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Modelling traumatic brain injury and posttraumatic epilepsy in rodents

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Abstract

Posttraumatic epilepsy (PTE) is one of the most debilitating and understudied consequences of traumatic brain injury (TBI). It is challenging to study the effects, underlying pathophysiology, biomarkers, and treatment of TBI and PTE purely in human patients for a number of reasons. Rodent models can complement human PTE studies as they allow for the rigorous investigation into the causal relationship between TBI and PTE, the pathophysiological mechanisms of PTE, the validation and implementation of PTE biomarkers, and the assessment of PTE treatments, in a tightly controlled, time- and cost-efficient manner in experimental subjects known to be experiencing epileptogenic processes. This article will review several common rodent models of TBI and/or PTE, including their use in previous studies and discuss their relative strengths, limitations, and avenues for future research to advance our understanding and treatment of PTE.

Keywords

Posttraumatic epilepsy; Traumatic brain injury; Review; Translational research

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1. Introduction

Traumatic brain injury (TBI), is induced by external mechanical forces to the brain, is a leading cause of death and morbidity worldwide, and can have chronic neurodegenerative effects (Xiong et al., 2013). Amongst the long-term consequences of TBI, one of the most common and debilitating, yet severely understudied, is posttraumatic epilepsy (PTE) (Banerjee et al., 2009). The definition of epilepsy requires the occurrence of at least one single unprovoked seizure, when there is high risk for another (Scheffer et al., 2016). Therefore, a single, late (>1 week post-TBI), unprovoked seizure in a person with a structural TBI fulfills the diagnostic criteria for epilepsy. (Christensen, 2012; Christensen et al., 2009; Fisher et al., 2014; Scheffer et al., 2016). While the exact incidence of PTE is unknown, it is estimated that 10–20% of TBI patients will develop PTE depending on the nature of the TBI (e.g., mild versus severe, penetrating versus closed head) (Hauser et al., 1993; Piccenna et al., 2017). Significant risk factors that contribute to the development of PTE are severe head injury (Glasgow coma scale 3–8), intracerebral and subdural hematomas, skull fractures, penetrating injuries and older age (>65 years old)(Annegers et al., 1998; Christensen, 2012; Salazar et al., 1985; Temkin, 2003; Tubi et al., 2018). To date there is still no therapy proven to prevent or reverse epileptogenesis in TBI patients.

To develop and implement such an intervention, the underlying disease mechanisms and related biomarkers of PTE must first be identified and validated so that therapies can subsequently be discovered. In the clinical setting, there are many determinants of outcome (e.g., age, injury severity, injury location, biological, sex) that confound the ability to study the effects, underlying pathophysiology, biomarkers, and treatment of TBI and PTE (Pitkänen et al., 2009). For example, it is challenging to study early epileptogenic processes in the clinical setting as epilepsy is diagnosed in TBI patients after the onset of spontaneous recurrent seizures, which represents the culmination of epileptogenesis and is typically months to years after the initial TBI (Petty et al., 2005). The invasive studies that would be required to comprehensively investigate underlying molecular and cellular changes in the brain throughout the epileptogenic process are not ethically feasible. Even when applying more non-invasive measures (e.g., MRI, EEG), it is also challenging for patients to participate in the detailed, serial, and longitudinal studies that are required to examine epileptogenesis. Taken together, the studies required to adequately study epileptogenesis in humans will be extremely difficult, expensive, could take decades to complete, and may ultimately be affected by selection biases, genetics, and socioeconomic and lifestyle factors (e.g., alcohol/drug use). Regarding potential therapeutic interventions, even if pharmacological targets are identified in humans, it is not ethical to study novel drugs in patients. Furthermore, it would take many years to determine whether the therapies effectively prevent PTE in the absence of reliable prognostic or early detection biomarkers. For such reasons, other strategies must be employed to provide insight into questions surrounding TBI, epileptogenesis, and PTE.

Rodent models of TBI and PTE allow for the rigorous investigation into the causal relationship between TBI and PTE, the pathophysiological mechanisms of PTE, the validation and implementation of PTE biomarkers, and the assessment of PTE treatments, in a tightly controlled, time- and cost-efficient manner in experimental subjects known to be

experiencing epileptogenic processes (Pitkänen and Mcintosh, 2006). The focus of this article is to review several common rodent models of TBI and/or PTE, including their strengths, limitations, and use in previous studies. Electrophysiological, imaging, proteomic and epigenomic biomarkers of epileptogenicity as well as mechanisms of PTE will be reviewed in separate manuscripts within this special issue.

Throughout this review, it is important for the reader to consider that a model of PTE is dependent on the presence of spontaneous seizures on EEG. Although this requirement would appear to be straightforward, it is one of the major issues in modelling PTE as there is no consensus on what is a seizure on EEG. Seizure characteristics vary depending on the site of the injury and the location of the seizure onset zone in relation to the injury. However, focal and secondary generalized convulsive seizures generally follow a pattern of regularly occurring electrographic spikes that are frequently followed by spikes occurring in a bursting mode, these events are at least twice the amplitude of the basal EEG (Dudek and Bertram, 2010). Furthermore, these seizures generally undergo a series of progressive changes, typical ictal progression and postictal suppression (D'Ambrosio et al., 2009; D'Ambrosio and Miller, 2010; Dudek and Bertram, 2010). Five to ten seconds have been the minimal duration of seizures that have been described in several PTE studies and the typical duration of the seizures varies between 30 seconds to 2 minutes (Kharatishvili et al., 2006b; Liu et al., 2016a; Reid et al., 2016; Semple et al., 2017b; Shultz et al., 2013).

Other discharges have also been described in PTE models, including non-progressive, rhythmic trains of activity of waxing, and waning amplitude, which are similar to human sleep spindles or alpha rhythm and 7–9 Hz events with a duration of 1–10 seconds that resemble spike and wave discharges which have been reported to be increased after TBI (D'Ambrosio et al., 2009; Dudek and Bertram, 2010; Kadam et al., 2017; Rodgers et al., 2015). However, these events have been challenged because there are essentially identical EEG discharges seen in agematched sham injured and TBI rats (Pearce et al., 2014; Reid et al., 2016; Rodgers et al., 2015). Similarly, discharges have been reported in other rat models of acquired epilepsy like the neonatal hypoxia (Rakhade et al., 2011), hyperthermia-induced febrile seizures in immature rats (Dubé et al., 2006) and pilocarpine and kainic acid induced post-status models (Smith et al., 2018). Moreover, these events and other paroxysmal rhythmic activities including bursts of spike-wave spikes, polyspikes or oscillations have also been reported in a variety of control and otherwise healthy outbred and inbred rat strains and become more prevalent with age (Kadam et al., 2017; Kelly, 2004; Pearce et al., 2014; Rodgers et al., 2015; Shaw, 2004; Taylor et al., 2017). It is important to note that the various terminologies, attributes, and proposed interpretations to describe these paroxysmal rhythmic activities, as presented by the authors of such studies, demonstrate the challenges and heterogeneous opinions in interpreting the nature and biological significance of these events. Interpretation and comparisons of most EEG patterns are complicated further by the different protocols used for EEG acquisition, presentation and analysis. It is imperative that common ways of describing such patterns, including the morphology and localization of the events in different montages, sleep-wake state, reactivity, and triggered factors, are adopted to facilitate comparisons between events, associated behaviors and underlying pathology (Kadam et al., 2017).

Clearly a comprehensive discussion amongst translational epilepsy researchers is necessary to achieve a consensus with regards to what EEG characteristics constitute a PTE seizure (D'Ambrosio et al., 2009; D'Ambrosio and Miller, 2010; Kadam et al., 2017; Rodgers et al., 2015). Indeed, this is the current focus of TASK1 of the ILAE/AES Joint Translational Task force as described by Kadam et al 2017. Until a communal consensus is achieved it is suggested that investigators carefully review the arguments from both sides of the controversy. For the purpose of this review, the models are described as they are presented in the literature without a judgement about the nature of the EEG findings.

2. Fluid percussion injury (FPI)

The FPI induces a mixed focal-diffuse brain injury pattern that models human closed-head TBI and is one of the most commonly used preclinical TBI methods (Kabadi et al., 2010; Thompson et al., 2005; Xiong et al., 2013). The FPI model is a highly adaptable technique, as the force of the fluid pulse/severity of the injury, the impact location, and species (e.g. mouse, rat, rabbit, cat, dog, swine, and sheep) can all be modified (Armstead and Kurth, 1994; Johnstone et al., 2018; Kabadi et al., 2010; Millen et al., 1985; Thompson et al., 2005; Xiong et al., 2013). To administer an FPI, the animal is placed under anesthetic and undergoes a craniotomy to reveal the intact dura matter of the brain. A hollow female luer lock is sealed over the craniotomy, and the animal is connected to the fluid percussion device via the luer lock. The fluid percussion device consists of an adjustable hammer pendulum that, once released, strikes the piston end of a fluid-filled horizontal cylinder. This generates a fluid pulse that is transmitted along the cylinder and onto the brain. For the purpose of this review, the remainder of the FPI section will focus on rat studies unless otherwise noted (Shultz et al., 2015).

There are a vast number of studies that have characterized the effects of an FPI, across the severity spectrum, on behavioral and pathophysiological outcomes in the rat. Importantly, many of these outcomes are similar to those that have been reported in the clinical TBI setting. Mild, moderate, and severe FPI have all been shown to induce cognitive deficits on a range of different tasks (Bao et al., 2012; DeRoss et al., 2002; Gurkoff et al., 2006; Hayward et al., 2010; Jones et al., 2008; Shultz et al., 2011; Shultz et al., 2015), though for the most part these effects are typically transient after a mild FPI and can persist with more severe FPI. Similar severity dependent effects have been reported for other outcomes, including abnormalities in sleep (Lim et al., 2013; Skopin et al., 2015), sensorimotor function (Bao et al., 2012; Hayward et al., 2010; Johnstone et al., 2018; Johnstone et al., 2014), anxiety-like behavior (Jones et al., 2012; Shultz et al., 2011; Shultz et al., 2015), electrophysiology (Aungst et al., 2014; Johnstone et al., 2014; Johnstone et al., 2015), and depression-like behavior (Jones et al., 2008; Shultz et al., 2012).

With regards to pathophysiology, a single mild FPI does not result in significant neuronal loss, visible brain contusion, or focal lesion (Aungst et al., 2014; Gurkoff et al., 2006; Hylin et al., 2013; Shultz et al., 2012; Shultz et al., 2011), but can induce transient neuroinflammation, axonal injury, and reduced cerebral blood flow (Hylin et al., 2013; Shultz et al., 2011). In contrast, moderate and severe FPI induces significant neuronal death, vascular injury, axonal damage, mossy fiber sprouting, neuroinflammation, and

proteinopathies, many of which persist chronically (Bao et al., 2012; Hayward et al., 2010; Hayward et al., 2011; Kharatishvili and Pitkänen, 2010; Shultz et al., 2015; Shultz et al., 2013; Wright et al., 2017). Furthermore, serial *in vivo* MRI studies have found progressive neurodegeneration of several grey and white matter structures, both ipsilateral and contralateral of the injury site, that extends into the chronic post-injury setting (Immonen et al., 2009; Johnstone et al., 2015; Laitinen et al., 2015; Shultz et al., 2013; Shultz et al., 2015; Wright et al., 2017)

The FPI is likely the most extensively studied and frequently applied model in the context of PTE. Specifically, a lateral FPI has been reported by a number of laboratories to induce PTE in a proportion of rats that is similar to the incidence of PTE reported in patients with TBI (Christensen et al., 2009; Englander et al., 2003; Frey, 2003). For example, Kharatishvili et al. (2007; 2006c) found incidence rates of PTE in 43–50% of rats in chronic stages after a severe lateral FPI. Using a similar seizure definition, Shultz et al., (2015; 2013) and Liu et al., (2016b) reported that 30–52% of rats given severe LFPI displayed either spontaneous seizures and/or epileptic discharges. Reid et al (2016) found that 50% of rats given an FPI had focal seizures and 17% had generalized seizures at chronic recovery times. With that said, other studies have reported evidence for much higher incidence of PTE in rats chronically after FPI. For example, based on electrocorticography (ECoG) recordings D'Ambrosio et al. (D'Ambrosio et al., 2004a; D'Ambrosio et al., 2005) reported that 92–100% of FPI rats had spontaneous chronic seizures. These seizures originated as partial seizures from the cortex at the injury site, and worsened and spread over time. Behaviorally these seizures were associated with pauses in their behavior, facial automatisms and myoclonus. Sick and colleagues (2017) examined cortical epileptiform 7–9Hz spike/wave discharges (SWDs) with ECoG recordings in rats one year after mild, moderate, or severe FPI. Regardless of severity, FPI resulted in an increased number of SWDs recorded in a 1 h session (naïve = 12.9 ± 10.3; sham 23.6 ± 8.2; mild FPI 78.9 ± 23.9; moderate FPI 61.3 ± 32.5; severe TBI 72.5 ± 28.3). However, another study by Rodgers et al. (2015) that examined ECoG recordings of SWDs in FPI, naïve and sham-control rats at different time points for up to one year post-injury found that the control and FPI rats were indistinguishable on all SWD measures examined. Furthermore, SWDs were consistently accompanied by behavioral arrest; a sensory stimulus consistently stopped the SWDs; and none of the FPI-treated rats developed non-convulsive or convulsive seizures that could be distinguished from SWDs. These findings challenge the relevance of SWDs in the context of PTE, and is an important issue for scientists to consider. Taken together, the variability in these PTE findings after an FPI may be in large part due to a number of key methodologic differences (i.e., age, rat strain, and injury parameters), as well as the differences in the definition of what is a seizure between these studies. It should also be noted that many of these issues are not specific to the FPI model.

While PTE measures are commonly assessed in rats given an FPI, few studies have investigated PTE-related outcomes in mice given an FPI. However, promising initial evidence suggests that similar PTE-related outcomes occur in both rats and mice. For example, Bolkvadze & Pitkanen (Bolkvadze and Pitkanen, 2012) administered an FPI to C57BL/6 adult male mice and followed them for 9 months. Late spontaneous electrographic seizures were detected in 3% of mice after FPI. Furthermore, 71% had spontaneous

epileptiform spiking and 58% had spontaneous epileptiform discharges. A pentylenetetrazol (PTZ) test demonstrated increased seizure susceptibility in the majority of mice compared to control mice. Similarly, Mukherjee et al. (2013) also found that mice given an FPI exhibited an increased severity, frequency, and duration of seizures in response to PTZ injection compared with the sham and naïve control groups on day 30 post-injury. As such, it appears that FPI in the mouse may provide an additional rodent model of PTE, though further studies are required to reproduce and expand on these initial studies.

While the FPI model has been useful in the study of TBI and PTE, there are a number of limitations that should be considered. The required craniotomy and use of anesthetic do not occur in the clinical TBI setting prior to injury and may affect injury outcomes. These issues are somewhat addressed by the use of sham-injured controls and delaying the injury until the return of pain reflex (i.e., the majority of anesthetic has been metabolized). The quality of the sham-injury is also dependent on the skill of the experimenter, and previous studies have reported that the sham injury itself can result in significant damage (Cole et al., 2011), though other studies dispute this (Martens et al., 2012). The FPI may also result in a greater degree of heterogeneity relative to more homogenous TBI models, although it has been suggested that this heterogeneity within TBI models should be embraced as it models the heterogeneity that occurs clinically (Shultz et al., 2017). Furthermore, researchers could capitalize on injury variability by correlating the differences in animal responses to FPI with other outcomes of interest (e.g., PTE). Despite the above limitations, the FPI method represents a well-characterized, validated, reproducible, and adaptable technique that successfully models many of the key features of TBI. Of particular relevance to this review, the FPI is arguably the most well-characterized and dependent model of PTE that is currently available.

3. Controlled cortical impact (CCI)

Controlled cortical impact (CCI) is another of the most commonly used techniques to study TBI mechanisms and evaluate potential therapies. First developed with ferrets in the 1980’s, the model is now frequently used in both rats (Dixon et al., 1992) and mice (Smith et al., 1995). Using a pneumatic or electromagnetic piston, injury is induced by direct impact of a rapidly accelerating rod onto the intact dura through a craniotomy, resulting in deformation of the underlying cortex (Osier and Dixon, 2016). The craniotomy is typically located unilaterally between Bregma and Lambda, and the surgery is performed under general anesthesia aided by a stereotaxic frame. Compared to most other models, CCI affords a high degree of control over biomechanical parameters including the impact velocity, angle, depth of penetration, and duration, as well as the impactor tip’s size and geometry. Such control ensures reproducibility and consistency of injuries generated, and also allows for scalability across different species and different age groups. A lower mortality rate relative to FPI also facilitates the usefulness of CCI to study the chronic effects of TBI (Osier and Dixon, 2016).

In general, CCI produces a more focal injury compared to FPI, which influences the observed neuropathology and behavioral consequences (Dunn-Meynell and Levin, 1997). Consistent with aspects of human TBI, CCI results in graded histological and axonal injuries, necrotic and apoptotic cell death, cerebrovascular injury including disruption of the

blood-brain barrier, edema, inflammation, and alterations in cerebral blood flow (Cernak, 2005; Osier and Dixon, 2016). Chronically, the CCI-injured brain is characterized by a pronounced lesion cavity in the ipsilateral cortex, global loss of gray and white matter coinciding with ventricle enlargement, loss of hippocampal neurons, and persistent activation of neuroinflammation (Osier et al., 2015). Mossy fiber sprouting has also been reported in the ipsilateral hippocampus, weeks to months post-CCI (Hunt et al., 2009b; Kelly et al., 2015; Semple et al., 2017c).

On a functional level, neurobehavioral and cognitive dysfunction including memory and learning deficits are common after CCI (Fox et al., 1998; Scheff et al., 1997), and these may persist up to one year post-injury (Lindner et al., 1998). Sensorimotor deficits are typically more transient, and may affect gross motor function and/or fine motor coordination (Morales et al., 2005). Psychosocial and emotional behaviors are also influenced by CCI injury, although these symptoms are typically less dependent on injury severity compared to cognitive and motor deficits (Semple et al., 2012; Washington et al., 2012).

Several laboratories have demonstrated the presence of spontaneous seizures in rodents after CCI. Early seizures have been reported within 24 h of the impact (Guo et al., 2013; Hunt et al., 2009b; Kochanek et al., 2006), although whether such events are predictive of later PTE development after CCI remains unclear. For example, a large study of CCI in adult rats observed seizures in 12% of animals within the first week post-injury, yet none of these animals went on to develop spontaneous convulsive seizures long-term (mean monitoring period of 270 h over mean of 217 days) (Kelly et al., 2015). Chronically, Hunt and colleagues (2009) were the first to recognize CCI as a model of PTE in mice. Adult mice were subjected to CCI (3.5 m/s, 400 ms) and observed up to 71 days post-injury, when spontaneous behavioral seizures were detected in 20% of mice after mild injury (0.5 mm depth), and 36% of mice with severe injury (1.0 mm depth) (Hunt et al., 2009b). Guo and colleagues employed continuous video-EEG monitoring across a 16 week period after CCI (5 m/s, 100 ms, 2 mm depth), and detected PTE (spontaneous seizures > 1 week after injury) in 50% of injured mice (Guo et al., 2013). Latency to first seizure was typically weeks to months, and the average seizure frequency was quite low (0.55 seizures/day). In contrast, Bolkvadze and Pitkanen reported late post-traumatic electrographic seizures in only 9% of mice after CCI (5 m/s, 100 ms, 0.5 mm depth), based on two 2-week periods of continuous video-EEG monitoring at 6 and then 9 months post-injury (Bolkvadze and Pitkanen, 2012). However, the majority of CCI-injured mice exhibited spontaneous epileptiform spiking on EEG, and challenge with PTZ demonstrated increased seizure susceptibility in most TBI mice compared to controls.

In adult rats, epileptic seizures have been observed in 20% of animals after CCI (4 m/s, 100 ms, 2.8 mm depth), using intermittent video-EEG monitoring between 8–619 days post-injury (Kelly et al., 2015). Other investigators have demonstrated that CCI in rats accelerates the rate of seizure acquisition compared to sham-operated or uninjured mice, when animals were exposed to a ‘second-hit’ of either electrical (amygdala-kindling) or chemical (PTZ) stimulation (Eslami et al., 2016). Such findings are consistent with the hypothesis that TBI results in a lower seizure threshold, and an environment more susceptible to seizure generation.

Limited studies to date have utilized CCI in immature rodents. Statler and colleagues (2008) subjected a small number of rats at post-natal day (pnd) 16–18 (4 m/s, 100 ms, 2 mm depth; n=8). Video-EEG monitoring between 4–11 months post-CCI injury found that most of the injured rats showed abnormal epileptiform spiking on EEG, and one exhibited spontaneous, recurrent convulsive seizures (Statler et al., 2009a). In another study, the same investigators employed electroconvulsive seizure paradigms involving trans-corneal stimulation, to assess hindlimb, forelimb and limbic seizure thresholds. Here, CCI injury at pnd 16–18 reduced in the minimal clonic seizure threshold by adulthood (6 weeks post-injury) compared to during adolescence (2 weeks post-injury), which was attributed to a combination of maturational changes and progressive epileptogenesis (Statler et al., 2008). Young brain-injured mice also show an increased propensity to develop seizures in response to a stimulus. After CCI to pnd 21 mice (4.5 m/s, 150 ms, 1.7 mm depth), PTZ evoked a significantly more pronounced seizure response in TBI mice compared to sham controls as early as 2 weeks post-injury, which persisted for at least 6 months (Semple et al., 2017c). Video-EEG for 7 continuous days at 5–6 months post-injury also revealed at least 1 spontaneous epileptic seizure in 95% of TBI mice (average of approximately 1 seizure/day). Additional cohorts are required to determine whether the high incidence of PTE in this study is due to the age-at-insult, model severity, or other factors.

In addition to the *in vivo* animal work described above, several electrophysiology experiments utilizing *ex vivo* brain slices collected from rodents after CCI have shed light on the timing and development of neuronal excitability after TBI. In slices with MFS collected 2 months after CCI in adult mice, stimulation of the perforant pathway revealed spontaneous and evoked epileptiform activity indicative of functional network changes, similar to those associated with temporal lobe epilepsy (Hunt et al., 2009b). Spontaneous and evoked epileptiform activity has also been observed in the adult and juvenile rat cortex, providing evidence of a rapid epileptogenic process as early as 1–2 weeks after CCI (Nichols et al., 2015; Yang et al., 2010). Most recently, single-unit recordings from layer V pyramidal neurons in the peri-lesional cortex revealed a sequence of time-dependent changes in neuronal activity that may contribute to the development of hyperexcitability after injury (Ping and Jin, 2016).

Taken together, use of CCI as a model of PTE remains in its infancy. Comparison between studies is challenging due to the lack of standardization of injury parameters (e.g., impact velocity, depth and duration) in the published literature (Osier and Dixon, 2016). The potential relationship between injury severity and PTE has not been fully characterized; however, several studies have failed to find a correlation between the extent of neuropathology and the development of PTE (Bolkvadze and Pitkanen, 2012; Kelly et al., 2015). In contrast to other TBI models, CCI induces a pronounced cortical contusion with a limited extent of diffuse pathology (Osier and Dixon, 2016). In this regard, CCI is an excellent model of patients with contusional TBI, but is less suitable for the investigation of diffuse injuries. Other limitations of CCI, such as the use of anesthesia and necessity for a surgical procedure (craniotomy) in addition to the impact itself, are common to many other TBI models, and can be somewhat mitigated by the inclusion of sham controls. Nonetheless, studies to date have demonstrated that CCI can result in both an increased propensity for evoked epileptiform activity as well as the presence of late spontaneous recurrent seizures.

These post-CCI seizures are similar to the spontaneous behavioral and electrographic seizures that have been observed in rats after lateral FPI (Kharatishvili et al., 2006a), and in models of TLE (Hunt et al., 2013). Further, the onset latency of spontaneous seizures after CCI appears to be shorter than that induced by FPI (D'Ambrosio et al., 2004b; Kharatishvili et al., 2006a).

4. Blast-induced TBI (bTBI)

TBI caused by exposure to explosive blast is the most complex and least understood form of TBI due to the complexity of physical forces and limited knowledge about how the brain responds to blast overpressure. The primary component of an explosion is the high energy, supersonic shockwave that triggers a unique pathological response characterized by rapid onset of malignant cerebral edema and delayed vasospasm in the severe form of primary bTBI (Ling et al., 2009). Explosion also creates high-speed winds that can cause kinetic movements (secondary bTBI), combustion gases, extreme temperature, and projectiles (tertiary bTBI) (Masel et al., 2012). While severe bTBI includes unique clinical symptoms and pathomechanisms, the pathobiology of moderate and mild forms of bTBI shares components of other forms of TBI.

High-fidelity modeling of bTBI is performed outside of the laboratory where real explosives can be used and various field conditions (e.g., free-field blast, bare vs. cased charge, walled structures) can be factored in (Ritzel et al., 2011). These experiments typically use large animals, pigs or sheep, and various forms of explosives (Bauman et al., 2009). The laboratory equivalent is a long tube representing the cut-out segment of the spherical blast (Bauman et al., 2009; Masel et al., 2012). The blast tube uses explosive charge as the "driver" to generate the shockwave (Risling and Davidsson, 2012; Risling et al., 2011), whereas the shock tube uses compressed air or other gas (e.g., helium). The shock tube consists of two compartments, the compression chamber and the expansion chamber separated by a Mylar or other type of diaphragm (Andersen and Louie, 1978; Celander et al., 1955; Chen and Constantini, 2013; Mediavilla Varas et al., 2011). The compression chamber is either connected to high-pressure gas cylinders or an air compressor that pumps air inside the compression chamber, and a high velocity shock wave is generated when the Mylar membrane ruptures. The physical parameters of the shock wave (Friedlander, 1946), including peak pressure and positive phase duration, are determined by the thickness of the Mylar membrane in the shock tube, the quantity and type of explosive charge in the blast tube, as well as by tube geometry (Masel et al., 2012; Needham et al., 2015; Ritzel et al., 2011). The resulting shock wave travels along the expansion chamber where the experimental subject (typically a rat) is placed. In order to expose animals to the shock wave, thus modeling primary bTBI, the animal must be placed inside the tube with its torso protected to mimic field conditions (Needham et al., 2015). Exposure without body protection significantly increases lethality due to lung injury (Ling et al., 2009). Furthermore, animals placed outside of the tube are exposed to blast wind, causing rapid acceleration/deceleration. Injury severity, including lethality, is also affected by the position of the animal inside the tube (Cernak, 2010). For this reason, the use of prone position and lateral (right) side exposure of the head to the blast wave seems optimal (Kamnaksh et al., 2011; Koliatsos et al., 2011; Long et al., 2009). Exposing the head only to blast creates an

artifact not only for reasons discussed above but also because in real life bTBI is part of a complex whole body exposure, and systemic responses are likely part of the bTBI pathology (Cernak, 2010). Due to general cost-effectiveness, availability of well-established behavioral tests, speciesspecific antibodies enabling immunohistochemistry and antibody-based proteomics, and comparability of bTBI outcomes with other TBI models, rats and mice are the animals of choice for most bTBI studies (Koliatsos et al., 2011; Long et al., 2009). In addition, genetically modified mouse strains enable researchers to study the effect of specific genes in the pathobiological response to bTBI (Rubovitch et al., 2011). However, rodents have issues regarding scalability and neuroanatomical differences between rodents and humans (Nakagawa et al., 2011; Saatman et al., 2008).

Approximately 85% of military bTBI cases are mild and most soldiers suffer from additional blast exposures. Before modeling repeated mild bTBI, one needs to consider the period of increased cerebral vulnerability following the first exposure. Available literature indicates that the length of increased cerebral vulnerability is measured in hours in rodents vs. days/weeks in humans (Ahmed et al., 2013; Kamnaksh et al., 2014; Povlishock, 2013). Although the real conversion rate between rodent and human pathological timescales is unknown, cumulative effects of mild bTBI have been seen when the interval was less than 24 hours (Ahlers et al., 2012; Ahmed et al., 2013; Huang et al., 2013; Kamnaksh et al., 2012).

Primary bTBI (except in severe cases with penetrating injuries) is a closed head-injury; however, available data indicates that the pathobiology of primary bTBI is different from the acceleration/deceleration type of closed head injury (Cernak et al., 2011; Cernak and Noble-Haeusslein, 2010; Masel et al., 2012). The shock wave exerts its damage by dissipating energy at boundaries of biological structures with differing acoustic impedances, such as white and gray matter, or the brain parenchyma and blood (Nakagawa et al., 2011). Primary bTBI pathology includes altered cellular metabolism, cell–cell adhesion, neuron, axon and glia damage, and vascular abnormalities (Agoston and Elsayed, 2012; Ahmed et al., 2015; Garman et al., 2011; Kochanek et al., 2013; Nakagawa et al., 2011; Shively et al., 2016). Exposure to a single moderate blast results in a robust increase in the serum levels of glial fibrillary acidic protein (GFAP), S100β, and myelin basic protein (MBP) (Agoston et al., 2009). The leading neurobehavioral impairments of bTBI are learning and memory deficits, anxiety, and depression (Elder et al., 2012; Kamnaksh et al., 2011; Kamnaksh et al., 2012; Kovesdi et al., 2012; Kwon et al., 2011). Experimentally, these deficits are mitigated by acute anti-inflammatory treatment (Kovesdi et al., 2012). It should be noted here that the neurobehavioral deficits of mild bTBI partly overlap with the symptomatology of post-traumatic stress disorder (PTSD), making the clinical diagnosis and experimental interpretation challenging.

In contrast to the well-established link between moderate and severe penetrating TBI and PTE (Raymont et al., 2011), the role of bTBI as a risk factor for PTE is currently poorly understood (Chen et al., 2014). There are several reasons for this discrepancy but the most important is the lack of longitudinal studies including Veterans that have suffered bTBIs. Such studies, similar to the Vietnam Veterans Head Injury Study (Raymont et al., 2011) would provide critical information about the prevalence of PTE among Veterans of the recent military conflicts in Afghanistan and in Iraq. Approximately 80% of Veterans with a

history of TBI were exposed to blast; the majority to mild blasts and typically more than one. The overwhelming majority did not suffer penetrating head injury, which is a major risk factor for PTE, but ~80% of those with mild bTBI had PTSD (Chen et al., 2014). In this limited study, only ~20% of Veterans suffered PTE with 44% experiencing psychogenic, non-epileptic seizures.

Animal models of bTBI can help to determine if bTBI is a risk factor for PTE. However, high fidelity modeling of bTBI has its unique challenges. Differences in neuroanatomy and cellular architecture play a much larger role in bTBI modeling than other forms of head injury (Saatman et al., 2008). As human neuropathology and modeling studies indicate, shock waves interact differently with gyrencephalic (human) vs. lissencephalic (rodent) brains (Gupta and Przekwas, 2013; Nakagawa et al., 2011; Saatman et al., 2008). Large animals with gyrencephalic brains, like swine but especially nonhuman primates, offer high-fidelity and scalable bTBI modeling as well as clinically relevant monitoring of biological outcomes (Bauman et al., 2009; Masel et al., 2012). Because of cost and ethical considerations, large animal models are unlikely to be used in any future bTBI studies. Therefore, much work needs to be done to close the translational gap between rodent modeling of bTBI and clinical bTBI cases, including: the differing time frames between rodent and human biology and pathologies (Agoston, 2017); the size and anatomical differences that are required for scalability (i.e., the development of “dosimetry”); and establishing the precise relationship between the physical forces of blast, such as peak pressure and duration, and the biological response to injury, including epileptogenesis and PTE.

5. Penetrating brain injury

Of all of the types of TBI associated with epilepsy, penetrating injuries have the greatest risk, with a prevalence that can approach 60% if the injury is extensive and there are retained foreign materials such as bone or metal fragments (Agrawal et al., 2006; Lowenstein, 2009; Sights and Bye, 1970). Gunshot wounds to the head are one of the most common sources of this type of injury. Penetrating ballistic-like brain injuries are caused by a penetrating bullet that creates a cavity that is greater than the size of the bullet itself (Williams et al., 2005). There have been a number of rat models of penetrating ballistic-like brain injury that include an inflatable small balloon probe into the brain (Lu et al., 2011; Shear et al., 2010; Williams et al., 2005). This model mimics the acute hemispheric swelling, increased intracranial pressure and significant intracerebral hemorrhage observed in patients. Although acute nonconvulsive seizures have been reported, there are no long-term studies to determine whether these rats develop epilepsy. There are other models using pistons that are driven into the brain by a pellet (Plantman et al., 2012). There are no long-term EEG studies in these animals either.

These models lack the foreign materials that remain *in situ*, which commonly occurs in patient with penetrating brain injuries (typically from a firearm or shrapnel from an explosive device) (Eftekhar et al., 2009). In some cases, the fragments are of steel, but in the case of bullets they typically consist of copper coverings over a lead core. It has been noted by a number of authors that copper placed in the brain experimentally induces a significant

inflammatory reaction (Babb and Kupfer, 1984; Dymond et al., 1970; Robinson and Johnson, 1961) and lead is a well-known metabolic toxin.

A recent study developed a simple rodent model of penetrating injury with retained fragments that requires minimal equipment and which had a high incidence of subsequent epilepsy (up to 90%). Importantly, this model replicates several key features of penetrating brain injury (i.e., traumatic brain penetration and the deposition of foreign materials that remain *in situ*) (Kendirli et al. 2014). The model involves a small caliber drill burr (1.5mm diameter) to drill through the skull and into the hippocampus while the drill is rotating at a high speed (1000rpm). Either copper wire or stainless-steel wire were inserted into the drill track.

Five to nine months post-injury rats were implanted with recording electrodes, and were placed on continuous EEG video monitoring for a minimum total of four weeks to identify the presence, the frequency and the behavioral nature of the seizures. Almost all of the rats with copper had a recognized seizure, but almost none of the rats with a lesion only or lesion plus stainless steel did (Kendirli et al., 2014). Twenty-two of the twenty-three rats with copper wire developed epilepsy (96%) whereas only three of the twenty combined control group (15%; lesion with or without stainless steel wire) had late spontaneous seizures. There was no difference between the two control groups. Of the animals with epilepsy, the ones with implanted copper wire had a higher seizure frequency (over 3 seizures per day compared to 0.2 seizures per day for controls) and the seizure severity score was higher as well (Racine score 4 as opposed to 1 among the controls). Seizure frequency was quite variable from animal to animal(Kendirli et al., 2014). One may conclude that the presence of copper greatly increases the probability of developing epilepsy and an epilepsy that is more severe compared to those rats without copper.

To determine whether there was a difference among the animals in the development of acute seizures as opposed to chronic epilepsy, in a separate group of rats, recording electrodes were placed at the time of the injury, and the rats were placed on continuous video EEG monitoring the following day. A high percentage of rats in both groups (70% for injury with copper and 83% with stainless steel) had acute seizures in the first 7–10 days following the injury. There were also no differences in seizure duration or behavioral severity. These observations would suggest that because rats with stainless steel are at low risk for chronic epilepsy that the acute seizures are not predictive of subsequent epilepsy development. This observation supports the conclusion that the pathophysiology of acute seizures after an injury is different from that of the chronic spontaneous seizures. The data suggest that the acute seizures cease and that there is a latent period before the appearance of the long-term seizures. However, further studies that follow individual animals with EEG from the time of injury for an additional six to nine months are needed to confirm that conclusion.

There are clear differences in the gross pathology of the brains of the lesion only and the lesion with copper rats. In the uncut brains at 7 months post-injury the brains from the copper rats had a green discoloration, presumably for precipitated copper carbonate in much of the lesioned hemisphere, especially around the copper wire. In cut brains, the lesion only animals showed a vertical, narrow penetrating injury with little volume loss beyond the

primary injury whereas the copper wires had extensive volume loss and degeneration that extended millimeters in all directions from the primary lesion. Whether the epilepsy results from the damage that develops over time or from the known inflammatory reaction to the metal is unknown.

This model has many parallels to its human counterpart, though there are limitations that should be considered. For example, the size of the lesion in this model is typically smaller when compared to patients with penetrating brain injury. Initial attempts to create larger lesions were met with an unacceptable mortality, usually from acute hemorrhage. Even with its limitations this model has the potential to answer a number of questions about the underlying pathophysiology of epilepsy following a penetrating brain injury. The time to development of chronic seizures in this trauma model, which is likely a number of months may seem prohibitive to some labs, but the simplicity in creating the model should mitigate this concern and make the model a valuable tool for epilepsy research.

6. Other models

The animal models of PTE described above involve a moderate to severe TBI. However, mild TBI (mTBI) accounts for the large majority of TBI cases, and there is evidence that mTBI is a risk factor for PTE. Therefore, this section will briefly review other TBI models which result in injuries that are less severe. Although the majority of these models have yet to examine for the presence of spontaneous seizures, they may be of great importance in the study of PTE once appropriately characterized.

6.1. Weight-drop models

Rodent weight-drop methods are most frequently used to model closed-head TBI. The first weight-drop model was a cortical contusion model developed in rats (Feeney et al., 1981). In Feeney's model, anesthetized rats are given a craniotomy over the right frontal-parietal cortex, and a cylinder guiding a weight onto a footplate is positioned over the craniotomy. The weight is released impacting the footplate and delivering an injury to the exposed dura. This injury is associated with localized hemorrhages (Lewen et al., 1996), glial cell activation (Allen et al., 2000; Lewen et al., 1996), cortical neuron loss (Allen et al., 2000; Lewen et al., 1996), increases in extracellular glutamate (Nilsson et al., 1990), and altered calcium homeostasis (Nilsson et al., 1993). Importantly, this injury has been demonstrated to increase susceptibility to PTZinduced seizures; however, whether spontaneous seizures occur in these animals is yet to be established (Golarai et al., 2001).

Marmarou's impact acceleration weight-drop model is often used to induce a diffuse axonal injury pattern. In Marmarou's model, anesthetized rodents receive a midline incision to expose the skull and a flat, stainless steel disc is attached (commonly glued) to the midline of the skull between Lambda and Bregma (Marmarou et al., 1994a). The rat is placed on a foam platform and a brass weight is dropped down a guided cylinder directly on the stainless steel disc. In this model, the head was not fixed and was allowed to rotate downward. It has been suggested that this motion, in combination with the impact, results in widespread axonal injury, particularly, in the corpus callosum, optic tracts and long tracts in the brainstem as well as reactive microglia (Beaumont et al., 1999; Xu et al., 2014). The effect

this injury model/pattern has on seizure susceptibility and the generation of recurrent spontaneous seizures is yet to be determined. However, a modification of this model whereby a pneumatic impactor was used to accelerate a 2.00mm steel tip onto concave metallic disk was found to increase seizure susceptibility to electroconvulsive shock (Chrzaszcz et al., 2010).

Shohami's closed-skull mouse model is widely used to induce a mixed focal-diffuse injury pattern that is common for human patients with concussion or mTBI (Flierl et al., 2009). In order to induce the injury, anesthetized mice receive a midline incision to expose the skull, and the head is held in position on a solid platform. A blunt-tipped rod is then released, typically from a height of 1.5–2 cm, to create impact lateral to the junction of the coronal and sagittal sutures. Skull fracture is usually avoided in the mild form of this model. A single TBI with Shohami's weight-drop can induce neuroinflammation, hyperphosphorylated tau, and edema (Webster et al., 2015), along with temporary neurological impairments (Flierl et al., 2009), whereas repeated TBI with this model can induce persisting cognitive deficits (DeFord et al., 2002). However, seizure susceptibility and the prevalence of epilepsy in these animals remains unknown. Of note, this model may have advantages over the previously mentioned weightdrop protocols, as the quick surgery allows for a relatively light depth of anesthesia and high throughput, and importantly the impact produces a mixed focal-diffuse injury frequently seen in human TBI.

6.3. Repetitive mild TBI models

In recent years there has been increased research efforts investigating the potential effects of repeated mild TBI. This is in large part due to clinical findings in athletes and military personnel linking repetitive mild brain traumas with a spectrum of long-term neurological consequences (Clough et al., 2018; Guskiewicz et al., 2007; McKee et al., 2014; McKee et al., 2013; Tarazi et al., 2018).

Initially, preclinical models of repeated mild TBI were mostly based on adaptations of the common models described earlier in this review (e.g., repeated FPI; Shultz et al., 2012). However, it is now recognized by the field that there are major limitations in adapting experimental TBI models that involve substantial anesthetic as well as surgical procedures (e.g., craniotomy), as these factors may significantly confound mild TBI outcome and do not occur in the clinical setting (Shultz et al., 2017). As such, new models of mTBI have been developed to avoid these issues.

The lateral impactor model induces lateral acceleration/deceleration and rotational forces that produce an injury that mimics mTBI which are often observed in sports-related concussion (Viano et al., 2007; Viano and Pellman, 2005). In this model, animals are lightly anesthetized for less than 30 seconds until no pain response is elicited. Using a pneumatic barrel, a 100g weight is accelerated toward a small helmet on the rat's head, producing an impact which propelled the rat into a 180° rotation (Mychasiuk et al., 2016). The lateral impactor model has been used only in mild TBI and repetitive mild TBI (Wright et al., 2017). Animals that received repetitive mTBI using this model have cumulative behavioral deficits and structural brain damage (Wright et al., 2017).

Petraglia and colleagues (2014) described a closed-head CCI variant in awake mice, in which the injury is given with a modified 5mm rubber tip to a mouse secured in a conical restraint bag, placing a helmet on its head, and positioning the mouse on a foam platform (Petraglia et al., 2014a; Petraglia et al., 2014b). Mice given repetitive mTBI daily for 7 days had persisting behavioral deficits and sleep disturbances demonstrated on EEG and electromyography (Petraglia et al., 2014a). Notably, this awake closed head CCI model of single and repeated mTBI has now been adapted to rats (Meconi et al., 2018).

The Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA) is a nonsurgical mouse mTBI model that delivers impacts of variable dynamic characteristics to a closed skull while enabling kinematic analysis of unconstrained head movement. Repeated mTBI using this model mimics many of the functional and pathological characteristics of human TBI with a reliable biomechanical response of the head, including motor deficits, anxiety-like behavior, memory impairment, persistent diffuse axonal injury with extensive white matter inflammation and increased phosphorylation of endogenous tau (Namjoshi et al., 2017; Namjoshi et al., 2014).

While there is some clinical evidence linking mild TBI to an increased likelihood of developing epilepsy (Christensen et al., 2009; Keret et al., 2017; Sick et al., 2017; Yeh et al., 2013), this topic remains highly controversial, with other findings disputing a significant relationship (Gilad et al., 2013; Huguenard et al., 2016; Wennberg et al., 2018). Due to the relatively mild nature of mTBI and delayed onset of PTE it is immensely challenging to adequately study this relationship in humans, which supports the use of animal models to provide insight into this question. The incidence of PTE after repeated TBI has also been poorly characterized in both preclinical models and in human patients. While it is possible that these preclinical studies may result in negative findings in terms of PTE (i.e., animals will not develop spontaneous recurring chronic seizures), these findings will be informative nonetheless and should be pursued.

7. Future directions & conclusions.

Animal models provide essential tools to further our understanding of PTE, establish causal mechanisms of disease, facilitate hypothesis testing, enable systematic exploration of pathophysiology and biomarkers, and conduct rigorously controlled experiments to evaluate new diagnostics and therapeutics that will ultimately lead to better informed medical decisions and improved outcomes for patients. As summarized in Table 1, there are a number of preclinical TBI models that replicate some aspects of PTE, it may be valuable if their limitations are recognized and considered in the study design and the interpretation of the results. Amongst these limitations, the significant heterogeneity of preclinical and clinical TBI and PTE is one of the greatest challenges. Given that some models model aspects of human-PTE better than others, one strategy to help overcome this problem is the application of complementary models (e.g., comparing across blast, focal, diffuse, mixed focal-diffuse, penetrating models) to ultimately help understand PTE. This will require large scale multi-center pre-clinical trials in the context of consortiums. This approach may be particularly useful to trial prospective biomarkers and novel antiepileptogenic and disease modifying therapies. Moreover, another strategy is to embrace and capitalize on the inherent

heterogeneity within TBI and PTE models, by studying and correlating the variability of the injury and development of PTE with different outcomes of interest. To further reduce variability between the different PTE models, preclinical researchers must also ensure to standardize aspects of data collection and provide more complete, comprehensive, and equivalent data across studies. This means to incorporate objective indicators of injury, recovery and endpoints into their studies, particularly when investigating biomarkers and disease modifying therapies.

By including details of the injury parameters, as well as serial measures of the presence or absence of any pathophysiological, structural, and functional changes induced by the model, the relevance and significance of findings will become less subjective, and findings more likely to reproduced in different laboratories. Common data elements and case report forms are strategies that have been proposed to standardize epilepsy research as discussed in another chapter of this special issue.

Confounding factors such as craniotomies and anesthetic are also important to consider, as they are not normally present in TBI patients at the time of injury, although craniotomy and anesthetic may be induced in the acute management of more severe TBI. The craniotomy and anesthetic may also be necessary in order to deliver a consistently severe epileptogenic brain injury that would not be technically or ethically possible in a closed head and/or conscious model.

Cross-species validation is necessary to help minimize future translational failures. Pre-clinical research would be improved by incorporating more clinically relevant functional and neuroimaging measures in addition to the more commonly used cellular and molecular endpoints. For example, before embarking on testing presumed disease modifying drugs in long term preclinical or early clinical trials based on only animal pathophysiological findings, it would be useful to confirm those pathophysiological findings in human cohorts, at least to best of our ability (Casillas Espinosa et al., 2012). For example, tau a microtubule associated protein, is hyperphosphorylated after brain insults and destabilizes microtubules leading to the formation of neurofibrillary tangles, which induce cell damage, neuronal dysfunction and ultimately neuronal death (Ittner and Götz, 2011; Sen et al., 2007). Hyperphosphorylated tau has been found to be in multiple degenerative neurological diseases such as Alzheimer’s, focal cortical dysplasia, traumatic brain injury and epilepsy-PTE, in both experimental models and patients (Corcoran et al., 2010; Ittner and Götz, 2011; Jones et al., 2012; Liu et al., 2016b; Sen et al., 2007; Shultz et al., 2015; Thom et al., 2011; van Eersel et al., 2010), which makes tau an attractive drug target in several neurological disorders, including PTE.

Related to the above point, if human studies are not possible it may be beneficial to validate rodent findings in larger animal studies. Large mammal models of TBI represent an advantage in that their brains are more structurally similar to the human brain. This similarity encompasses the gyrencephalic morphology, grey and white matter ratio, developmental patterns, degree of myelination, cerebrovascular anatomy, physiology and pathophysiology. Most of the principal models described in this paper, including the FPI, CCI, bTBI, and penetrating models can be applied in large mammals which further

facilitates cross-species validation (Dai et al., 2018; Shultz et al., 2017). Despite the advantages that represent larger animal models of TBI, the study of PTE is complicated because of the long-term nature of the experiments. Moreover, the large animals are less well characterized than rodents with respect to motor and behavioral deficits, biomarkers, pathophysiology and functional outcome tests. In addition, ethical and financial considerations, also limit enthusiasm in using larger species. As described in detail in the introduction, determination of what is a seizure in rodent-PTE models is a highly controversial area, with no generally accepted criteria. Another related issue is the most appropriate time post-TBI to record EEG in preclinical models. One cannot definitely establish that TBI "non-epileptic" animals won't develop spontaneous seizures outside of the monitoring period. This represents a conundrum, because no duration of followup could definitively rule out if an animal would develop PTE, because no matter how long the time interval at which the recording was undertaken after the TBI epileptogenic insult it would not exclude that after this time the animals would not ultimately develop spontaneous seizures. Most of the experimental PTE studies use males in an attempt to reduce variability related to the estrus cycle (Wright et al., 2017). Experimental animal studies suggest that female sex entails a lower rate of complications and comorbidities after experimental TBI than male sex does (Berry et al., 2009; Reid et al., 2010; Semple et al., 2017a; Wright et al., 2017). Evidence has also shown that female sex hormones may have a neuroprotective effect in TBI (Reid et al., 2010; Stein, 2011; Wright et al., 2017).

There is an unmet need to better understand the role of brain maturation and age on acquired epileptogenesis. In the clinical setting, the incidence of PTE is particularly high in young children under 2 years of age (Arndt et al., 2013; Ates et al., 2006). On the other hand. elderly individuals with TBI differ from younger adults with TBI in their PTE incidence rates, nature of complications, functional outcomes, and mortality (Flanagan et al., 2005). Despite these age-related differences, the majority of pre-clinical research has primarily focused on young adult rodents. While this population does represent a high proportion of the clinical cases of TBI, preclinical models must be used to further study how age can affect TBI and PTE. Such studies might identify age-specific pathophysiological and/or epileptogenic changes that may dictate different treatment approaches depending on the age of the individual (Hoane et al., 2004).

In conclusion, the study of clinically relevant models of PTE is critical to advance our understanding of the pathophysiological mechanisms that result in the development of epilepsy. This review has provided an overview of a number of commonly used rodent models of TBI and PTE that can identify subjects with the highest risk for PTE and producing breakthroughs in the discovery and development of novel antiepileptogenic treatments.

References

Agoston DV, 2017 How to translate time? The temporal aspect of human and rodent biology. Frontiers in Neurology.

Agoston DV, Elsayed M, 2012 Serum-Based Protein Biomarkers in Blast-Induced Traumatic Brain Injury Spectrum Disorder. Front Neurol. 3, 107. [PubMed: 22783223]

Agoston DV, et al., 2009 Proteomic biomarkers for blast neurotrauma: targeting cerebral edema, inflammation, and neuronal death cascades. J Neurotrauma. 26, 901–11. [PubMed: 19397421]

Agrawal A, et al., 2006 Post-traumatic epilepsy: an overview. Clinical neurology and neurosurgery. 108, 433–439. [PubMed: 16225987]

Ahmed F, et al., 2015 The temporal pattern of changes in serum biomarker levels reveals complex and dynamically changing pathologies after exposure to a single lowintensity blast in mice. Frontiers in neurology. 6, 114. [PubMed: 26124743]

Ahmed FA, et al., 2013 Long-term consequences of single and multiple mild blast exposure on select physiological parameters and blood-based biomarkers. Electrophoresis. 34, 2229–33. [PubMed: 23712899]

Allen GV, et al., 2000 Conditioning effects of repetitive mild neurotrauma on motor function in an animal model of focal brain injury. Neuroscience. 99, 93–105. [PubMed: 10924955]

Andersen WH, Louie NA, 1978 Shock tube for simulating nuclear blast durations. Rev Sci Instrum. 49, 1729. [PubMed: 18699045]

Annegers JF, et al., 1998 A population-based study of seizures after traumatic brain injuries. The New England Journal of Medicine. 338, 20–24. [PubMed: 9414327]

Armstead WM, Kurth CD, 1994 Different cerebral hemodynamic responses following fluid percussion brain injury in the newborn and juvenile pig. Journal of Neurotrauma. 11, 487–497. [PubMed: 7861442]

Arndt DH, et al., 2013 Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. Epilepsia. 54, 1780–8. [PubMed: 24032982]

Ates O, et al., 2006 Post-traumatic early epilepsy in pediatric age group with emphasis on influential factors. Childs Nerv Syst. 22, 279–84. [PubMed: 15889309]

Aungst S, et al., 2014 Repeated mild traumatic brain injury causes chronic neuroinflammation, changes in hippocampal synaptic plasticity, and associated cognitive deficits. Journal of Cerebral Blood Flow and Metabolism. 34, 1223–1232. [PubMed: 24756076]

Babb TL, Kupfer W, 1984 Phagocytic and metabolic reactions to chronically implanted metal brain electrodes. Exp Neurol. 86, 171–82. [PubMed: 6489492]

Banerjee PN, et al., 2009 The descriptive epidemiology of epilepsy—a review. Epilepsy research. 85, 31–45. [PubMed: 19369037]

Bao F, et al., 2012 A CD11d monoclonal antibody treatment reduces tissue injury and improves neurological outcome after fluid percussion brain injury in rats. Journal of Neurotrauma. 29, 2375–2392. [PubMed: 22676851]

Bauman R, et al., 2009 An introductory characterization of a combat-casualty-care relevant swine model of closed head injury resulting from exposure to explosive blast. J Neurotrauma. 26, 841–60. [PubMed: 19215189]

Beaumont A, et al., 1999 The impact-acceleration model of head injury: injury severity predicts motor and cognitive performance after trauma. Neurol Res. 21, 742–54. [PubMed: 10596383]

Berry C, et al., 2009 The effect of gender on patients with moderate to severe head injuries. Journal of Trauma-Injury Infection & Critical Care. 67, 950–953.

Bolkvadze T, Pitkanen A, 2012 Development of post-traumatic epilepsy after controlled cortical impact and lateral fluid-percussion-induced brain injury in the mouse. J Neurotrauma. 29, 789–812. [PubMed: 22023672]

Casillas Espinosa P, et al., 2012 Regulators of synaptic transmission: roles in the pathogenesis and treatment of epilepsy. Epilepsia. 53 Suppl 9, 41–58. [PubMed: 23216578]

Celander H, et al., 1955 The use of a compressed air operated shock tube for physiological blast research. Acta Physiol Scand. 33, 6–13. [PubMed: 14349723]

Cernak I, 2005 Animal models of head trauma. NeuroRx. 2, 410–22. [PubMed: 16389305]

Cernak I, 2010 The importance of systemic response in the pathobiology of blast-induced neurotrauma. Front Neurol. 1, 151. [PubMed: 21206523]

Chen LL, et al., 2014 Posttraumatic epilepsy in Operation Enduring Freedom/Operation Iraqi Freedom veterans. Mil Med. 179, 492–6. [PubMed: 24806494]

Chen Y, Constantini S, 2013 Caveats for using shock tube in blast-induced traumatic brain injury research. Front Neurol. 4, 117. [PubMed: 23986741]

Christensen J, 2012 Traumatic brain injury: risks of epilepsy and implications for medicolegal assessment. Epilepsia. 53 Suppl 4, 43–47. [PubMed: 22946720]

Christensen J, et al., 2009 Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. Lancet (British edition). 373, 1105–1110.

Chrzaszcz M, et al., 2010 Minozac treatment prevents increased seizure susceptibility in a mouse "two-hit" model of closed skull traumatic brain injury and electroconvulsive shock-induced seizures. J Neurotrauma. 27, 1283–95. [PubMed: 20486807]

Clough M, et al., 2018 Oculomotor Cognitive Control Abnormalities in Australian Rules Football Players with a History of Concussion. Journal of Neurotrauma. 35, 730–738. [PubMed: 29228862]

Cole JT, et al., 2011 Craniotomy: true sham for traumatic brain injury, or a sham of a sham? J Neurotrauma. 28, 359–69. [PubMed: 21190398]

Corcoran N, et al., 2010 Sodium selenate specifically activates PP2A phosphatase, dephosphorylates tau and reverses memory deficits in an Alzheimer's disease model. Journal of clinical neuroscience. 17, 1025–1033. [PubMed: 20537899]

D'Ambrosio R, et al., 2004a Post-traumatic epilepsy following fluid percussion injury in the rat. Brain. 127, 304–314. [PubMed: 14607786]

D'Ambrosio R, et al., 2004b Post-traumatic epilepsy following fluid percussion injury in the rat. Brain. 127, 304–14. [PubMed: 14607786]

D'Ambrosio R, et al., 2005 Progression from frontal-parietal to mesial-temporal epilepsy after fluid percussion injury in the rat. Brain. 128, 174–88. [PubMed: 15563512]

D'Ambrosio R, et al., 2009 Functional definition of seizure provides new insight into posttraumatic epileptogenesis. Brain. 132, 2805–2821. [PubMed: 19755519]

D'Ambrosio R, Miller J, 2010 What is an epileptic seizure? Unifying definitions in clinical practice and animal research to develop novel treatments. Epilepsy Currents. 10, 6166.

Dai J-X, et al., 2018 Large animal models of traumatic brain injury. International journal of neuroscience. 128, 243–254. [PubMed: 28918695]

DeFord SM, et al., 2002 Repeated mild brain injuries result in cognitive impairment in B6C3F1 mice. J Neurotrauma. 19, 427–38. [PubMed: 11990349]

DeRoss A, et al., 2002 Multiple head injuries in rats: effects on behavior. Journal of Trauma-Injury Infection & Critical Care. 52, 708–714.

Dixon CE, et al., 1992 A controlled cortical impact model of traumatic brain injury in the rat. Journal of Neuroscience Methods. 39, 253–62.

Dixon CE, et al., 1987 A fluid percussion model of experimental brain injury in the rat. Journal of Neurosurgery. 67, 110–119. [PubMed: 3598659]

Dubé C, et al., 2006 Temporal lobe epilepsy after experimental prolonged febrile seizures: prospective analysis. Brain. 129, 911–922. [PubMed: 16446281]

Dudek FE, Bertram E, 2010 Counterpoint to "what is an epileptic seizure?" by D'Ambrosio and Miller. Epilepsy Currents. 10, 91–94. [PubMed: 20697504]

Dunn-Meynell AA, Levin BE, 1997 Histological markers of neuronal, axonal and astrocytic changes after lateral rigid impact traumatic brain injury. Brain Res. 761, 2541.

Dymond AM, et al., 1970 Brain tissue reaction to some chronically implanted metals. J Neurosurg. 33, 574–80. [PubMed: 5479495]

Eftekhar B, et al., 2009 Prognostic factors in the persistence of posttraumatic epilepsy after penetrating head injuries sustained in war. Journal of neurosurgery. 110, 319–326. [PubMed: 18976060]

Elder GA, et al., 2012 Blast exposure induces post-traumatic stress disorder-related traits in a rat model of mild traumatic brain injury. J Neurotrauma. 29, 2564–75. [PubMed: 22780833]

Englander J, et al., 2003 Analyzing risk factors for late posttraumatic seizures: a prospective, multicenter investigation. Archives of physical medicine and rehabilitation. 84, 365–373. [PubMed: 12638104]

Eslami M, et al., 2016 Traumatic brain injury accelerates kindling epileptogenesis in rats. Neurol Res. 38, 269–74. [PubMed: 26315855]

Feeney DM, et al., 1981 Responses to cortical injury: I. Methodology and local effects of contusions in the rat. Brain Res. 211, 67–77. [PubMed: 7225844]

Fisher RS, et al., 2014 ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 55, 475–482. [PubMed: 24730690]

Flanagan S, et al., 2005 The impact of age on traumatic brain injury. Physical medicine and rehabilitation clinics of North America. 16, 163–177. [PubMed: 15561549]

Flierl MA, et al., 2009 Bench-to-bedside review: Burn-induced cerebral inflammation--a neglected entity? Crit Care. 13, 215. [PubMed: 19638180]

Fox GB, et al., 1998 Sustained sensory/motor and cognitive deficits with neuronal apoptosis following controlled cortical impact brain injury in the mouse. J Neurotrauma. 15, 599–614. [PubMed: 9726259]

Frey L, 2003 Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia. 44 Suppl 10, 11–17.

Friedlander FG, 1946 The diffraction of sound pulses; diffraction by a semi-infinite plane. Proc R Soc Lond A Math Phys Sci. 186, 322–44. [PubMed: 20998736]

Garman RH, et al., 2011 Blast exposure in rats with body shielding is characterized primarily by diffuse axonal injury. J Neurotrauma. 28, 947–59. [PubMed: 21449683]

Gilad R, et al., 2013 Seizures after very mild head or spine trauma. Journal of Neurotrauma. 30, 469–472. [PubMed: 23227924]

Golarai G, et al., 2001 Physiological and structural evidence for hippocampal involvement in persistent seizure susceptibility after traumatic brain injury. Journal of Neuroscience. 21, 8523–8537. [PubMed: 11606641]

Guo D, et al., 2013 Rapamycin attenuates the development of posttraumatic epilepsy in a mouse model of traumatic brain injury. PLoS One. 8, e64078. [PubMed: 23691153]

Gupta RK, Przekwas A, 2013 Mathematical Models of Blast-Induced TBI: Current Status, Challenges, and Prospects. Front Neurol. 4, 59. [PubMed: 23755039]

Gurkoff G, et al., 2006 Lateral fluid percussion injury in the developing rat causes an acute, mild behavioral dysfunction in the absence of significant cell death. Brain research. 1077, 24–36. [PubMed: 16490184]

Guskiewicz K, et al., 2007 Recurrent concussion and risk of depression in retired professional football players. Medicine & Science in Sports & Exercise. 39, 903–909. [PubMed: 17545878]

Hauser WA, et al., 1993 Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia. 34, 453–458. [PubMed: 8504780]

Hayward NMEA, et al., 2010 Association of chronic vascular changes with functional outcome after traumatic brain injury in rats. Journal of Neurotrauma. 27, 2203–2219. [PubMed: 20839948]

Hayward NMEA, et al., 2011 Magnetic resonance imaging of regional hemodynamic and cerebrovascular recovery after lateral fluid-percussion brain injury in rats. Journal of Cerebral Blood Flow and Metabolism. 31, 166–177. [PubMed: 20485295]

Hicks R, et al., 1996 Temporal and spatial characterization of neuronal injury following lateral fluid-percussion brain injury in the rat. Acta neuropathologica. 91, 236–246. [PubMed: 8834535]

Hoane M, et al., 2004 Middle age increases tissue vulnerability and impairs sensorimotor and cognitive recovery following traumatic brain injury in the rat. Behavioural brain research. 153, 189–197. [PubMed: 15219720]

Huguenard A, et al., 2016 Mild traumatic brain injury in children is associated with a low risk for posttraumatic seizures. Journal of Neurosurgery: Pediatrics. 17, 476–482. [PubMed: 26613272]

Hunt R, et al., 2009a Posttraumatic epilepsy after controlled cortical impact injury in mice. Experimental neurology. 215, 243–252. [PubMed: 19013458]

Hunt RF, et al., 2013 Neural circuit mechanisms of post-traumatic epilepsy. Front Cell Neurosci. 7, 89. [PubMed: 23785313]

Hunt RF, et al., 2009b Posttraumatic epilepsy after controlled cortical impact injury in mice. Exp Neurol. 215, 243–252. [PubMed: 19013458]

Hylin M, et al., 2013 Behavioral and histopathological alterations resulting from mild fluid percussion injury. Journal of Neurotrauma. 30, 702–715. [PubMed: 23301501]

Immonen R, et al., 2009 Quantitative MRI predicts long-term structural and functional outcome after experimental traumatic brain injury. NeuroImage (Orlando, Fla. Print). 45, 1–9.

Ittner L, Götz J, 2011 Amyloid-β and tau--a toxic pas de deux in Alzheimer's disease. Nature Reviews. Neuroscience. 12, 65–72.

Johnstone M, et al., 2018 Gambogic amide, a selective TrkA agonist, does not improve outcomes from traumatic brain injury in mice. Brain injury. 32, 257–268. [PubMed: 29227174]

Johnstone VPA, et al., 2014 The acute phase of mild traumatic brain injury is characterized by a distance-dependent neuronal hypoactivity. Journal of Neurotrauma. 31, 1881–1895. [PubMed: 24927383]

Johnstone VPA, et al., 2015 Experimental Traumatic Brain Injury Results in Long-Term Recovery of Functional Responsiveness in Sensory Cortex but Persisting Structural Changes and Sensorimotor, Cognitive, and Emotional Deficits. Journal of Neurotrauma. 32, 1333–1346. [PubMed: 25739059]

Jones N, et al., 2012 Targeting hyperphosphorylated tau with sodium selenate suppresses seizures in rodent models. Neurobiology of disease. 45, 897–901. [PubMed: 22182692]

Jones NC, et al., 2008 Experimental traumatic brain injury induces a pervasive hyperanxious phenotype in rats. J Neurotrauma. 25, 1367–74. [PubMed: 19061380]

Kabadi S, et al., 2010 Fluid-percussion-induced traumatic brain injury model in rats. Nature Protocols. 5, 1552–1563. [PubMed: 20725070]

Kadam S, et al., 2017a Methodological standards and interpretation of videoelectroencephalography in adult control rodents. A TASK1-WG1 report of the AES/ILAE Translational Task Force of the ILAE. Epilepsia. 58 Suppl 4, 10–27.

Kamnaksh A, et al., 2014 Molecular mechanisms of increased vulnerability after repeated mild blast-induced traumatic brain injury. Translational Proteomics. 3, 22–37.

Kamnaksh A, et al., 2011 Factors affecting blast traumatic brain injury. J Neurotrauma. 28, 2145–53. [PubMed: 21861635]

Kamnaksh A, et al., 2012 Neurobehavioral, cellular, and molecular consequences of single and multiple mild blast exposure. Electrophoresis. 33, 3680–92. [PubMed: 23161523]

Kelly K, 2004 Spike-wave discharges: absence or not, a common finding in common laboratory rats. Epilepsy Currents. 4, 176–177. [PubMed: 16059491]

Kelly KM, et al., 2015 Posttraumatic seizures and epilepsy in adult rats after controlled cortical impact. Epilepsy Res. 117, 104–16. [PubMed: 26432760]

Kendirli MT, et al., 2014 A model of posttraumatic epilepsy after penetrating brain injuries: effect of lesion size and metal fragments. Epilepsia. 55, 1969–77. [PubMed: 25470332]

Keret A, et al., 2017 Posttraumatic epilepsy: long-term follow-up of children with mild traumatic brain injury. Journal of Neurosurgery: Pediatrics. 20, 64–70. [PubMed: 28474982]

Kharatishvili I, et al., 2007 Quantitative diffusion MRI of hippocampus as a surrogate marker for post-traumatic epileptogenesis. Brain. 130, 3155–68. [PubMed: 18055492]

Kharatishvili I, et al., 2006a A model of posttraumatic epilepsy induced by lateral fluidpercussion brain injury in rats. Neuroscience. 140, 685–697. [PubMed: 16650603]

Kharatishvili I, et al., 2006b A model of posttraumatic epilepsy induced by lateral fluidpercussion brain injury in rats. Neuroscience. 140, 685–97. [PubMed: 16650603]

Kharatishvili I, et al., 2006c A model of posttraumatic epilepsy induced by lateral fluidpercussion brain injury in rats. Neuroscience. 140, 685–697. [PubMed: 16650603]

Kharatishvili I, Pitkänen A, 2010 Association of the severity of cortical damage with the occurrence of spontaneous seizures and hyperexcitability in an animal model of posttraumatic epilepsy. Epilepsy research. 90, 47–59. [PubMed: 20435440]

Kobeissy FH, 2015 Controlled Cortical Impact Model Brain Neurotrauma.

Kochanek PM, et al., 2013 Screening of biochemical and molecular mechanisms of secondary injury and repair in the brain after experimental blast-induced traumatic brain injury in rats. J Neurotrauma. 30, 920–37. [PubMed: 23496248]

Kochanek PM, et al., 2006 Adenosine A1 receptor knockout mice develop lethal status epilepticus after experimental traumatic brain injury. J Cereb Blood Flow Metab. 26, 565–75. [PubMed: 16121125]

Koliatsos VE, et al., 2011 A mouse model of blast injury to brain: initial pathological, neuropathological, and behavioral characterization. J Neuropathol Exp Neurol. 70, 399–416. [PubMed: 21487304]

Kovesdi E, et al., 2012 Acute minocycline treatment mitigates the symptoms of mild blastinduced traumatic brain injury. Front Neurol. 3, 111. [PubMed: 22811676]

Kwon SK, et al., 2011 Stress and traumatic brain injury: a behavioral, proteomics, and histological study. Front Neurol. 2, 12. [PubMed: 21441982]

Laitinen T, et al., 2015 Diffusion tensor imaging detects chronic microstructural changes in white and gray matter after traumatic brain injury in rat. Frontiers in neuroscience. 9, 128–128. [PubMed: 25954146]

Lewen A, et al., 1996 Changes in microtubule-associated protein 2 and amyloid precursor protein immunoreactivity following traumatic brain injury in rat: influence of MK801 treatment. Brain Res. 719, 161–71. [PubMed: 8782876]

Lim M, et al., 2013 Dietary therapy mitigates persistent wake deficits caused by mild traumatic brain injury. Science Translational Medicine. 5, 215ra173–215ra173.

Lindner MD, et al., 1998 Dissociable long-term cognitive deficits after frontal versus sensorimotor cortical contusions. J Neurotrauma. 15, 199–216. [PubMed: 9528920]

Ling G, et al., 2009 Explosive blast neurotrauma. J Neurotrauma. 26, 815–25. [PubMed: 19397423]

Liu S-J, et al., 2016a Sodium selenate retards epileptogenesis in acquired epilepsy models reversing changes in protein phosphatase 2A and hyperphosphorylated tau. Brain. 139, 1919–1938. [PubMed: 27289302]

Liu SJ, et al., 2016b Sodium selenate retards epileptogenesis in acquired epilepsy models reversing changes in protein phosphatase 2A and hyperphosphorylated tau. Brain. 139, 1919–38. [PubMed: 27289302]

Long JB, et al., 2009 Blast overpressure in rats: recreating a battlefield injury in the laboratory. Journal of neurotrauma. 26, 827–40. [PubMed: 19397422]

Lowenstein DH, 2009 Epilepsy after head injury: an overview. Epilepsia. 50 Suppl 2, 4–9.

Lu X-CM, et al., 2011 Electrocortical pathology in a rat model of penetrating ballisticlike brain injury. Journal of neurotrauma. 28, 71–83. [PubMed: 20964535]

Marmarou A, et al., 1994a A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics. J Neurosurg. 80, 291–300. [PubMed: 8283269]

Marmarou A, et al., 1994b A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics. Journal of Neurosurgery. 80, 291–300. [PubMed: 8283269]

Martens KM, et al., 2012 A discrimination task used as a novel method of testing decision-making behavior following traumatic brain injury. J Neurotrauma. 29, 250512.

Masel BE, et al., 2012 Galveston Brain Injury Conference 2010: clinical and experimental aspects of blast injury. J Neurotrauma. 29, 2143–71. [PubMed: 22655746]

McKee A, et al., 2014 The neuropathology of sport. Acta neuropathologica. 127, 29–51. [PubMed: 24366527]

McKee A, et al., 2013 The spectrum of disease in chronic traumatic encephalopathy. Brain. 136, 43–64. [PubMed: 23208308]

Mediavilla Varas J, et al., 2011 Physics of IED Blast Shock Tube Simulations for mTBI Research. Front Neurol. 2, 58. [PubMed: 21960984]

Millen JE, et al., 1985 A comparison of physiological responses to percussive brain trauma in dogs and sheep. Journal of Neurosurgery. 62, 587–591. [PubMed: 3973730]

Morales DM, et al., 2005 Experimental models of traumatic brain injury: do we really need to build a better mousetrap? Neuroscience. 136, 971–89. [PubMed: 16242846]

Mountney A, et al., 2017 Functional and Molecular Correlates after Single and Repeated Rat Closed-Head Concussion: Indices of Vulnerability after Brain Injury. Journal of Neurotrauma. 34, 2768–2789. [PubMed: 28326890]

Mukherjee S, et al., 2013 Increased seizure susceptibility in mice 30 days after fluid percussion injury. Front Neurol. 4, 28. [PubMed: 23519723]

Mychasiuk R, et al., 2016 The direction of the acceleration and rotational forces associated with mild traumatic brain injury in rodents effect behavioural and molecular outcomes. Journal of neuroscience methods. 257, 168–178. [PubMed: 26484783]

Nakagawa A, et al., 2011 Mechanisms of primary blast-induced traumatic brain injury: insights from shock-wave research. J Neurotrauma. 28, 1101–19. [PubMed: 21332411]

Namjoshi D, et al., 2017 Defining the biomechanical and biological threshold of murine mild traumatic brain injury using CHIMERA (Closed Head Impact Model of Engineered Rotational Acceleration). Experimental neurology. 292, 80–91. [PubMed: 28274861]

Namjoshi D, et al., 2014 Merging pathology with biomechanics using CHIMERA (ClosedHead Impact Model of Engineered Rotational Acceleration): a novel, surgery-free model of traumatic brain injury. Molecular Neurodegeneration. 9, 55–55. [PubMed: 25443413]

Needham CE, et al., 2015 Blast Testing Issues and TBI: Experimental Models That Lead to Wrong Conclusions. Front Neurol. 6, 72. [PubMed: 25904891]

Nichols J, et al., 2015 Traumatic brain injury induces rapid enhancement of cortical excitability in juvenile rats. CNS Neurosci Ther. 21, 193–203. [PubMed: 25475223]

Nilsson P, et al., 1993 Regional changes in interstitial K+ and Ca2+ levels following cortical compression contusion trauma in rats. J Cereb Blood Flow Metab. 13, 18392.

Nilsson P, et al., 1990 Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive brain injury in rats. J Cereb Blood Flow Metab. 10, 631–7. [PubMed: 2384536]

Osier ND, et al., 2015 Chronic Histopathological and Behavioral Outcomes of Experimental Traumatic Brain Injury in Adult Male Animals. J Neurotrauma. 32, 1861–82. [PubMed: 25490251]

Osier ND, Dixon CE, 2016 The Controlled Cortical Impact Model: Applications, Considerations for Researchers, and Future Directions. Front Neurol. 7, 134. [PubMed: 27582726]

Pearce P, et al., 2014 Spike-wave discharges in adult Sprague-Dawley rats and their implications for animal models of temporal lobe epilepsy. Epilepsy & behavior. 32, 121–131. [PubMed: 24534480]

Petraglia A, et al., 2014a The spectrum of neurobehavioral sequelae after repetitive mild traumatic brain injury: a novel mouse model of chronic traumatic encephalopathy. Journal of Neurotrauma. 31, 1211–1224. [PubMed: 24766454]

Petraglia A, et al., 2014b The pathophysiology underlying repetitive mild traumatic brain injury in a novel mouse model of chronic traumatic encephalopathy. Surgical Neurology International. 5, 184–184. [PubMed: 25593768]

Petty S, et al., 2005 Effect of antiepileptic medication on bone mineral measures. Neurology. 65, 1358–1365. [PubMed: 16275821]

Piccenna L, et al., 2017 Management of post-traumatic epilepsy: An evidence review over the last 5 years and future directions. Epilepsia Open. 2, 123–144. [PubMed: 29588942]

Ping X, Jin X, 2016 Chronic Posttraumatic Epilepsy following Neocortical Undercut Lesion in Mice. PLoS One. 11, e0158231. [PubMed: 27348225]

Pitkänen A, et al., 2009 From traumatic brain injury to posttraumatic epilepsy: what animal models tell us about the process and treatment options. Epilepsia. 50, 21–29.

Pitkänen A, Mcintosh TK, 2006 Animal models of post-traumatic epilepsy. Journal of neurotrauma. 23, 241–261. [PubMed: 16503807]

Povlishock JT, 2013 The window of risk in repeated head injury. J Neurotrauma. 30, 1. [PubMed: 23259734]

Rakhade S, et al., 2011 Development of later life spontaneous seizures in a rodent model of hypoxia-induced neonatal seizures. Epilepsia. 52, 753–765. [PubMed: 21366558]

Raymont V, et al., 2011 “Studying injured minds” - the Vietnam head injury study and 40 years of brain injury research. Front Neurol. 2, 15. [PubMed: 21625624]

Reid A, et al., 2016 The progression of electrophysiologic abnormalities during epileptogenesis after experimental traumatic brain injury. Epilepsia. 57, 1558–1567. [PubMed: 27495360]

Reid W, et al., 2010 Strain-related differences after experimental traumatic brain injury in rats. Journal of Neurotrauma. 27, 1243–1253. [PubMed: 20392137]

Risling M, Davidsson J, 2012 Experimental animal models for studies on the mechanisms of blast-induced neurotrauma. Front Neurol. 3, 30. [PubMed: 22485104]

Risling M, et al., 2011 Mechanisms of blast induced brain injuries, experimental studies in rats. Neuroimage. 54 Suppl 1, S89–97. [PubMed: 20493951]

Ritzel D,V, et al., 2011 Experimental blast simulation for injury studies. NATO, RTO, HFM-207. 11–1.

Robinson FR, Johnson MT, 1961 Histopathological studies of tissue reactions to various metals implanted in cat brains. ASD Tech Rep. 61, 13. [PubMed: 24546838]

Rodgers K, et al., 2015 Progressive, Seizure-Like, Spike-Wave Discharges Are Common in Both Injured and Uninjured Sprague-Dawley Rats: Implications for the Fluid Percussion Injury Model of Post-Traumatic Epilepsy. The Journal of neuroscience. 35, 9194–9204. [PubMed: 26085641]

Rubovitch V, et al., 2011 A mouse model of blast-induced mild traumatic brain injury. Exp Neurol. 232, 280–9. [PubMed: 21946269]

Saatman KE, et al., 2008 Classification of traumatic brain injury for targeted therapies. J Neurotrauma. 25, 719–38. [PubMed: 18627252]

Salazar AM, et al., 1985 Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. Neurology. 35, 1406–1414. [PubMed: 3929158]

Santhakumar V, et al., 2001 Long-term hyperexcitability in the hippocampus after experimental head trauma. Annals of Neurology. 50, 708–717. [PubMed: 11761468]

Scheff SW, et al., 1997 Morris water maze deficits in rats following traumatic brain injury: lateral controlled cortical impact. J Neurotrauma. 14, 615–27. [PubMed: 9337124]

Scheffer I, et al., 2016 Classification of the epilepsies: New concepts for discussion and debate-Special report of the ILAE Classification Task Force of the Commission for Classification and Terminology. Epilepsia Open. 1, 37–44. [PubMed: 29588927]

Semple B, et al., 2017a Sex-dependent changes in neuronal morphology and psychosocial behaviors after pediatric brain injury. Behavioural brain research. 319, 48–62. [PubMed: 27829127]

Semple B, et al., 2017b Interleukin-1 Receptor in Seizure Susceptibility after Traumatic Injury to the Pediatric Brain. The Journal of neuroscience. 37, 7864–7877. [PubMed: 28724747]

Semple BD, et al., 2012 Deficits in social behavior emerge during development after pediatric traumatic brain injury in mice. J Neurotrauma. 29, 2672–83. [PubMed: 22888909]

Semple BD, et al., 2017c Interleukin-1 receptor in seizure susceptibility after traumatic injury to the pediatric brain. J Neurosci.

Sen A, et al., 2007 Pathological tau tangles localize to focal cortical dysplasia in older patients. Epilepsia. 48, 1447–1454. [PubMed: 17441989]

Shaw F-Z, 2004 Is spontaneous high-voltage rhythmic spike discharge in Long Evans rats an absence-like seizure activity? Journal of Neurophysiology. 91, 63–77. [PubMed: 12826656]

Shear DA, et al., 2010 Longitudinal characterization of motor and cognitive deficits in a model of penetrating ballistic-like brain injury. Journal of neurotrauma. 27, 19111923.

Shively SB, et al., 2016 Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series. Lancet Neurol.

Shohami E, et al., 1988 Experimental closed head injury in rats: prostaglandin production in a noninjured zone. Neurosurgery. 22, 859–63. [PubMed: 3164097]

Shultz S, et al., 2012 Repeated mild lateral fluid percussion brain injury in the rat causes cumulative long-term behavioral impairments, neuroinflammation, and cortical loss in an animal model of repeated concussion. Journal of Neurotrauma. 29, 281–294. [PubMed: 21933013]

Shultz S, et al., 2011 A single mild fluid percussion injury induces short-term behavioral and neuropathological changes in the Long-Evans rat: support for an animal model of concussion. Behavioural brain research. 224, 326–335. [PubMed: 21704658]

Shultz S, et al., 2017 The potential for animal models to provide insight into mild traumatic brain injury: Translational challenges and strategies. Neuroscience and biobehavioral reviews. 76, 396–414. [PubMed: 27659125]

Shultz S, et al., 2015 Sodium selenate reduces hyperphosphorylated tau and improves outcomes after traumatic brain injury. Brain. 138, 1297–313. [PubMed: 25771151]

Shultz SR, et al., 2013 Can structural or functional changes following traumatic brain injury in the rat predict epileptic outcome? Epilepsia. 54, 1240–50. [PubMed: 23718645]

Sick T, et al., 2017 Increased Expression of Epileptiform Spike/Wave Discharges One Year after Mild, Moderate, or Severe Fluid Percussion Brain Injury in Rats. Journal of Neurotrauma. 34, 2467–2474. [PubMed: 28388862]

Sights WP, Bye RJ, 1970 The fate of retained intracerebral shotgun pellets. An experimental study. J Neurosurg. 33, 646–53. [PubMed: 5482795]

Skopin M, et al., 2015 Chronic decrease in wakefulness and disruption of sleep-wake behavior after experimental traumatic brain injury. Journal of Neurotrauma. 32, 289296.

Smith DH, et al., 1995 A model of parasagittal controlled cortical impact in the mouse: cognitive and histopathologic effects. J Neurotrauma. 12, 169–78. [PubMed: 7629863]

Smith Z, et al., 2018 Progression of Convulsive and Nonconvulsive Seizures During Epileptogenesis After Pilocarpine-Induced Status Epilepticus. Journal of Neurophysiology.

Statler KD, et al., 2009a A potential model of pediatric posttraumatic epilepsy. Epilepsy Research. 86, 221–223. [PubMed: 19520549]

Statler KD, et al., 2009b A potential model of pediatric posttraumatic epilepsy. Epilepsy research. 86, 221–223. [PubMed: 19520549]

Statler KD, et al., 2008 Traumatic brain injury during development reduces minimal clonic seizure thresholds at maturity. Epilepsy Res. 80, 163–170. [PubMed: 18490145]

Stein DG, 2011 Progesterone in the treatment of acute traumatic brain injury: a clinical perspective and update. Neuroscience. 191, 101–106. [PubMed: 21497181]

Tarazi A, et al., 2018 Motor Function in Former Professional Football Players with History of Multiple Concussions. Journal of Neurotrauma. 35, 1003–1007. [PubMed: 29256818]

Taylor J, et al., 2017 Voluntary Control of Epileptiform Spike-Wave Discharges in Awake Rats. The Journal of neuroscience. 37, 5861–5869. [PubMed: 28522734]

Temkin N, 2003 Risk factors for posttraumatic seizures in adults. Epilepsia. 44, 18–20. [PubMed: 14511390]

Thom M, et al., 2011 Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a postmortem study. Brain. 134, 2969–2981. [PubMed: 21903728]

Thompson H, et al., 2005 Lateral fluid percussion brain injury: a 15-year review and evaluation. Journal of Neurotrauma. 22, 42–75. [PubMed: 15665602]

Tubi M, et al., 2018 Early seizures and temporal lobe trauma predict post-traumatic epilepsy: A longitudinal study. Neurobiology of disease.

van Eersel J, et al., 2010 Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. Proceedings of the National Academy of Sciences of the United States of America. 107, 13888–13893. [PubMed: 20643941]

Viano D, et al., 2007 Concussion in professional football: biomechanics of the struck player--part 14. Neurosurgery. 61, 313–27; discussion 327. [PubMed: 17762744]

Viano D, Pellman E, 2005 Concussion in professional football: biomechanics of the striking player--part 8. Neurosurgery. 56, 266–80; discussion 266. [PubMed: 15670375]

Washington PM, et al., 2012 The effect of injury severity on behavior: a phenotypic study of cognitive and emotional deficits after mild, moderate, and severe controlled cortical impact injury in mice. J Neurotrauma. 29, 2283–96. [PubMed: 22642287]

Webster KM, et al., 2015 Progesterone treatment reduces neuroinflammation, oxidative stress and brain damage and improves long-term outcomes in a rat model of repeated mild traumatic brain injury. J Neuroinflammation. 12, 238. [PubMed: 26683475]

Wennberg R, et al., 2018 Is Concussion a Risk Factor for Epilepsy? Canadian journal of neurological sciences. 1–8.

Williams AJ, et al., 2005 Characterization of a new rat model of penetrating ballistic brain injury. Journal of neurotrauma. 22, 313–331. [PubMed: 15716636]

Wright D, et al., 2017 Sex matters: repetitive mild traumatic brain injury in adolescent rats. Annals of Clinical and Translational Neurology. 4, 640–654. [PubMed: 28904986]

Xiong Y, et al., 2013 Animal models of traumatic brain injury. Nature Reviews Neuroscience. 14, 128–142. [PubMed: 23329160]

Xu L, et al., 2014 Repetitive mild traumatic brain injury with impact acceleration in the mouse: Multifocal axonopathy, neuroinflammation, and neurodegeneration in the visual system. Exp Neurol.

Yang L, et al., 2010 Spontaneous epileptiform activity in rat neocortex after controlled cortical impact injury. J Neurotrauma. 27, 1541–8. [PubMed: 20504156]

Yeh C-C, et al., 2013 Risk of epilepsy after traumatic brain injury: a retrospective population-based cohort study. Journal of neurology, neurosurgery and psychiatry. 84, 441–445.

Table 1

summarizes the seizure outcomes, advantages/limitations for each PTE model.

Model	Species	Animals with spontaneous seizures	latency to spontaneous seizures	Average seizures/day	Mean Seizure duration(s)	Epileptiform discharges	Seizure susceptibility in vivo	Advantages/ similarities with human PTE	Limitations	References
LFPI	Rat	50 % at 12 months	4–11 weeks	0.3–0.5	50–100	Yes, in 2280 %	1wk, 2wk, 12wk and 12 months after TBI - Increased susceptibility to PTZ	Can be used to induce a severe, highly reproducible and mixed type of injury, local cortical contusion and diffuse subcortical neuronal injury extended to the hippocampus and thalamus. Pulse duration, magnitude of force, relative mortality, behavioural and cognitive deficits similar to the human condition. Electrophysiological properties associated with brain injury at acute time points similar to those observed in human TBI	High mortality, no skull fracture, craniotomy	(Dixon et al., 1987; Hicks et al., 1996; Kharatishvili et al., 2006c; Liu et al., 2016a; Reid et al., 2016; Shultz et al., 2015)
LFPI	Mice	3–6 % at 9 months	-	0.1	91	71% epileptiform spiking 58% epileptiform discharges	1 and 6 months after TBI - Increased susceptibility to PTZ	Highly reproducible injury, mixed type of injury similar to severe TBI in humans. behavioural and cognitive deficits similar to the human condition	High mortality, no skull fracture, craniotomy	(Bolkvadze and Pitkanen, 2012; Mukherjee et al., 2013)
Central FPI	Rat	-	-	-	-	-	24h after TBI - Unalter ed susceptibility to PTZ-kindling, started 24h post TBI	Highly reproducible injury, mixed type of injury similar to human TBI. Neuromotor deficits similar to human TBI	High mortality, no skull fracture, craniotomy, needs to study the rate of spontaneous seizures. Hemorrhage in central structures.	(Dixon et al., 1987; Santhakumar et al., 2001)
Parasagittal FPI	Rat	100 % (7 month follow up)	2 weeks	maximum 7/h	-	-	12wk after TBI - Increas ed susceptibility to PTZ	Highly reproducible injury, mixed type of injury	High mortality, no skull fracture, craniotomy, not	(D'Ambrosio et al., 2004b; D'Ambrosio et al., 2005)

Model	Species	Animals with spontaneous seizures	latency to spontaneous seizures	Average seizures/day	Mean Seizure duration(s)	Epileptiform discharges	Seizure susceptibility in vivo	Advantages/ similarities with human PTE	Limitations	References
Blast TBI	Rat	-	-	-	-	-	-	Injury mechanism close to military TBI electrophysio logical properties associated with brain injury at acute time points similar to those observed in human TBI	Needs standardization and longterm studies for seizure characterization	(Kamnaksh et al., 2011; Koliatsos et al., 2011; Long et al., 2009)
Penetrating TBI	Rat	70–83% early seizures 96% copper and 15% stainless steel chronic seizures	7–10 days early seizures 6–9 months chronicseizures	3/day copper 0.2/day in stainless steel	-	-	-	Penetrating injury that damages several structures, can leave foreign materials, similar to gunshot wounds, key risk factors in the development of PTE.	More limited damage in comparison to human. Time to develop spontaneous chronic seizures	(Kendirli et al., 2014)