat hippocampus measured by atomic force microscope indentation. J. Neurotrauma 24, 812–822.
Elkin, B.S., Shaik, M.A., Morrison 3rd, B., 2010b. Fixed negative charge and the Donnan effect: a description of the driving forces associated with brain tissue swelling and oedema. Philos. Trans. R. Soc. London, Ser. A 368, 585–603.
Elkin, B.S., Ilankovan, A.I., Morrison 3rd, B., 2011a. A detailed viscoelastic characterization of the P17 and adult rat brain. J. Neurotrauma 28, 2235–2244.
Elkin, B.S., Shaik, M.A., Morrison 3rd, B., 2011b. Chondroitinase ABC reduces brain tissue swelling in vitro. J. Neurotrauma 28, 2277–2285.
Fallenstein, G.T., Hulce, V.D., Melvin, J.W., 1969. Dynamic mechanical properties of human brain tissue. J. Biomech. 2, 217–226.
Faul, M.X.L., Wald, M.M., Coronado, V., 2010. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths, 2002–2006. CDC, National Center for Injury Prevention and Control, Atlanta, GA.
Fijalkowski, R.J., Stemper, B.D., Pintar, F.A., Yoganandan, N., Crowe, M.J., Gennarelli, T.A., 2007. New rat model for diffuse brain injury using coronal plane angular acceleration. J. Neurotrauma 24, 1387–1398.
Fijalkowski, R.J., Yoganandan, N., Zhang, J., Pintar, F.A., 2009. A finite element model of region-specific response for mild diffuse brain injury. Stapp Car Crash J. 53, 193–213.
Finan, J.D., Elkin, B.S., Pearson, E.M., Kalbian, I.L., Morrison 3rd, B., 2012a. Viscoelastic properties of the rat brain in the sagittal plane: effects of anatomical structure and age. Ann. Biomed. Eng. 40, 70–78.
Finan, J.D., Pearson, E.M., Morrison III, B., 2012b. In: Viscoelastic Properties of the Rat Brain in the Horizontal Plane. IRCOBI Conference, Dublin, Ireland. pp. 474–485.
Finan, J.D., Fox, P.M., Morrison 3rd, B., 2014. Non-ideal effects in indentation testing of soft tissues. Biomech. Model. Mechanobiol. 13, 573–584.
Finan, J.D., Cho, F.S., Kernie, S.G., Morrison 3rd, B., 2016. Intracerebroventricular administration of chondroitinase ABC reduces acute edema after traumatic brain injury in mice. BMC. Res. Notes 9, 160.
Finan, J.D., Sundaresh, S.N., Elkin, B.S., McKhann 2nd, G.M., Morrison 3rd, B., 2017. Regional mechanical properties of human brain tissue for computational models of traumatic brain injury. Acta Biomater. 55, 333–339.

Galford, J.E., McElhaney, J.H., 1970. A viscoelastic study of scalp, brain, and dura. J. Biomech. 3, 211–221.
Gardner, R.C., Burke, J.F., Nettiksimmons, J., Goldman, S., Tanner, C.M., Yaffe, K., 2015. Traumatic brain injury in later life increases risk for Parkinson disease. Ann. Neurol. 77, 987–995.
Garo, A., Hrapko, M., van Dommelen, J.A., Peters, G.W., 2007. Towards a reliable characterisation of the mechanical behaviour of brain tissue: the effects of post-mortem time and sample preparation. Biorheology 44, 51–58.
Gefen, A., Margulies, S.S., 2004. Are in vivo and in situ brain tissues mechanically similar? J. Biomech. 37, 1339–1352.
Gefen, A., Gefen, N., Zhu, Q., Raghupathi, R., Margulies, S.S., 2003. Age-dependent changes in material properties of the brain and braincase of the rat. J. Neurotrauma 20, 1163–1177.
Gennarelli, T.A., 1994. Animate models of human head injury. J. Neurotrauma 11, 357–368.
Gurdjian, E.S., Lissner, H.R., 1944. Mechanics of head injuries. Lancet 389–390.
Gurdjian, E.S., Roberts, V.L., Thomas, L.M., 1966. Tolerance curves of acceleration and intracranial pressure and protective index in experimental head injury. J. Trauma 6, 600.
Hardy, W.N., Foster, C.D., Mason, M.J., Yang, K.H., King, A.I., Tashman, S., 2001. Investigation of head injury mechanisms using neutral density technology and high-speed biplanar X-ray. Stapp Car Crash J. 45, 337–368.
Hayes, W.C., Keer, L.M., Herrmann, G., Mockros, L.F., 1972. A mathematical analysis for indentation tests of articular cartilage. J. Biomech. 5, 541–551.
Hetzer, S., Birr, P., Fehlner, A., Hirsch, S., Dittmann, F., Barnhill, E., Braun, J., Sack, I., 2018 Jan. Perfusion alters stiffness of deep gray matter. J. Cereb. Blood Flow Metab. 38 (1), 116–125 (271678x17691530).
Holbourn, A.H.S., 1943. Mechanics of head injuries. Lancet 243, 483.
Hua, Y., Akula, P., Kelso, M., Gu, L., 2015. Characterization of closed head impact injury in rat. Biomed. Res. Int. 2015, 272976.
Jin, X., Zhu, F., Mao, H., Shen, M., Yang, K.H., 2013. A comprehensive experimental study on material properties of human brain tissue. J. Biomech. 46, 2795–2801.
Kabadi, S.V., Faden, A.I., 2014. Neuroprotective strategies for traumatic brain injury: improving clinical translation. Int. J. Mol. Sci. 15, 1216–1236.
Kang, W.H., Morrison 3rd, B., 2015. Predicting changes in cortical electrophysiological function after in vitro traumatic brain injury. Biomech. Model. Mechanobiol. 14, 1033–1044.
Kaster, T., Sack, I., Samani, A., 2011. Measurement of the hyperelastic properties of ex vivo brain tissue slices. J. Biomech. 44, 1158–1163.
Kim, B., Haque, A., Arnaud, F.G., Teranishi, K., Steinbach, T., Auker, C.R., McCarron, R.M., Freilich, D., Scultetus, A.H., 2014. Use of recombinant factor VIIa (rFVIIa) as pre-hospital treatment in a swine model of fluid percussion traumatic brain injury. J. Emergencies Trauma Shock 7, 102–111.
Kimpara, H., Nakahira, Y., Iwamoto, M., Miki, K., Ichihara, K., Kawano, S., Taguchi, T., 2006. Investigation of anteroposterior head-neck responses during severe frontal impacts using a brain-spinal cord complex FE model. Stapp Car Crash J. 50, 509–544.
Klatt, D., Johnson, C.L., Magin, R.L., 2015. Simultaneous, multidirectional acquisition of displacement fields in magnetic resonance elastography of the in vivo human brain. J. Magn. Reson. Imaging 42, 297–304.
Lai, W.M., Hou, J.S., Mow, V.C., 1991. A triphasic theory for the swelling and deformation behaviors of articular cartilage. J. Biomech. Eng. 113, 245–258.
Lamy, M., Baumgartner, D., Yoganandan, N., Stemper, B.D., Willinger, R., 2013. Experimentally validated three-dimensional finite element model of the rat for mild traumatic brain injury. Med. Biol. Eng. Comput. 51, 353–365.
Lee, E.H., Radok, J.R.M., 1960. The contact problem for viscoelastic bodies. J. Appl. Mech. 27, 438–444.
Levchakov, A., Linder-Ganz, E., Raghupathi, R., Margulies, S.S., Gefen, A., 2006. Computational studies of strain exposures in neonate and mature rat brains during closed head impact. J. Neurotrauma 23, 1570–1580.
MacManus, D.B., Pierrat, B., Murphy, J.G., Gilchrist, M.D., 2015. Dynamic mechanical properties of murine brain tissue using micro-indentation. J. Biomech. 48, 3213–3218.
MacManus, D.B., Pierrat, B., Murphy, J.G., Gilchrist, M.D., 2016. Mechanical characterization of the P56 mouse brain under large-deformation dynamic indentation. Sci. Rep. 6, 21569.
MacManus, D.B., Pierrat, B., Murphy, J.G., Gilchrist, M.D., 2017. A viscoelastic analysis of the P56 mouse brain under large-deformation dynamic indentation. Acta Biomater. 48, 309–318.
Maikos, J.T., Elias, R.A., Shreiber, D.I., 2008. Mechanical properties of dura mater from the rat brain and spinal cord. J. Neurotrauma 25, 38–51.
Manley, G.T., Rosenthal, G., Lam, M., Morabito, D., Yan, D., Derugin, N., Bollen, A., Knudson, M.M., Panter, S.S., 2006. Controlled cortical impact in swine: pathophysiology and biomechanics. J. Neurotrauma 23, 128–139.
Mao, H., Zhang, L., Yang, K.H., King, A.I., 2006. Application of a finite element model of the brain to study traumatic brain injury mechanisms in the rat. Stapp Car Crash J. 50, 583–600.
Mao, H., Jin, X., Zhang, L., Yang, K.H., Igarashi, T., Noble-Haeusslein, L.J., King, A.I., 2010a. Finite element analysis of controlled cortical impact-induced cell loss. J. Neurotrauma 27, 877–888.
Mao, H., Yang, K.H., King, A.I., Yang, K., 2010b. Computational neurotrauma–design, simulation, and analysis of controlled cortical impact model. Biomech. Model. Mechanobiol. 9, 763–772.
Mao, H., Wagner, C., Guan, F., Yeni, Y.N., Yang, K.H., 2011. Material properties of adult rat skull. J. Mech. Med. Biol. 11, 1199–1212.
Mao, H., Elkin, B.S., Genthikatti, V.V., Morrison 3rd, B., Yang, K.H., 2013. Why is CA3 more vulnerable than CA1 in experimental models of controlled cortical impact-induced brain injury? J. Neurotrauma 30, 1521–1530.
Mao, H., Unnikrishnan, G., Rakesh, V., Reifman, J., 2015. Untangling the effect of head acceleration on brain responses to blast waves. J. Biomech. Eng. 137, 124502.
Margulies, S.S., Kilbaugh, T., Sullivan, S., Smith, C., Propert, K., Byro, M., Saliga, K., Costine, B.A., Duhaime, A.C., 2015. Establishing a clinically relevant large animal model platform for TBI therapy development: using cyclosporin a as a case study. Brain Pathol. 25, 289–303.
Marmarou, A., Foda, M.A., van den Brink, W., Campbell, J., Kita, H., Demetriadou, K., 1994. A new model of diffuse brain injury in rats. Part I: pathophysiology and biomechanics. J. Neurosurg. 80, 291–300.
McKee, A.C., Stein, T.D., Kiernan, P.T., Alvarez, V.E., 2015. The neuropathology of chronic traumatic encephalopathy. Brain Pathol. 25, 350–364.
McKee, A.C., Cairns, N.J., Dickson, D.W., Folkerth, R.D., Keene, C.D., Litvan, I., Perl, D.P., Stein, T.D., Vonsattel, J.P., Stewart, W., Tripodis, Y., Crary, J.F., Bieniek, K.F., Dams-O'Connor, K., Alvarez, V.E., Gordon, W.A., group, T.C, 2016. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathol. 131, 75–86.
Meaney, D.F., Smith, D.H., Shreiber, D.I., Bain, A.C., Miller, R.T., Ross, D.T., Gennarelli, T.A., 1995. Biomechanical analysis of experimental diffuse axonal injury. J. Neurotrauma 12, 689–694.
Miller, K., Chinzei, K., 1997. Constitutive modelling of brain tissue: experiment and theory. J. Biomech. 30, 1115–1121.
Miller, K., Chinzei, K., 2002. Mechanical properties of brain tissue in tension. J. Biomech. 35, 483–490.
Moeendarbary, E., Weber, I.P., Sheridan, G.K., Koser, D.E., Soleman, S., Haenzi, B., Bradbury, E.J., Fawcett, J., Franze, K., 2017. The soft mechanical signature of glial scars in the central nervous system. Nat. Commun. 8, 14787.
Morrison 3rd, B., Cater, H.L., Wang, C.C., Thomas, F.C., Hung, C.T., Ateshian, G.A., Sundstrom, L.E., 2003. A tissue level tolerance criterion for living brain developed with an in vitro model of traumatic mechanical loading. Stapp Car Crash J. 47, 93–105.
Namjoshi, D.R., et al., 2014. Merging pathology with biomechanics using CHIMERA (Closed-Head Impact Model of Engineered Rotational Acceleration): a novel, surgery-free model of traumatic brain injury. Mol. Neurodegener. 9, 55. http://dx.doi.org/10.1186/1750-1326-9-55.
Ommaya, A.K., 1968. Mechanical properties of tissues of the nervous system. J. Biomech. 1, 127–138.
Ommaya, A.K., Hirsch, A.E., 1971. Tolerances for cerebral concussion from head impact and whiplash in primates. J. Biomech. 4, 13–21.
Ommaya, A.K., Hirsch, A.E., Flamm, E.S., Mahone, R.H., 1966. Cerebral concussion in the monkey: an experimental model. Science 153, 211–212.
Ommaya, A.K., Yarnell, P., Hirsch, A.E., Harris, E.H., 1968. Scaling of experimental data on cerebral concussion in sub-human primates to concussion threshold for man. SAE Trans. 76, 172.
Owens, B.D., Kragh Jr., J.F., Wenke, J.C., Macaitis, J., Wade, C.E., Holcomb, J.B., 2008. Combat wounds in operation Iraqi freedom and operation enduring freedom. J. Trauma 64, 295–299.
Panzer, M.B., Matthews, K.A., Yu, A.W., Morrison 3rd, B., Meaney, D.F., Bass, C.R., 2012a. A multiscale approach to blast neurotrauma modeling: part I - development of novel test devices for in vivo and in vitro blast injury models. Front. Neurol. 3, 46.
Panzer, M.B., Myers, B.S., Capehart, B.P., Bass, C.R., 2012b. Development of a finite element model for blast brain injury and the effects of CSF cavitation. Ann. Biomed. Eng. 40, 1530–1544.
Panzer, M.B., Wood, G.W., Bass, C.R., 2014. Scaling in neurotrauma: how do we apply animal experiments to people? Exp. Neurol. 261, 120–126.
Petraglia, A.L., Plog, B.A., Dayawansa, S., Chen, M., Dashnaw, M.L., Czerniecka, K., Walker, C.T., Viterise, T., Hyrien, O., Iliff, J.J., Deane, R., Nedergaard, M., Huang, J.H., 2014. The spectrum of neurobehavioral sequelae after repetitive mild traumatic brain injury: a novel mouse model of chronic traumatic encephalopathy. J. Neurotrauma 31, 1211–1224.
Pierrat, B., MacManus, D.B., Murphy, J.G., Gilchrist, M.D., 2018 Feb. Indentation of heterogeneous soft tissue: Local constitutive parameter mapping using an inverse method and an automated rig. J. Mech. Behav. Biomed. Mater. 78, 515–528.
Pleasant, J.M., Carlson, S.W., Mao, H., Scheff, S.W., Yang, K.H., Saatman, K.E., 2011. Rate of neurodegeneration in the mouse controlled cortical impact model is influenced by impactor tip shape: implications for mechanistic and therapeutic studies. J. Neurotrauma 28, 2245–2262.
Pong, A.C., Juge, L., Cheng, S., Bilston, L.E., 2016. Longitudinal measurements of post-natal rat brain mechanical properties in-vivo. J. Biomech. 49, 1751–1756.
Prange, M.T., Margulies, S.S., 2002. Regional, directional, and age-dependent properties of the brain undergoing large deformation. J. Biomech. Eng. 124, 244–252.
Prins, M.L., Hales, A., Reger, M., Giza, C.C., Hovda, D.A., 2010. Repeat traumatic brain injury in the juvenile rat is associated with increased axonal injury and cognitive impairments. Dev. Neurosci. 32, 510–518.
Roozenbeek, B., Maas, A.I., Menon, D.K., 2013. Changing patterns in the epidemiology of traumatic brain injury. Nat. Rev. Neurol. 9, 231–236.
Sack, I., Beierbach, B., Wuerfel, J., Klatt, D., Hamhaber, U., Papazoglou, S., Martus, P., Braun, J., 2009. The impact of aging and gender on brain viscoelasticity. NeuroImage 46, 652–657.
Schwerin, S.C., Hutchinson, E.B., Radomski, K.L., Ngalula, K.P., Pierpaoli, C.M., Juliano, S.L., 2017. Establishing the ferret as a gyrencephalic animal model of traumatic brain injury: optimization of controlled cortical impact procedures. J. Neurosci. Methods 285, 82–96.
Shafieian, M., Darvish, K.K., Stone, J.R., 2009. Changes to the viscoelastic properties of brain tissue after traumatic axonal injury. J. Biomech. 42, 2136–2142.
Sherman, S.A., Phillips, J.K., Costa, J.T., Cho, F.S., Oungoulian, S.R., Finan, J.D., 2016.

Stretch injury of human induced pluripotent stem cell derived neurons in a 96 well format. Sci. Rep. 6, 34097.
Shreiber, D.I., Bain, A.C., Meaney, D.F., 1997. In: In vivo thresholds for mechanical injury to the blood brain barrier. 41st Annual Stapp Car Crash Conference, Warrendale, PA.
Shuck, L.Z., Advani, S.H., 1972. Rheological response of human brain-tissue in shear. J. Basic Eng. 94, 905–911.
Sindelar, B., Bailes, J.E., Sherman, S.A., Finan, J.D., Stone, J., Lee, J.M., Ahmadian, S., Zhou, Y., Patel, V., Smith, D., 2017 April 15. Effect of internal jugular vein compression on intracranial hemorrhage in a porcine controlled cortical impact model. J. Neurotrauma 34 (8), 1703–1709.
Stein, D.G., 2015. Embracing failure: what the phase III progesterone studies can teach about TBI clinical trials. Brain Inj. 29, 1259–1272.
Stone, J.L., Patel, V., Bailes, J.E., 2016. Sir Hugh Cairns and World War II British advances in head injury management, diffuse brain injury, and concussion: an Oxford tale. J. Neurosurg. 125, 1301–1314.
Sundaramurthy, A., Alai, A., Ganpule, S., Holmberg, A., Plougonven, E., Chandra, N., 2012. Blast-induced biomechanical loading of the rat: an experimental and anatomically accurate computational blast injury model. J. Neurotrauma 29, 2352–2364.
Thomsen, G.M., Ma, A.M., Ko, A., Harada, M.Y., Wyss, L., Haro, P.S., Vit, J.P., Shelest, O., Rhee, P., Svendsen, C.N., Ley, E.J., 2016. A model of recurrent concussion that leads to long-term motor deficits, CTE-like tauopathy and exacerbation of an ALS phenotype. J. Trauma Acute Care Surg. 81, 1070–1079.
Thurman, D.J., Alverson, C., Dunn, K.A., Guerrero, J., Sniezek, J.E., 1999. Traumatic brain injury in the United States: a public health perspective. J. Head Trauma Rehabil. 14, 602–615.
Timaru-Kast, R., Luh, C., Gotthardt, P., Huang, C., Schafer, M.K., Engelhard, K., Thal, S.C., 2012. Influence of age on brain edema formation, secondary brain damage and inflammatory response after brain trauma in mice. PLoS One 7, e43829.
Tu, T.W., Williams, R.A., Lescher, J.D., Jikaria, N., Turtzo, L.C., Frank, J.A., 2016. Radiological-pathological correlation of diffusion tensor and magnetization transfer imaging in a closed head traumatic brain injury model. Ann. Neurol. 79, 907–920.
UNECE, 2017a. UNECE Regulation 22.05: Uniform Provisions Concerning the Approval of Protective Helmets and Their Visors for Drivers and Passengers of Motor Cycles and Mopeds.
UNECE, 2017b. UNECE Regulation 94: Uniform Provisions Concerning the Approval of Vehicles with Regard to the Protection of the Occupants in the Event of a Frontal Collision.
Vappou, J., Breton, E., Choquet, P., Willinger, R., Constantinesco, A., 2008. Assessment of in vivo and post-mortem mechanical behavior of brain tissue using magnetic resonance elastography. J. Biomech. 41, 2954–2959.
Vink, R., Bahtia, K.D., Reilly, P.L., 2008. The relationship between intracranial pressure and brain oxygenation following traumatic brain injury in sheep. Acta Neurochir. Suppl. 102, 189–192.
Zhang, L., Yang, K.H., Dwarampudi, R., Omori, K., Li, T., Chang, K., Hardy, W.N., Khalil, T.B., King, A.I., 2001. Recent advances in brain injury research: a new human head model development and validation. Stapp Car Crash J. 45, 369–394.
Zhang, L., Yang, K.H., King, A.I., 2004. A proposed injury threshold for mild traumatic brain injury. J. Biomech. Eng. 126, 226–236.
Zhang, Y.P., Cai, J., Shields, L.B., Liu, N., Xu, X.M., Shields, C.B., 2014. Traumatic brain injury using mouse models. Transl Stroke Res 5, 454–471.
Zhu, F., Mao, H., Dal Cengio Leonardi, A., Wagner, C., Chou, C., Jin, X., Bir, C., Vandevord, P., Yang, K.H., King, A.I., 2010. Development of an FE model of the rat head subjected to air shock loading. Stapp Car Crash J. 54, 211–225.