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Review article

The potential for animal models to provide insight into mild traumatic brain injury: Translational challenges and strategies

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ABSTRACT

Mild traumatic brain injury (mTBI) is a common health problem. There is tremendous variability and heterogeneity in human mTBI, including mechanisms of injury, biomechanical forces, injury severity, spatial and temporal pathophysiology, genetic factors, pre-injury vulnerability and resilience factors, and clinical outcomes. Animal models greatly reduce this variability and heterogeneity, and provide a means to study mTBI in a rigorous, controlled, and efficient manner. Rodent models, in particular, are time- and cost-efficient, and they allow researchers to measure morphological, cellular, molecular, and behavioral variables in a single study. However, inter-species differences in anatomy, morphology, metabolism, neurobiology, and lifespan create translational challenges. Although the term "mild" TBI is used often in the pre-clinical literature, clearly defined criteria for mild, moderate, and severe TBI in animal models have not been agreed upon. In this review, we introduce current issues facing the mTBI field, summarize the available research methodologies and previous studies in mTBI animal models, and discuss how a translational research approach may be useful in advancing our understanding and management of mTBI.

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1. Introduction

This review is based on topics covered in the 2015 International Behavioral Neuroscience Society symposium titled "From the lab bench to the field: translational research approaches for investigating mild traumatic brain injury (mTBI)." Mild injuries to the brain occur during athletic participation, daily life, and military service. There is a broad range of injury severity within the mTBI classification range, from sporting injuries that involve modest biomechanical forces and clinical symptoms that resolve within hours, to injuries sustained in high-speed motor vehicle accidents that result in macrostructural damage to the brain and that abut the moderate TBI classification range. The biomechanical forces that result in mTBI are believed to initiate a pathophysiological cascade in the central nervous system that is heterogeneous in nature but can involve a combination of inflammatory, metabolic, neuronal, and axonal abnormalities or changes (Blennow et al., 2012; Carroll et al., 2004; Giza and Hovda, 2014; Jordan, 2013). Mild injuries to the brain are associated with large adverse effects on balance and cognition within the first 24 h (Broglio and Puetz, 2008), often extending well into the first week following injury (Dougan et al., 2014; Williams et al., 2015), and these deficits improve and typically resolve within the first month after injury in athletes (Cancelliere et al., 2014) and within three months of injury in civilians (Rohling et al., 2011). A subgroup, however, report symptoms long after injury (Carroll et al., 2014). The clinical symptoms and problems in the initial days following mTBI might be caused in large part by cellular, sub-cellular, and molecular pathophysiology that cannot be currently measured in clinical settings. The cause of persistent symptoms, however, is likely multifactorial and a biopsychosocial perspective is needed to better understand and predict clinical outcomes (Iverson et al., 2012). A number of studies have also found the presence of postconcussion-like symptoms in healthy individuals (Iverson and Lange, 2003; Wang et al., 2006), suggesting that post-concussion symptoms are neither specific nor reliable indicators of mTBI. Because of the variable clinical presentation of mild brain injuries, there have been efforts to identify more sensitive, reliable, and/or objective indicators of brain injury and recovery, such as serum biomarkers, microstructural changes in white matter, neurometabolic alterations and differences in neurochemistry, and functional physiological changes in neural networks.

1.1. Blood biomarkers

Blood biomarkers may be helpful for mTBI diagnosis, monitoring injury progression and recovery, and providing pertinent information about ongoing pathophysiological changes to guide management (Zetterberg et al., 2013). There are a number of potential blood-based biomarkers that may be sensitive to the neuronal and glial cell loss, metabolic abnormalities, neuroinflammation, axonal injury, and other pathophysiological changes associated with mTBI (see Zetterberg et al., 2013 for a comprehensive review on fluid biomarkers for mTBI). Briefly, initial studies report increased levels of S100 calcium-binding protein B (S100B), glial fibrillary acidic protein (GFAP), tau, galectin 3, matrix metalloproteinase 9, occludin, plasma soluble cellular prion protein, calpain-cleaved αII-spectrin N-terminal fragment (SNTF) and decreased levels of copeptin in plasma and/or serum at various acute and subacute post-mTBI time points (Metting et al., 2012; Pham et al., 2015; Shahim et al., 2014; Shan et al., 2016; Siman et al., 2013; Siman et al., 2015). Other studies demonstrate the potential of microRNA as a blood biomarker in mTBI (Redell et al., 2010; Sharma et al., 2014). However, longitudinal studies that have assessed blood biomarkers in mTBI patients to validate their diagnostic and prognostic usefulness are limited (Zetterberg et al., 2013). Furthermore, the lack of standardized methods to quantify some blood biomarkers, and the need for either baseline measures for each individual or validated cut-off points, are additional limitations (Zetterberg et al., 2013).

1.2. Neuroimaging

Advanced magnetic resonance imaging (MRI) techniques have been developed that could be sensitive to pathophysiological changes that occur in the injured brain, and might contribute to cumulative and long-term effects of repeated mTBIs (Baugh et al., 2012; Hunter et al., 2012; Jeter et al., 2013). Diffusion MRI measures are sensitive to axonal injury and have been utilized in previous studies to identify abnormalities in the white matter tracts of mTBI patients at acute, sub-acute, and chronic post-injury time points (Dimou and Lagopoulos, 2014; Dodd et al., 2014; Gardner et al., 2012; Lancaster et al., 2016; Shenton et al., 2012; Wilde et al., 2015; Xiong et al., 2014). For example, a recent study used diffusion MRI to serially examine white matter changes at 24 h and 1 week after a sports-related concussion (Lancaster et al., 2016). Diffusion MRI revealed that the concussed group exhibited widespread changes compared with control subjects 24 h after the concussion. Furthermore, at one-week follow up the differences in these diffusion measures were even more widespread. Notably, although the concussed group reported more symptoms and worse cognitive performance than a control group at 24 h, there were no significant differences on these measures one week later despite the presence of the diffusion MRI abnormalities.

Magnetic resonance spectroscopy (MRS) provides measurements of brain metabolites that may be affected by mTBI including N-acetylaspartate, glutathione, glutamate, and myo-inosotol (Gardner et al., 2014; Johnson et al., 2012a; Tremblay et al., 2014; Vagnozzi et al., 2010, 2008; Xiong et al., 2014). A multicenter MRS study examined 40 concussed athletes, as well as 30 healthy subject controls at 3, 15, 22, and 30 days post-injury for the determination of *N*-acetylaspartate, creatine, and choline (Vagnozzi et al., 2010). Concussed patients had the most significant alteration of metabolite ratios at day 3 post-injury. These neurometabolic changes gradually recovered, and by 30 days post-injury all concussed athletes had their metabolite ratios return to values detected in controls. Self-reported symptoms in the patients resolved between 3 and 15 days after concussion.

Susceptibility-weighted imaging (SWI) is a technique that exploits differences in magnetic susceptibility between tissues, and is sensitive to microhemorrhages that might occur in some people as a result of mTBI (Huang et al., 2015; Kenney et al., 2016; Wang et al., 2014). Huang et al. (2015) compared the frequency of microbleeds identified by SWI in 111 patients with mTBI

without parenchymal hemorrhage on CT/conventional MRI and 111 normal healthy controls, and correlated these findings with neuropsychological outcomes. Twenty-six patients with mTBI and 12 control subjects had microbleeds detected by SWI, and the mTBI group showed more microbleeds in the cortex/subcortical region. The presence of mTBI-related microbleeds was also associated with neuropsychological defects in short-term memory. Similarly, a study examining 200 patients with mild TBI and normal CT/conventional MRI found that SWI detected microbleed lesions in 19% of patients, and that among these patients the distribution and location of the microbleed lesions were correlated with depression after mTBI (Wang et al., 2014).

Functional MRI (fMRI) can provide measurements of the brain's functional connectivity networks (i.e., resting state fMRI) as well as neural activity/cerebral blood flow (i.e., BOLD fMRI), both of which may be altered when an mTBI occurs (Ellis et al., 2016; Graner et al., 2013; Johnson et al., 2012b; Lovell et al., 2007; Talavage et al., 2014). For example, Johnson et al. (2012b) used resting state fMRI to evaluate the default mode network in the subacute phase of mTBI. mTBI patients who were asymptomatic showed a reduced number of connections and strength of connections in the posterior cingulate and lateral parietal cortices compared to controls with no history of TBI. Regression analysis also indicated an overall loss of connectivity as the number of mTBIs increased. In another study, Lovell et al. (2007) examined concussed athletes using BOLD fMRI, neurocognitive tests, and a symptom scale within 1 week of injury and again after clinical recovery. It was found that concussed participants that had hyperactivation on their initial fMRI scans had prolonged clinical recovery compared to those who did not.

Arterial spin labeling (ASL) is a MRI method that is capable of providing a direct measurement of cerebral blood flow (Doshi et al., 2015; Kim et al., 2010; Wang et al., 2016). To date, relatively few published studies have applied ASL in the mTBI setting. Wang et al. (2016) recently used ASL to compare cerebral blood flow changes in 18 concussed athletes and 19 matched non-concussed control athletes at 24 h and 8 days after concussion. The concussed athletes demonstrated a significant *decrease* in cerebral blood flow relative to the control group. Furthermore, within the concussed group there was a decrease in cerebral blood flow at 8 days relative to 24 h, whereas the control group did not show any changes in cerebral blood flow between 24 h and 8 days. Clinical symptoms and neurocognitive impairments were present at 24 h but returned to baseline by 8 days. These initial findings suggest that physiological changes persist beyond the point of clinical recovery after concussion and that ASL may be useful in detecting and tracking aspects of neurophysiological recovery from concussion. However, another recent study that assessed 7 mTBI patients and 12 controls with ASL within one week after the injury found that there was *increased* regional cerebral blood flow in the left striatum, and in frontal and occipital lobes, in mTBI patients compared to controls (Doshi et al., 2015). Thus, while ASL may be a useful marker of changes in cerebral blood flow in mTBI, additional studies utilizing larger sample sizes are clearly required to better understand the complexities of these changes.

In addition to MRI, positron emission tomography (PET) imaging agents sensitive to metabolism, neuroinflammation, and protein aggregates are a means to monitor *in vivo* neurophysiological changes in mTBI (Barrio et al., 2015; Byrnes et al., 2014; Coughlin et al., 2015; Wilde et al., 2015). [^{18}F]fluorodeoxyglucose (FDG)-PET provides a marker for glucose uptake and metabolism, and has been the most commonly used PET method in the mTBI literature. Although FDG-PET consistently identifies abnormalities in mTBI patient studies, these results can vary depending on the brain structure and time post-injury (Byrnes et al., 2014). Other recent PET studies report increased binding of [^{11}C]DPA-713 to translocator protein, an indicator of neuroinflammation, and increased [F-18]FDDNP signal, a marker of insoluble tau and amyloid protein aggregates, in patients with a history of repetitive mild brain trauma (Barrio et al., 2015; Coughlin et al., 2015).

Taken together neuroimaging has the potential to provide insight into brain abnormalities induced by mTBI, and should continue to be refined in future investigations. In particular, studies involving larger sample sizes might better characterize the temporal progression of injury and recovery with neuroimaging, and whether these changes relate to symptoms and neuropsychological deficits. No imaging modality to date has provided a strong association between neurobiology and persistent symptoms following mTBI.

2. Animal models of mTBI

There is tremendous variability and heterogeneity in all aspects of human mTBI, including mechanisms of injury, biomechanical forces, injury severity, spatial and temporal pathophysiology, genetic factors, pre-injury vulnerability and resilience factors, and clinical outcomes. There are also many other limitations and confounding factors involved in studying the effects, pathophysiology, biomarkers, and treatment of mTBI in the clinical setting. For example, invasive studies to investigate underlying molecular and cellular changes in the brain are not ethically feasible, and mTBI patients may be less willing to participate in detailed, serial, and longitudinal studies when they are no longer suffering any ill effects from the injury—which typically occurs within days, weeks, or months following injury. In addition, the possible cumulative and long-term effects of repetitive mTBI may progress over time and not fully manifest until years after the injuries occurred. Therefore, the studies required to adequately monitor these progressive changes 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). There are also a number of issues related to the identification and implementation of biomarkers. Although initial blood and imaging studies show promise in detecting mTBI at a group level, in all cases more detailed and invasive studies are required to characterize and validate these methods as reliable mTBI management tools for individual patients. Moreover, longitudinal studies must be conducted to determine if there are early biomarkers to predict long-term changes, or if the use of biomarkers in the acute and sub-acute management of mTBI (e.g., when to return to play) can reduce or prevent cumulative or long-term effects of repeated mTBI. Regarding potential therapeutic interventions for mTBI, even if pharmacological targets are identified, it is not ethical to study novel drugs in patients. Furthermore, it would take many years to determine whether the therapies effectively prevent any cumulative and/or chronic effects in the absence of reliable prognostic or early detection biomarkers. For such reasons, other strategies must be employed to provide insight into questions surrounding mTBI.

Pre-clinical animal models greatly reduce mTBI variability and heterogeneity, and allow for the rigorous investigation of the effects and pathophysiological mechanisms of mTBI, the validation and implementation of mTBI biomarkers, and the assessment of treatments, in a tightly controlled, time- and cost-efficient manner. Here we present a number of common animal models of mTBI, including discussion on their use in previous studies and their limitations. We also describe a number of next generation mTBI models that address some of the key issues facing the traditional models.

2.1. Weight-drop models

Rodent weight-drop methods are commonly used to model closed-head mTBI. The basis for most weight-drop TBI models is

impact from a free-falling guided weight onto the exposed skull (with or without craniotomy) in lightly anaesthetized animals. TBI severity can be controlled via adjustments to the weight mass or release height, and the nature of injury and associated neurological deficits are dependent on injury location (central or lateral) and biomechanics (geometry of weight and degree of head movement post-impact). For example, depending on the type of weight-drop model, more severe forms of weight-drop may result in skull fractures, increased mortality rates, and significant brain atrophy, all of which more closely resemble features of moderate or severe TBI but are typically avoided in the milder forms of the models. The most commonly used weight-drop TBI models are Feeney's [a primarily focal injury; (Feeney et al., 1981)], Marmarou's [primarily diffuse injury; (Marmarou et al., 1994)] and Shohami's [mixed focal/diffuse injury; (Flierl et al., 2009)], though several studies have incorporated adaptations of these protocols in attempt to better replicate specific characteristics of clinical mTBI.

The original weight-drop model was a cortical contusion model developed in rats (Feeney et al., 1981). In this model, anaesthetized and restrained rats first receive a craniotomy over the right frontal-parietal cortex, with a cylinder guiding a weight onto a footplate positioned upon the exposed dura to create a focalized contusion. TBI induced by Feeney's weight-drop 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). However, this injury model has fallen out of favor in recent times, possibly due to the need for craniotomy, the highly focalized injury pattern less common in clinical mTBI, and the rise of the controlled cortical impact (CCI) device which generates similar injury profiles with greater control over parameters (see Section 3.2).

Marmarou's impact acceleration weight-drop model is used to induce a diffuse axonal injury pattern. To administer mTBI using the original form of this model (see Section 3.5 for description of Marmarou variants), anaesthetized rodents receive a midline incision to expose the skull, followed by attachment of a flat, stainless steel disc to the skull midline (Marmarou et al., 1994). The rodent is then placed on a foam platform and a brass weight is dropped down a guided cylinder directly on the stainless steel disc. Graded severities of TBI have been demonstrated using Marmarou's weight-drop via adjustments to brass weight mass (Xu et al., 2016) or release height (Beaumont et al., 1999), with a single mTBI induced by this model presenting evidence of widespread axonal injury, reactive microglia, an absence of h-tau, and transient motor and cognitive deficits (Beaumont et al., 1999; Xu et al., 2016). This model also been used to simulate repeated diffuse mTBI, with repeated injuries resulting in heightened axonal injury, retinal ganglion cell loss, and long-term cognitive deficits (Creeley et al., 2004; Xu et al., 2016). Though protocols based on Marmarou's weight drop induce a diffuse injury pattern, the reproducibility of these models can be limited by the potential for lateral movements during weight fall or secondary hits due to weight rebound post-impact.

Shohami's closed-skull mouse model of mTBI is described in detail elsewhere (Flierl et al., 2009), and is widely used to induce a mixed focal-diffuse injury pattern. Briefly, to induce mTBI in adult mice, lightly anaesthetized mice receive a midline incision to expose the skull and are held in position on a solid platform, with a blunt-tipped rod then released from 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, and secondary hits are prevented by manual retraction of the rod post-impact. Single mTBI with Shohami's weight-drop can induce neuroinflammation and subtle edema (Shultz et al., 2015a) along with a temporary neurological impairments (Flierl et al., 2009), whereas repeated mTBI with this model can induce persisting cognitive deficits (DeFord et al., 2002). This model may have advantages over the previously mentioned weight-drop protocols, in that the brief surgery allows for a relatively light depth of anesthesia and high throughput. Notably, Shohami's TBI protocol has been applied in the recent development of a novel model of multi-trauma, in which mice are given a TBI and a tibial fracture (Shultz et al., 2015a). The goal was to give the mice a mild form of TBI. Using this model, it was demonstrated that mice with isolated TBI displayed only a subtle neuroinflammatory response and no gross behavioral or structural deficits, but mice also given a tibial fracture displayed evidence of neuroinflammation, blood-brain barrier breakdown, edema, enlarged ventricles, diffusion abnormalities, and behavioral deficits. (Shultz et al., 2015a). This study is important because humans can likewise experience multiple bodily injuries, including long bone fractures, in the same accident or event in which they experience a TBI—and these fractures might be associated with magnified pathophysiology (McDonald et al., 2016).

2.2. Controlled cortical impact

CCI, sometimes referred to as cortical contusion injury, is a method for inducing direct focal damage to the exposed dura of the subject. Initially developed in the ferret (Lighthall, 1988), it has since most commonly been applied to the laboratory rat and mouse (Dixon et al., 1991; Smith et al., 1995), but has also been adapted for larger animals such as swine (Duhaime et al., 2000). To perform the injury, the subject is anesthetized and placed in a stereotaxic frame. A craniotomy is then performed over the desired injury coordinates. A piston is positioned above the exposed dura and driven to a given depth at a given velocity, typically via pneumatic or electromagnetic force. The primary parameters that can be manipulated in a CCI are the depth, velocity, dwell (impact) time, and size of the impactor tip.

The vast majority of literature on CCI has focused on the effects of moderate to severe injuries that typically result in persisting functional deficits and a large degree of brain cavitation/atrophy. However, there are now an increasing number of studies that have tried to model mTBI. Because there are many parameters that can be manipulated, a milder form of CCI can be achieved in multiple ways – reducing the depth of impact, reducing the velocity of impact, or reducing the tip size. Most laboratories have elected to reduce either the velocity or depth to achieve a milder injury. Mild CCI in rats typically uses a depth of up to 1.5 mm and a velocity from 2 to 6 m/s (Baki et al., 2009; Igarashi et al., 2007; Sauerbeck et al., 2012; Scheff et al., 1997), while in mice, depth is typically less than 1 mm with a velocity of 3–6 m/s (Fox et al., 1998; Hunt et al., 2009; Tajiri et al., 2014; Yager et al., 2008). It should be noted that because there has been no consensus designation for what types of CCI are considered mild versus moderate or severe, many articles claim a mild injury while delivering forces equivalent to what others term moderate-to-severe and destroying a large portion of the cortex (Gatson et al., 2013; Golding et al., 2000; Golding et al., 1999; Obenaus et al., 2007; Venturi et al., 2009). Therefore, the mild CCI literature must be interpreted carefully, with studies reporting significant structural brain damage/cavitation, mortality, and severe and/or lasting functional consequences being more representative of moderate-severe TBI.

The initial studies using milder forms of CCI identified subtle behavioral deficits in the absence of significant lesion cavity formation (Fox et al., 1998; Scheff et al., 1997). Since these early studies, a large range of behavioral abnormalities after mild CCI has been reported; however, there is considerable variation in the detection of these deficits both between and within laboratories. Sensorimotor function appears to be altered following mild CCI in the acute and subacute post-injury phase, with six studies showing gross motor impairments (Anderson et al., 2008; Chen et al., 2014; 8;

Lee et al., 2014; Sword et al., 2013; Tajiri et al., 2014), two showing fine motor impairments (Lee et al., 2014; Tajiri et al., 2014), and only two studies failing to find gross motor impairment (Gabbita et al., 2005; Sauerbeck et al., 2012). Memory impairments are minimal after mild CCI. Only three studies have found spatial memory deficits (Anderson et al., 2008; Scheff et al., 1997; Watanabe et al., 2013), while six studies have reported no spatial problems (Baki et al., 2009; Fox et al., 1998; Haber et al., 2013; Hemerka et al., 2012; Tajiri et al., 2014; Washington et al., 2012). Additionally, no deficits were found in non-spatial memory tasks (Baki et al., 2009; Chen et al., 2014; Haber et al., 2013), and classical conditioning processes seem to be unaffected (Washington et al., 2012). However, animals with mild CCI have difficulty performing reversals of previously learned behaviors (Baki et al., 2009; Haber et al., 2013).

Pathological and histological results after mild CCI demonstrate more consistent findings than behavioral outcomes. The largest point of contention across studies is in the development of a lesion cavity. Almost equal numbers of studies have demonstrated cavitation (Colgan et al., 2010; Donovan et al., 2012; Hemerka et al., 2012; Ringger et al., 2004; Sword et al., 2013; Taylor et al., 2008; Villapol et al., 2014; Washington et al., 2012) and no change in cortical volume as a result of mild injury (Baskaya et al., 2000; Fox et al., 1998; Gao and Chen, 2011; Sauerbeck et al., 2012; Scheff et al., 1997; Verbois et al., 2003). Arguably, studies utilizing high-resolution MRI, all of which have detected lesion formation (Colgan et al., 2010; Donovan et al., 2012; Ringger et al., 2004), may have a decided advantage over previous techniques such as Nissl staining. Regardless of substantial cavitation, all studies found increased neuronal cell death or fewer surviving neurons in the injury region (Chen et al., 2014; Gao and Chen, 2011; Igarashi et al., 2007; Tajiri et al., 2014; Taylor et al., 2010; Villapol et al., 2014). Glial cells also undergo considerable change after mild CCI. All studies examining astrocyte activation found significant changes in astrocyte activity (Chen et al., 2014; Haber et al., 2013; Susarla et al., 2014; Villapol et al., 2014). Additionally, studies have found changes in neuroinflammatory signaling including microglia, cytokines, and chemokines (Chen et al., 2014; Haber et al., 2013; Lee et al., 2014; Susarla et al., 2014; Watanabe et al., 2013), while only a single study found no change in microglia activity (Igarashi et al., 2007). Many researchers have also demonstrated cell-level changes in neurons, including receptor down-regulation, changes in dendritic spines, and alterations to calcium channels (Gao and Chen, 2011; Sword et al., 2013; Verbois et al., 2003). Although the pathology of mild CCI is more consistent, additional work is needed to understand how physiological changes contribute to neuroplastic adaptation versus behavioral dysfunction after injury.

The application of the CCI method to mild injuries requires careful consideration. Adjustment of parameters from traditionally severe injury models can generate a reasonable mild injury, but it may be difficult to detect behavioral deficits, and as with other mild injuries, more sensitive behavioral outcomes may be needed. Other concerns when considering the CCI method is the requirement of a craniotomy and anesthetic in order to perform the injury. There is evidence that a craniotomy affects rodent physiology and behavior in a manner that can confound TBI studies (Cole et al., 2011; Lagraoui et al., 2012; Olesen, 1987; Sashindranath et al., 2015). Although others have reported no differences between intact and craniotomy animals (Martens et al., 2012), considering that skull fractures are uncommon and craniotomies are rare in humans with mTBIs, ideally craniotomies would be avoided. As described in greater detail below (see Section 2.5), the potential confounding effects of exposure to anesthetic is another possible limitation with the traditional CCI model. These methodological issues in combination with previous findings of significant structural brain damage/cavitation and mortality after a “mild” CCI are important limitations that must be considered when the traditional CCI model is applied in the context of mTBI.

2.3. Mild fluid percussion injury model

The fluid percussion injury (FPI) is a commonly used animal TBI method to induce a mixed focal-diffuse brain injury pattern that models human closed-head TBI (Kabadi et al., 2010; Thompson et al., 2005; Xiong et al., 2013). Briefly, the FPI model involves an anesthetized animal undergoing 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 from the opposite end of the cylinder onto the brain. In most cases, the administration of the injury is delayed until the animal displays a withdrawal reflex, which signals that most of the anesthetic has been metabolized (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; Kabadi et al., 2010; Millen et al., 1985; Thompson et al., 2005; Xiong et al., 2013). However, the use of a mild FPI to model mTBI is most commonly done in the rat. A number of studies have found that a single mild FPI can result in motor and cognitive deficits (DeRoss et al., 2002; Gurkoff et al., 2006; Hylin et al., 2013b; Shultz et al., 2011), as well as abnormalities in sleep (Lim et al., 2013), electrophysiology (Aungst et al., 2014; Greer et al., 2012; Johnstone et al., 2014), the stress response (Griesbach et al., 2011, 2012), and other behaviors (Shultz et al., 2011). A single mild FPI can induce neuroinflammation, axonal injury, alterations in neurotrophic factors, and reduced cerebral blood flow (Greer et al., 2013; Griesbach et al., 2002; Hylin et al., 2013b; Shultz et al., 2012a,b, 2011), but does not result in significant neuronal loss, visible brain contusion, focal lesion, or enduring cognitive and behavioral impairments (Aungst et al., 2014; Gurkoff et al., 2006; Hylin et al., 2013b; Sanders et al., 1999; Shultz et al., 2012a, 2011, 2012b). Taken together, these findings are consistent with those occurring in mTBI patients and support the use of the mild FPI to model a single mTBI. Because the FPI can be used to model more severe TBI, it is important to distinguish that a single moderate-severe FPI can result in persisting motor, cognitive, and emotional abnormalities in the presence of significant neuronal loss and brain atrophy/cavitation (Shultz et al., 2014, 2015b), which do not occur after a single mild FPI.

Based on the abovementioned single mild FPI findings, numerous studies have now administered repeated mild FPIs to rats to study the effects of multiple mild brain injuries, and conditions such as chronic traumatic encephalopathy (CTE). Although the inter-injury interval and number of injuries vary between the studies, the results consistently indicate that repeated mild FPIs induce cumulative and persisting cognitive deficits (Aungst et al., 2014; DeRoss et al., 2002; Shultz et al., 2012a, 2013; Tan et al., 2016; Wang et al., 2013), sensorimotor impairments (Shultz et al., 2012a, 2013; Tan et al., 2016), and increased anxiety- and depression-like behaviors (Shultz et al., 2012a, 2013; Tan et al., 2016). These cognitive and behavioral consequences occur in the presence of progressive cortical atrophy (Aungst et al., 2014; Shultz et al., 2012a), neuronal loss (Shultz et al., 2013; Wang et al., 2013), diffuse axonal injury (Shultz et al., 2012a, 2013; Tan et al., 2016), h-tau (Tan et al., 2016), chronic neuroinflammation (Aungst et al., 2014; Shultz et al., 2012a, 2013; Webster et al., 2015), alterations in excitatory synaptic neurotransmission (Aungst et al., 2014), and impaired long-term potentiation (Aungst et al., 2014).

The single and repeated mild FPI models have also been employed to investigate potential mTBI treatment strategies. For example, treatment with a CD11d-integrin antibody (Shultz et al., 2013; Weaver et al., 2014) or progesterone (Webster et al., 2015) in rats given repeated mild FPIs have been reported to reduce inflammation, oxidative stress, brain damage, and cognitive and motor impairments. Sodium selenate, a protein phosphatase 2A activator known to reduce h-tau after experimental TBI (Shultz et al., 2015b), has also been reported to improve long-term outcomes after repeated mild FPIs (Tan et al., 2016). Furthermore, combined pre- and post-injury dietary supplementation with fish oil was reported to improve cognitive outcomes in the water maze 14 days after repeated mild FPIs (Wang et al., 2013). Notably, although each of these treatments resulted in some benefit, none of them completely prevented the long-term consequences of repeated injuries. This suggests that the neurodegenerative aftermath of repeated mild FPIs involves a complex and multi-factorial pathophysiology that may require combination or pleiotropic treatment strategies. It is also important to consider that many of these treatments have already been demonstrated to be safe and well-tolerated in clinical trials, and therefore represent interventions that could one day be translated to mTBI patients.

While the mild FPI model has been useful in the study of mTBI, there are a number of important limitations that must be considered. The required craniotomy and exposure to anesthetic rarely occur in the clinical mTBI setting and may affect injury outcomes. While these issues are somewhat controlled for 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), ideally a craniotomy and anesthetic would be avoided.

2.4. Blast injury models

There has been tremendous interest in blast-related TBI (bTBI) in active duty military service members and veterans (Bass et al., 2012; Hicks et al., 2010), such as the synaptic mechanisms of blast-induced brain injury (Przekwas et al., 2016), vestibular injuries (Akin and Murnane, 2011), relationship between blast-induced mTBI and traumatic stress (Tschiffely et al., 2015), effects on cognitive functioning (Karr et al., 2014), and treatment and rehabilitation (Cooper et al., 2015). In the laboratory, there are numerous ways of simulating conditions associated with bTBI in humans. These range from detonating explosives at a given distance to more controlled 'shock tubes' which allow for a precise pressure shock wave to be directed at the animal (Cernak et al., 2011; Cheng et al., 2010; Kaur et al., 1995; Long et al., 2009). Early work focused primarily on the effects of blast on soft, compressible tissues, mainly lung (Huller and Bazini, 1970; Zuckerman and Groome, 1940). However, as awareness of TBI has increased, many researchers have become interested in the detrimental brain changes and alterations to behavior that occur after blast (Bass et al., 2012; Kovesdi et al., 2011; Ling et al., 2009).

Mild bTBI shares several similarities with other forms of mTBI. With regards to function, behavioral changes after mild bTBI are limited. Sensorimotor disruptions are typically mild or resolve rapidly in the early post-injury period (Ahlers et al., 2012; Kamnaksh et al., 2012; Koliatsos et al., 2011; Kwon et al., 2011; Vandevord et al., 2012; Walls et al., 2016), although a major concern is ocular, vestibular, and aural damage due to the blast which could affect sensory abilities (Cockerham et al., 2009; Cohen et al., 2002). The lack of gross sensory and motor disruptions, compared to what is seen in other models of TBI, is not particularly surprising considering the mechanism of damage. Whereas other injuries cause focal damage, typically including sensorimotor areas, bTBI has a very diffuse injury pattern which may only affect sensorimotor processes indirectly (e.g., through neural conductivity problems). For instance, several studies have identified diffuse axonal injury following blast (Garman et al., 2011; Kamnaksh et al., 2012), and it has been shown that repeated blasts can exacerbate this effect (Calabrese et al., 2014) and even produce lesions along blood vessels due to shearing forces (Sosa et al., 2013). Alterations to cognitive functions following bTBI demonstrate a spectrum of consequences ranging from some memory impairments and slowing of reaction time (Ahlers et al., 2012; Koliatsos et al., 2011; Kovesdi et al., 2011, 2012; Kwon et al., 2011; Vandevord et al., 2012) to no impairment whatsoever (Kamnaksh et al., 2012; Koliatsos et al., 2011; Vandevord et al., 2012; Walls et al., 2016). Of particular note, a comprehensive study by Ahlers et al. (2012) assessed the effects of acute and repeated exposure to blast overexposure in unanaesthetized rats. The study involved varying levels of blast overexposure (116.7 kPA, 74.5 kPA, and 36.6 kPA), and different injury orientations (lateral versus frontal). It was found that a single exposure to a 116 kPA blast resulted in alterations/loss of consciousness, transient motor impairments, and memory deficits, as well as subdural hemorrhage and cortical contusions in some of the cases (Ahlers et al., 2012). However, all 116.7 kPA rats also suffered pulmonary hemorrhage. Thus the 116.7 kPA-induced injury may better model more severe bTBI/polytrauma. A single 74.5 kPA blast in the frontal orientation resulted in memory deficits. Finally, although a single 36.6 kPA overexposure did not result in any apparent functional deficits, repeated frontal 36.6 kPA overexposures given daily for 12 consecutive days induced subtle cognitive deficits. Thus the 36.6 kPA overexposure may induce a sub-concussive injury. Although a detailed neuropathological analysis was not done in this study, alterations in blood-brain barrier permeability, neuroinflammation, and increases in detrimental proteins such as phosphorylated tau can occur even after single exposures (Huber et al., 2013; Tompkins et al., 2013; Walls et al., 2016).

Outcome measures assessing emotional reactivity are of particular interest due to the comorbidity between brain injury and mood disorders such as posttraumatic stress disorder (PTSD) (Bass et al., 2012; Ling et al., 2009). However, even these show a range of effects in rodents from large increases in responsivity (Elder et al., 2012; Heldt et al., 2014; Kovesdi et al., 2012; Kwon et al., 2011) to no effects (Ahlers et al., 2012) to reduced sensitivity to emotional stimuli (Genovese et al., 2013). One major hypothesis of why emotional changes are common in humans following bTBI is that the pituitary is particularly sensitive to damage and thus affects the entire hypothalamic-pituitary-adrenal axis (Tanriverdi et al., 2015; Wilkinson et al., 2012). This effect may not be replicated as readily in the rodents most often used for blast injury assessment due to structural differences of the brain.

Though mild bTBI shares certain commonalities with other methods of inducing brain damage, it is still a relatively new technique that requires further exploration to truly determine whether there are unique contributions independent of the pathophysiology of other forms of mTBI. Many studies have explored the physical characteristics of the blast and the associated damage (Cernak et al., 2011; Moore et al., 2009), however some researchers have suggested that blast injury may be fundamentally the same as other acceleration/concussive models, in which the blast wave provides the acceleration (Goldstein et al., 2012). To date, it has been difficult to compare results from laboratory-based blast studies due to the use of different types of shock tubes and insufficient information about shock wave characteristics and animal positioning.

2.5. The next generation of rodent mTBI models

In addition to the traditional mTBI models described above, there are a number of new models emerging, largely in response to the increasing interest in mTBI and limitations with existing mod-

els. In particular, these next generation models have prioritized replication of the head-acceleration dynamics that are commonly seen in human mTBI, as well as reducing or eliminating the influence of anesthesia and surgery. Several recent studies have adapted the original Marmarou weight-drop protocol where surgery duration and anesthesia is minimized through elimination of both scalp incision and the use of a steel helmet, and the head-acceleration component of the model is increased through use of a breakaway platform, allowing rotational motion after the impact (Kane et al., 2012; Meehan et al., 2012; Mychasiuk et al., 2014a,b; Zohar et al., 2003). This impact acceleration model has much promise for use in repeated mTBI studies, with one study reporting that mice given either 5 or 10 mTBIs (1 per day) display elevated GFAP and h-tau expression in the absence of both edema and blood brain barrier damage (Kane et al., 2012). Furthermore, Meehan et al. (2012) found cognitive deficits that persisted for at least 1 year post injury in mice given 5 injuries (1/day). Importantly, when the inter-injury interval for the 5 injuries was increased to 1/month, the cognitive deficits were mitigated, suggesting a period of cerebral vulnerability to repeated mTBIs (Meehan et al., 2012).

Other laboratories have adapted CCI devices in order to deliver closed-head injuries, with worsening behavioral and pathophysiological disturbances as the number of impacts is increased (Bennett et al., 2012; Bolton Hall et al., 2016; Hylin et al., 2013a; Mouzon et al., 2014; Ojo et al., 2015; Shitaka et al., 2011). Using an adapted closed-head CCI model in mice, Mouzon et al. (2014) conducted a comprehensive study to investigate the long-term effects of single and repetitive mTBI. Mice administered repetitive mTBI had persisting cognitive deficits and progressive behavioral impairments up to 18 months post injury, and these changes occurred in the presence of progressive neuroinflammation and white matter degradation (Mouzon et al., 2014). Interestingly, this study did not identify any abnormalities in h-tau, which is in contrast to findings from the repeated mild FPI and the impact acceleration models; however, tau abnormalities were observed when repeated closed-head CCIs were given to mice with a human tau genetic background (Ojo et al., 2016). It should also be noted that a single closed-head CCI resulted in persisting learning deficits for 18 months post injury, which is atypical of what is observed in the large majority of clinical mTBI cases and might suggest a more severe injury with this model. A recent study that used the same single closed-head CCI model found that mice given a mTBI had lower levels of several major phospholipid classes compared to controls at chronic post-injury time points (Emmerich et al., 2016b). These findings are similar to changes in phospholipid levels observed in human mTBI subjects [i.e., cross-species validation; (Emmerich et al., 2016a)], and may provide insight into persisting pathophysiology after a mTBI. This closed-head CCI model has also been combined with a PTSD paradigm to create a novel model of co-morbid PTSD and mTBI that may be relevant to mTBIs occurring in the warzone environment (Ojo et al., 2014).

To avoid the confounding issues of anesthetic, the CCI has now been further adapted to perform mild closed head injury to awake animals. The use of common anesthetics in mTBI models may be a serious limitation (Gray et al., 2005; Hendrich et al., 2001; Luh et al., 2011; Patel et al., 1995; Statler et al., 2006a,b). Ethical concerns underlying modern animal care practices have led to the widely accepted use of anesthetics in these models. This is potentially problematic because common anesthetics like isoflurane alter GABAergic and glutamatergic signaling (Kotani and Akaike, 2013; Patel et al., 1995), cerebral blood flow (Hendrich et al., 2001), mitochondrial function (Zhang et al., 2012), and apoptosis (Gray et al., 2005). Given that excitotoxicity, cerebral hypoperfusion, metabolic distress, and cell death may be important components in mTBI (Giza and Hovda, 2014), the use of anesthetics in mTBI models must be carefully considered.

The awake closed-head CCI procedure involves securing a mouse in a conical restraint bag, placing a helmet on its head, and positioning the mouse on a foam platform (Petraglia et al., 2014a,b). A CCI modified with a 5 mm rubber tip is positioned over a target on the helmet, then the mouse is impacted and removed from the bag. This simple and high throughput procedure creates a mild, diffuse injury absent of skull fracture, focal contusion, hemorrhage, or significant tissue damage. Single and repeated injuries were associated with elevated neurological severity score, sleep disturbance, and increased anxiety-like behavior accompanied by astrocytic activation and acute h-tau. Repeat injury also altered depression- and anxiety-related behaviors, impaired spatial memory and motor function, and initiated astrogliosis, microglial activation, and chronic h-tau (Petraglia et al., 2014a,b). In a minor modification to this procedure, the same group induced awake mTBI by suspending the bag-restrained mouse vertically from the rostral end of the restraint (Plog et al., 2015). The modified CCI is positioned laterally towards the target, and as the mouse is impacted it swings freely into a flat board placed 5 cm behind. A single mTBI with this model significantly elevated serum levels of S100B and GFAP (Plog et al., 2015). Notably, this study also found that CSF movement through the glymphatic pathway transports TBI biomarkers to blood via the cervical lymphatics, and that clinically relevant manipulation of glymphatic activity, such as sleep deprivation, suppressed TBI-induced increases in serum S100B and GFAP. These findings may have important implications for the clinical use of blood-based biomarkers. Related to this, other studies have found that anesthetic affects glymphatic activity (Xie et al., 2013). Therefore, blood biomarker studies that employ pre-clinical mTBI models that require anesthetic may be confounded.

In addition to saving time and eliminating associated complications/confounds, omitting surgery and anesthesia also allows for behavioral observations to be made immediately after impact. The speed, location, and angle of impact are also easily manipulated and, unlike stereotaxic models, the head moves freely during the impact and mimics the rapid acceleration often seen in human mTBI (Viano et al., 2007). Although this feature improves relevance to the clinical condition, the inability to use stereotaxic coordinates to position the impactor may limit reproducibility. The potential for restraint stress to confound results is another possible disadvantage of this technique. The validity of this concern could be addressed by measuring serum corticosterone immediately after injury. Furthermore, stress associated with the impact procedure may better model environments where head injuries commonly occur such as a competitive sports or combat zones.

Moving forward, ongoing efforts to characterize awake mTBI should also attempt to directly compare outcomes in rodents impacted while awake and under anesthesia. If acute anesthesia does not significantly affect the relevant mTBI outcomes, such experiments will support the ethically preferable continuation of anesthesia in mTBI modeling. If acute anesthesia affects mTBI pathophysiology and recovery, comparing outcomes after awake and anaesthetized mTBI may reveal differential timelines or effect sizes in behavioral deficits and underlying injury mechanisms. Such comparisons could provide new insight on the extensive difficulties in translating promising pre-clinical therapeutics to meaningful results in the clinic.

New injury devices are also being developed to model forms of mTBI. The closed-head impact model of engineered rotational acceleration (CHIMERA) model involves a non-surgical and precise closed-head impact and kinematic analysis of unconstrained head movement in mice (Namjoshi et al., 2014). Repeated CHIMERA can result in neurological, motor, and cognitive deficits along with anxiety-like behavior, as well as axonal injury, neuroinflammation, and increased h-tau (Namjoshi et al., 2014). Although this procedure still requires anesthetic, it is minimal given the brief time

required for the injury to be administered. The CHIMERA model was recently used to investigate whether androgenic-anabolic steroids affects the vulnerability of the brain to mTBI (Namjoshi et al., 2016). From 8 to 16 weeks of age, mice received either vehicle or a cocktail of androgenic-anabolic steroids consisting of testosterone, nandrolone, and 17α-methyltestosterone. At the end of the 7th week of treatment, mice underwent two CHIMERA or sham procedures spaced 24 h apart, followed by a week of behavioral testing and then a post-mortem analysis. Although the steroid treatment did not worsen post-CHIMERA behavioral changes, it did exacerbate axonal injury and microgliosis.

Other researchers are developing a non-invasive method of closed-head projectile concussive impact (PCI) in rats to model closed-head injuries that can occur in the warzone (Chen et al., 2012; Leung et al., 2014). For this procedure, anesthetized rats are placed on a platform positioned above a torque-sealed microcentrifuge tube packed with dry ice. Upon heating, rapid sublimation of the dry ice triggers an eruptive force causing the cap to launch as an intact projectile, resulting in a targeted PCI head injury. A helmet can be used to protect the integrity of the head/skull. Mild PCIs result in no gross brain pathology, though protein changes, axonal injury, inflammation, and behavioral abnormalities can occur acutely post-injury (Chen et al., 2012; Leung et al., 2014).

Taken together, the models described in this section that incorporate the head acceleration mechanics and the surgery, and anaesthetic-free nature of human mTBI, are important advances in the experimental mTBI field. Though the translational benefits of these new rodent mTBI models remain to be determined and future studies are still required to better characterize and validate these methods, it is important that pre-clinical researchers acknowledge the limitations of traditional rodent models and embrace the next generation of models that attempt to address these limitations.

2.6. Non-rodent models

While rodent models are the most widely used animal models of TBI today, this was not always the case, with several species of larger animals being more commonly used in studies up until the 1980s (for review, see Cernak, 2005). However, ethical considerations, plus the low cost and ease of use of rodents, shifted research away from the larger species. Although this shift resulted in a rapid increase in TBI studies, largely focused on molecular pathology, there has notably been a lack of translation to the human condition that many now ascribe to the predominant use of rodents and their lissencephalic cortex as opposed to larger and phylogenetically higher species with gyrencephalic brains (Rosenfeld et al., 2012; Vink and Bullock, 2010). Moreover, few rodent studies either measure or report consistent changes in intracranial pressure and cerebral perfusion pressure after TBI, which was a focus of the early large animal studies. Hence, there is a growing interest in the use of non-rodent species to characterize TBI, and in particular, mTBI.

Most of the historical large animal studies used focal models of direct brain deformation to replicate aspects of human TBI. For example, fluid percussion injury has been previously used in cats (Sullivan et al., 1976), pigs (Lafrenaye et al., 2015; Pfenninger et al., 1989), rabbits (Hartl et al., 1997), as well as in dogs and sheep (Millen et al., 1985), while controlled cortical impact has been used in ferrets (Lighthall, 1988), and in pigs (Manley et al., 2006). In both models, injury severity can be titrated to levels believed to be representative of mild injury, although direct brain deformation does induce focal tissue damage and requires the presence of a craniotomy to provide access. These features are not typical of human mTBI. A further limitation is the inability to produce any rotational injury using these models, which has been previously shown to be a critical element in inducing loss of consciousness (Gennarelli et al., 1982).

The biomechanical limitations of the focal brain deformation models led to the development of various acceleration models, including the impact acceleration and non-impact acceleration models. Both models induce rotation through the different planes, with the versions without head restraint capable of producing rotations through several different planes with a single impact.

The impact acceleration model was first introduced in non-human primates (Gurdjian et al., 1954), successfully replicating many aspects of human TBI including systemic, cerebral metabolic, and histological changes plus transient loss of consciousness. This model was subsequently modified for application to cats (Tornheim and McLaurin, 1981), where it was plagued by the frequent occurrence of skull fracture and hemorrhage. The subsequent adaptation to sheep (Lewis et al., 1996) has seen the model successfully used to characterize graded traumatic insult. The impact is generated using a stunner whereby the injury is targeted at the temporal region of the unrestrained ovine head, allowing free axial and coronal rotation after impact. The widespread axonal injury observed in this model strongly correlates with systemic and cerebrovascular responses (Lewis et al., 1996), while the simultaneous measurement of intracranial pressure and brain oxygenation has given valuable insight into pressure perfusion dynamics after TBI (Vink et al., 2008). An attempt to adapt this model to pigs was unsuccessful, presumably because of the large subarachnoid space that was present in the pig strain that was used (Finnie et al., 2003).

The non-impact model was developed for non-human primates (Gennarelli et al., 1982), and subsequently applied to pigs (Ross et al., 1994) and rabbits (Gutierrez et al., 2001). In this model, it is the acceleration and deceleration of the brain mass that causes an inertial effect resulting in tissue deformation. While the initial application of the model was to a non-constrained head, the high variability of the outcome led to subsequent applications incorporating head constraint and limiting the head rotation to a single plane. The resultant non-human primate studies established that sagittal head motion almost always induced a brief loss of consciousness (<15 min) without widespread axonal injury while coronal rotation induced widespread axonal injury and prolonged coma (Gennarelli et al., 1982). In a carefully conducted series of studies (Browne et al., 2011), the force of angular rotation was reduced to more closely replicate that observed in concussive human TBI and demonstrated in pigs that even such low levels of injury produced brief loss of consciousness and extensive axonal injury. In their studies (Browne et al., 2011), the axial plane rotation, in contrast to coronal rotation, produced more extensive axonal injury in the brainstem and longer periods of unconsciousness up to 35 min. Although highly valuable in terms of the data produced, application of this inertial model has been limited to a single laboratory because of the high technical demands associated with the injury device, as well as the ethical concerns the model has historically raised.

The impact acceleration model has several advantages over the inertial acceleration model, thus favoring the use of impact acceleration in studies of mTBI. First, the device used to induce injury is relatively inexpensive and readily available throughout the world; indeed, the equipment is widely used in abattoirs. Second, the head and skull of the animals are directly struck, consistent with observations that unconsciousness is more readily induced where direct blows to the head produce rapid head rotations as opposed to whiplash induced head rotations without head contact (Ommaya and Gennarelli, 1974). Finally, recent inertial acceleration studies are limited to single plane rotations whereas the impact acceleration models induce rapid changes in head velocity that involve both rotational and angular acceleration, similar to what is observed in human concussive TBI.

As with all large animal models of TBI, there is a need to develop more reliable functional outcome tests, which together

with the higher costs associated with large animals, longer life spans required for chronic studies, and the more complex technical requirements, will discourage most researchers from pursuing such studies. Nonetheless, the similarity of the larger animal brains to human brains, particularly with respect to the convoluted folding of the cerebral cortex, permits investigation of the gray-white junction at the depths of the sulci that are not present in the rodent lissencephalic brain. It is in the depths of the sulci where tau containing neurofibrillary tangles associated with chronic traumatic encephalopathy are found (Barrio et al., 2015; McKee et al., 2013), a distribution pattern hypothesized to reflect the regions of greatest mechanical stress after a traumatic impact in the human brain.

3. Translational challenges and strategies

The primary goals of pre-clinical mTBI research are to further our understanding of mTBIs and their effects, and to provide representative and efficient screening methods for potential biomarkers and therapies that will ultimately lead to better informed medical decisions and improved outcomes for mTBI patients. We now discuss some of the major translational challenges and strategies that may assist to bridge the gap between pre-clinical and clinical mTBI research.

3.1. Choosing the appropriate animal model and accounting for the heterogeneity of mTBI

As summarized in Table 1, each of the aforementioned pre-clinical injury methods model at least some aspects of mTBI, and may be valuable if their limitations are recognized and considered in study design and the interpretation of the results. However, as mentioned to above, the involvement of craniotomy and/or anesthetic has the potential to falsify and/or substantially alter outcomes in the traditional mTBI models.

The significant heterogeneity of clinical mTBI is undoubtedly one of the greatest challenges facing the field. Because clinical mTBI is heterogeneous, there is no single model that is capable of capturing each of the possible features. There are a number of strategies that may minimize the impact of this inherent limitation of heterogeneity. First, although further pathophysiological characterization is required for many animal models of single and repeated mTBI, particularly at chronic stages post-injury, there is growing evidence that some models result in certain pathophysiological changes while others do not. Similarly, some models are better suited at replicating the particular biomechanics of certain mTBIs (e.g., blast-wave exposure most appropriate for studying mild bTBI). Therefore, a particular model can be chosen based on a specific research question. However, if this strategy is employed it is imperative that it is clearly stated that the findings may be model-dependent, and that findings are not generalized to all forms of mTBI.

A second strategy to help account for mTBI heterogeneity is to incorporate a number of complementary models into the study design. Ideally this would be done in a large scale, pre-clinical, multi-institute consortium that involved multiple injury models at multiple sites. Such an approach may be particularly useful to trial prospective therapy and biomarker candidates across a range of injury subtypes because it would provide insights as to whether a promising biomarker or therapy is applicable to a variety of mTBIs, or instead restricted to potential use in specific forms of injury. The development of such a consortium will require further characterization and standardization of the existing and emerging mTBI models.

A third strategy to help account for injury heterogeneity may be to *embrace the inherent variability* of injuries induced by certain models of mTBI. Researchers could attempt to capitalize on injury variability by correlating the differences in animal responses to mTBI with other outcomes of interest (e.g., expression of biomarkers, response to therapies). Though models inducing heterogeneous injury patterns will reduce statistical power, sub-group analysis may provide valuable insights that may otherwise be missed with traditional direct group comparisons between mTBI and control animals.

3.2. Choosing clinically relevant outcomes

In addition to judiciously deciding upon the appropriate injury model and accounting for mTBI heterogeneity, pre-clinical researchers must ensure that they incorporate clinically relevant/translatable outcomes into their studies. This is particularly important for improved translation of mTBI biomarkers and therapies. Several invasive and potentially harmful techniques can be conducted in rodents and offer the benefit of providing valuable insights into mTBI pathobiology where clinical studies cannot. However, pre-clinical researchers should also prioritize incorporating methods/outcomes that are applicable in both the experimental and clinical settings (see Table 2).

With the development of new technologies capable of identifying specific pathophysiologies *in vivo* in patients (e.g., neuroimaging and blood biomarkers), translational pathways for such approaches are now emerging, particularly when these methods are applicable in both the experimental and clinical settings (see Table 2). For example, many of the aforementioned MRI methods that are currently being used in clinical studies can also be applied in pre-clinical research. This includes diffusion MRI (Kamnaksh et al., 2014; Li et al., 2016; Long et al., 2015; Wright et al., 2016), MRS (Fatouros et al., 2000; Wright et al., 2016), fMRI (Mishra et al., 2014), ASL (Hayward et al., 2011), SWI (Benson et al., 2012; Shen et al., 2007), and PET (Brabazon et al., 2016; Byrnes et al., 2014; Okamura et al., 2013; Selwyn et al., 2016). Importantly, some of the pre-clinical mTBI neuroimaging findings, such as diffusion MRI and FDG-PET, bear some resemblance to those reported in initial clinical mTBI studies (e.g., Wright et al., 2016; Selwyn et al., 2016; Kamnaksh et al., 2014).

If cross-species validation on clinically relevant biomarkers is demonstrated it then enables pre-clinical researchers to implement these biomarkers in studies not possible in human patients. For example, there is currently no direct evidence that the possible cumulative and/or long-term effects of repeated mTBIs can be mitigated if mTBIs are managed by the use of biomarkers (e.g., an athlete or soldier is medically cleared to return to pre-injury activities based on biomarker recovery). While human studies to assess this would take decades to complete and would be confounded by a number of factors, animal models can assess this in a relatively efficient and well-controlled manner. Specifically, animal model studies that administer repeated mTBIs with the inter-injury times guided by biomarker recovery may provide evidence in support of using this biomarker to reduce the effects of repetitive mTBI. A recent study conducted by Selwyn et al. (2016) applied an approach similar to this by administering repeated mild FPIs to rats with the timing based on glucose uptake as measured by FDG-PET. After showing in an initial study that a single mild FPI results in depressed glucose uptake that peaks at 24 h but resolves by 16 days post-injury (Selwyn et al., 2013), they subjected rats to a second mild FPI with a latency of 24 h or 15 days after the initial injury. Rats that received a second mTBI 24 h after the initial injury showed significant deficits in motor function tasks, as well as significant increases in lesion volume and neuronal damage. Importantly, when the second injury was administered at 15 days (i.e., after FDG-PET abnormalities had resolved) the 2 injury group did not differ from the single injury group.

Table 1
Rodent models of a single TBI: Commonly described single injury characteristics and relevance to clinical mTBI.

TBI model	Injury Pattern/Pathology	Clinical Features	Strengths	Limitations	Clinical Relevance
Weight-Drop					
Feeney's	Focal injury; Hemorrhage; Neuroinflammation; Neuron loss; Metabolic changes	Poorly characterized in mTBI	Reproducibility	Craniotomy; Cavitation; Anesthetic	Models focalized TBI
Marmarou's	Diffuse injury; Widespread axonal injury; Vascular damage; Neuroinflammation	Heterogeneous outcomes; Cognitive/motor deficits, usually resolve by 48h	Widely utilized; Medium-high throughput	Reproducibility; Anesthetic	Mimics diffuse axonal injury; Adaptions maximize head acceleration mechanics
Shohami's	Mixed focal/diffuse injury; Neuroinflammation; Edema	Transient NSS/cognitive/motor deficits	Requires light anesthetic; High throughput	Reproducibility; Anesthetic	Mimics blunt, closed-headed impact
CCI					
Standard	Focal injury; Neuron loss/damage; Neuroinflammation; Potential cavitation and/or hemorrhage	Cognitive, motor, emotional deficits common but variable; Negligible memory deficits	Highly reproducible; Precise control of impact variables	Craniotomy; Potential cavitation; Deficits may persist; Anesthetic	Focalized and complicated mTBI
Closed-head	Diffuse injury; Neuroinflammation; Axonal injury	Transient cognitive/motor deficits	Avoids craniotomy; High throughput	Deficits may persist; Anesthetic	Blunt, closed-headed impact; Diffuse injury pattern
Closed-head awake	Diffuse injury; Neuroinflammation; h-tau	Transient NSS/motor/emotional deficits; Sleep disturbances	Avoids anesthetic and craniotomy confounds; High throughput	Potential for restraint stress; Further characterization required; Reproducibility	Blunt, closed-headed impact; Diffuse injury pattern
FPI	Mixed focal/diffuse injury; Transient inflammation and h-tau; Axonal injury; Reduced cerebral blood flow	Transient cognitive/motor/anxiety-related deficits; Sleep disturbances	Reproducibility; Minimal neuronal loss and cavitation	Craniotomy; Anesthetic; Low throughput	Coup-countercoup injury pattern
Blast	Diffuse injury; Axonal injury; inflammation; h-tau	Variable symptoms; Sensorimotor/emotional disturbances	Very diffuse injury pattern. May create unique pathophysiology	Lack of standardized injury model variables; Anesthetic; Injury to other organs	Mimics bTBI in military personnel

Note: CCI = Controlled cortical impact, FPI = fluid percussion injury, bTBI = blast TBI, NSS = neurological severity score, H-tau = hyperphosphorylated tau.

Table 2
Examples of biomarkers/indicators of mTBI applicable in patient and/or animal model studies.

	Patient tests, measures, and technologies	Animal model tests, measures, and technologies
Neurological/Neurocognitive/ Neurobehavioral/ Electrophysiology	• Conscious State - GCS • Loss of consciousness • Cognition - SCAT3, ImPACT™, CogSport™, CNS Vital Signs™ • Neuropsychological evaluation • Motor – SCAT3/Balance Error Scoring System • Depression, Anxiety, Depression – Neuropsychological evaluation • Oculomotor/visual-spatialSleep abnormalities – King-Devick test, NeuroTracker™ • Sleep abnormalities • Electroencephalography (EEG)	• Conscious State – Neurological severity score (NSS) • Pain and self-righting reflex • Cognition – Water maze, Y-Maze, Barnes Maze, Radial arm, Object recognition, 5 choice serial reaction time • Motor – Beam task, Rotarod, Gait, Open field • Depression, Anxiety, Depression – Elevated-plus, Forced swim, Open field • Sleep abnormalitiesOculomotor/visual-spatial – Eye-tracking paradigms, Oculomotor reflexes • Sleep abnormalities • Electroencephalography (EEG)
Neuroimaging	• X-ray computed tomography (CT) • Advanced magnetic resonance imaging (MRI) techniques – Diffusion-tensor imaging (DTI) • Magnetic resonance spectroscopy (MRS) • Susceptibility-weighted imaging (SWI) • Functional MRI (fMRI) • Arterial spin labeling (ASL) • Positron emission tomography (PET) imaging – Tau • Metabolism • Inflammation • Amyloid	• X-ray computed tomography (CT) • Advanced magnetic resonance imaging (MRI) techniques – Diffusion-tensor imaging (DTI) • Magnetic resonance spectroscopy (MRS) • Susceptibility-weighted imaging (SWI) • Functional MRI (fMRI) • Arterial spin labeling (ASL) • Positron emission tomography (PET) imaging – Tau • Metabolism • Inflammation • Amyloid
Blood-based biomarkers	• Proteins – e.g., tau, S100 calcium-binding protein (S100B), glial fibrillary acidic protein (GFAP), galectin 3, matrix metalloproteinase 9 (MMP9), occludin, plasma soluble cellular prion protein • microRNAs	• Proteins – e.g. tau, S100B, glial fibrillary acidic protein (GFAP), galectin 3, matrix metalloproteinase 9 (MMP9), occludin, plasma soluble cellular prion protein • microRNAs

With regards to treatment studies, pre-clinical research would be improved by incorporating more clinically relevant functional and neuroimaging measures into experiments, in addition to the more commonly used cellular and molecular endpoints. With the continued development of clinically relevant mTBI biomarkers that are capable of identifying specific pathophysiologies, and drugs that are able to target said pathophysiologies, a precision medicine approach in mTBI patients may one day be possible.

In addition to having more clinically relevant outcomes, pre-clinical researchers must also ensure that they incorporate objective indicators of injury and/or recovery into their studies, particularly with the contentious issue of what actually constitutes an animal model of mTBI and what distinguishes model severities (e.g., differentiation of a concussive model from a more substantial mild or moderate injury model). 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 using similar mTBI models across laboratories.

3.3. Recognize and attempt to account for inter-species differences

Other major challenges in translational research involve inter-species differences between humans and rodents (Seok et al., 2013). In addition to the aforementioned anatomical differences, one factor that is frequently overlooked is the duration of mTBI-associated deficits. For example, neurological deficits persisting for one week in the rodent may be vastly different from those lasting one week in humans. As such, it is important for researchers to consider whether the time course of functional deficits in rodents after an injury should be translated in absolute terms or relative to lifespan. Similarly, the temporal profile of pathophysiological changes in the rodent brain can often differ from what occurs in the human brain. This would be less of an issue if the pathophysiological changes of interest were adequately characterized in both species and any differences are carefully considered. Unfortunately, because the mild nature of mTBI makes it challenging to rigorously study pathophysiology in humans, there is currently a large knowledge gap in the clinical setting. Future clinical studies should strive to bridge these gaps when technically/ethically feasible in order to facilitate translation. Until these studies are completed, animal model findings related to pathophysiologies that are poorly characterized in humans must be interpreted with caution and findings should not be assumed to hold true across species. Inter-species differences in pathophysiological timecourse and metabolism are particularly important in the translation of pharmacological interventions. Moreover, the pharmacokinetics and pharmacodynamics of chemical agents can differ considerably in animals, which further complicates allometric scaling when translating to human studies. This may have been a major factor in the recent translational failures that occurred in the Phase III clinical trials with progesterone treatment (Howard et al., 2015; Stein, 2015). As such, future pre-clinical and clinical drug studies should incorporate serial analyses of drug levels, as well as markers for related pathologies, throughout the treatment period. When it is not possible to conduct detailed pathophysiology and treatment studies in humans, the use of larger non-rodent species that more closely resemble humans may be useful.

Table 3
Selection of repeated TBI studies: Injury schedule/details, pathology, symptoms, and clinical relevance.

Model	Author	Injury Schedule/Details	Pathological Findings	Symptom/Behavioral Findings	Clinical Relevance
Weight-Drop	Creeley et al. (2004)	Marmarou; mice; 3 TBIs; 24 h intervals	Histological evidence of brain damage at 24 h post-injury in 3 TBI mice	Increased righting reflex post 2 TBI; Impaired spatial learning after 3 TBIs at 2–3 weeks	Injury schedules/numbers resemble sports/military setting where multiple concussions can occur, although larger numbers (i.e., 10–12 TBIs) are unlikely with current concussion guidelines; Xu et al. (2016) injury schedule (i.e., 12 TBIs with 3/day) better represents sub-concussive insults, although dosimetry might be a major issue; Single injury very mild (i.e., sub-concussive?); Cumulative symptoms similar to repeated TBI in patients; Subtle pathology with some relevance to CTE; Period of cerebral vulnerability
	Xu et al. (2016)	Marmarou; mice; 4 TBI at 0, 1, 3, 7 days *or* 12 TBI at 0, 1, 3, 7 days (3/day)	Increased axonal injury but no h-tau expression in repeat TBI compared with single TBI at 7 days and 10 wks post-injury	Not investigated	
	Kane et al. (2012)	Marmarou (foil base); mice; 4, 5, or 10 TBIs; 24 h intervals	Mild increases in GFAP (at 7 days) and h-tau (at 30 days) in repeat TBI mice; No edema, microglial activation, nor BBB damage at 7 days	Transient impairments in motor function (at 1- but not 7-days) and activity (at 5- but not 30-days) in repeat mTBI compared with sham	
	Meehan et al. (2012)	Marmarou (paper base); mice; 1, 3, 5, or 10 TBIs (24 h interval); 5 TBI (1 wk, or 1 month intervals)	No evidence of hemorrhage or edema at 24 h post-injury; No evidence of axonal injury, BBB damage, or neuronal loss at 7 wks post-injury	No difference between sham and single mTBI; Repeated mTBI results in cognitive deficits; 5 mTBIs with 24 h or 1 wk intervals, but not 1 month intervals, induced lasting cognitive deficits	
	DeFord et al. (2002)	Shohami; mice; 4 TBI; 24 h intervals	No overt damage at 3 h, 48 h and 12 days; No evidence of BBB dysfunction at 3 h and 48h	Impaired spatial learning following 4 TBIs compared with sham at 1–2 weeks	Relevant injury schedule; Cognitive deficits; Sub-concussive?
Modified CCI	Mouzon et al. (2014)	Closed-head; mice; 1 or 5 TBI; 48 h intervals	Progressive neuroinflammation following 5 TBIs at 6- and 12 months; No h-tau; White matter loss in both 1- and 5-TBI models at 6 months, further loss following 5 TBIs at 12 months.	Spatial memory deficits at 6- and 12-months in 5 TBI; Learning deficits in 1 TBI at 18-months that are worse following 5 TBIs; No long term motor- or anxiety-related deficits	Injury schedule/number may occur in sports/military; Cognitive deficits and inflammation might be relevant to CTE; Injury a moderate or severe TBI?
	Petraglia et al., (2014a,b)	Closed-head (awake variant); mice; 42 TBI (6 daily for 7 days)	Widespread h-tau and neuroinflammation at 7 days, 1- and 6-months in repeat injured mice. No macroscopic brain damage at all time-points	Spatial learning deficits in repeat TBI at 1–5 days and at 1 month, but not 6 months; Increased risk taking behavior in repeat TBI at 1- and 6-months; Depressive-like behavior, sleep disturbances in repeat TBI at 1 month	Injury schedule better represents sub-concussive insults (i.e., this many concussions unlikely with current clinical management); Some changes similar to CTE
FPI	Shultz et al. (2012a,b)	Lateral FPI; rats; 1, 3, or 5 TBI (5 day intervals)	Neuroinflammation at 24 h post-injury with 3 and 5 TBIs, 8 wks post-injury following 5 TBIs; Cumulative and progressive cortical damage with 3 and 5 TBIs.	3 and 5 TBI rats had cognitive deficits at 8 wks; Anxiety- and depression-like behaviors at 8 wks following 5 TBIs	Injury schedule/number resembles what can occur in sports setting where multiple concussions occur in single season; Long-term symptoms, h-tau, neuroinflammation, and progressive brain damage similar to those reported in CTE cases

Table 3 (*Continued*)

Model	Author	Injury Schedule/Details	Pathological Findings	Symptom/Behavioral Findings	Clinical Relevance
	Webster et al. (2015)	Lateral FPI; rats; 3 TBI (5 day intervals)	Neuroinflammation, oxidative stress, axonal injury, and cortical atrophy at 12 wks post-injury	Cognitive, motor, and emotional abnormalities at 12 wks post-injury	
	Tan et al. (2016)	Lateral FPI; rats; 1–3 TBI (5 day intervals)	Transient h-tau with 1 TBI; Exacerbated and persisting h-tau with 2 TBIs; Persisting h-tau, axonal injury, and cortical atrophy with 3 TBIs	3 TBIs induced cognitive, motor, and emotional abnormalities at 12 wks post-injury	
	Aungst et al. (2014)	Lateral FPI; rats; 1 or 3 TBI (2 day intervals)	3 TBIs induced diffuse neuroinflammation, neuronal loss, lesion, and long-term potentiation deficits at 4 wks post-injury	Learning and memory impairments at 4 wks post-injury	
Blast	Elder et al. (2012)	Overpressure injury; rats; 3 TBI (24 h intervals)	No evidence of pathological changes following 3 mTBI at 4–12 months	Increased anxiety, increased contextual fear conditioning after 3 mTBI at 6 months	Models bTBI in military personal; Injury schedule/number may occur in military environment (e.g., 1 severe bTBI or 12 sub-concussive bTBIs); Adjustable injury severity; Anesthetic may be avoided. PTSD-like?
	Ahlers et al. (2012)	Blast overexposure; 116.7 or 74.5 (single injury); 36.6 kPA (1 or 12 injuries, 24 h intervals); Lateral versus frontal orientation; No anesthetic; rats	Single 116.7 kPA, but not 74.5 or 36.6 kPA, results in hemorrhage and contusion, as well as pulmonary hemorrhage; Detailed neuropathological analysis of not completed.	Single 116.7 kPA results in motor and memory deficits; Single 74.5 kPA results in transient memory deficits; Repeated, not single, 36.6 kPA results in cognitive deficits.	
CHIMERA	Namjoshi et al. (2014)	CHIMERA impactor; mice 2 TBI (24 h interval)	Neuroinflammation and DAI in 2 mTBI at 2–14 days; H-tau at 6-, 12- and 48 h, return to sham levels at 7 days	Increased NSS at 1 h that remains elevated at 7 days; Motor impairments in first week that return to baseline by 2 weeks post-injury; Cognitive deficits and anxiety-like behavior persists at 2 weeks post-injury	Injury schedule relevant to sports/military; CTE-related pathologies; Symptoms similar to mTBI patients; Further characterization needed (e.g., chronic effects)

Note: TBI = Traumatic brain injury, CCI = Controlled cortical impact, FPI = fluid percussion injury, bTBI = blast TBI, NSS = neurological severity score, H-tau = hyperphosphorylated tau, CTE = Chronic traumatic encephalopathy, mTBI = mild TBI, NSS = Neurological severity score, DAI = diffuse axonal injury, PTSD = Posttraumatic stress disorder, BBB = Blood-brain barrier, GFAP = Glial fibrillary acidic protein.

3.4. Choosing clinically relevant injury numbers and inter-injury intervals in repeated mTBI studies

Investigating the effects of repeated mTBIs adds further translational complexities, in large part due to the inter-species differences discussed above coupled with the variability in the number of mTBIs and inter-injury time that occurs in humans. Previous animal model studies have utilized a broad range of injury numbers and inter-injury intervals (see Table 3). For the most part these studies bear some resemblance to what might occur clinically. Historically, athletes were permitted to resume pre-injury activities acutely post-injury (e.g., in the same game), and it is individuals from these generations that have participated in previous studies investigating the long-term effects of mTBIs. Therefore, experimental repeated mTBI studies that involve daily mTBIs or multiple mTBIs/day may resemble scenarios that occurred in these participants. It could also be argued that studies using multiple mTBIs/day models what currently occurs in athletes who experience a high number of daily sub-concussive impacts. Alternatively, the recent adoption of a more conservative approach to mTBI management by many clinicians often results in individuals withheld from pre-injury activities for 1–4 weeks following injury. As such, studies utilizing inter-injury intervals of days-weeks may better model the current clinical management of mTBI. Once again, inter-species differences in the time course of functional deficits and pathophysiological changes (e.g., 5 days in rat > 5 days in humans) must also be considered. Another factor that is often overlooked in repeated mTBI studies in rodents is the timing of injuries, both in terms of the age at which injuries commence and finish. This may be particularly relevant for studies of sports related concussion, in which individuals in many sports are often exposed to impacts beginning in early adolescence and continuing well into adulthood.

In short, there are many challenges in translational research, and there is no simple equation/solution that can be applied to address these issues. Rather, each of the factors described in this section should be carefully considered, and inter-species comparison/validation between human and animal model findings should be attempted whenever possible, in order to optimize translation from bench to bedside.

4. Summary and conclusions

This review is based on the symposium titled “From the lab bench to the field: translational research approaches for investigating mild traumatic brain injuries” at the 2015 International Behavioral Neuroscience Society Meeting. It should be noted that some factors, such as sub-concussive injuries, age, sex, and genetics, were not discussed in detail here but represent other important areas of mTBI research [see Davidson et al., 2015; Semple et al., 2013; Semple et al., 2015; Weaver et al., 2014 for detailed reviews]. In this article we described a number of key issues that remain to be addressed in the field including: the need to better understand the underlying pathophysiological mechanisms of mTBI; the identification of sensitive, reliable, and objective biomarkers; and the possibility that other therapy strategies, such as pharmaceutical intervention, may be beneficial.

Although there has been a much needed influx of mTBI patient studies in recent years, due to various confounding variables (e.g., selection biases, genetics, and socioeconomic and lifestyle factors) and limitations (e.g., relatively mild nature of single mTBI, chronic effects of repeated mTBI, technology, ethics), it is not currently feasible to adequately address the abovementioned issues entirely in the clinical setting. Animal models allow for the rigorous, serial, and invasive investigation of the effects and pathophysiological mechanisms of mTBI, the validation and implementation of mTBI biomarkers, and the assessment of novel treatments, in a tightly controlled, time- and cost-efficient manner. Pre-clinical models also allow researchers to measure morphological, cellular, molecular, and behavioral variables in a single study. Therefore, we recommended a translational research approach incorporating animal models to provide insight into these types of questions, and provided an overview of currently available animal models of mTBI. Each model has a number of strengths and limitations that must be considered in study design. Although traditional rodent models, such as the CCI and FPI, are well-characterized, reproducible, and readily available to the research community, there are limitations with these models (e.g., anesthetic, craniotomy) that should not be overlooked. Newer rodent models have been developed to address these issues and should be integrated into the wider pre-clinical mTBI community. Although rodent models offer a number of advantages (e.g., ethical considerations, low cost and time), larger species with gyrencephalic brains more closely resemble the human brain and may be important to avoid future translational failures. It is also important to note that mTBI is a heterogeneous condition involving different injury mechanics, patterns, and pathophysiological mechanisms. Thus, there is no single animal model that is capable of encompassing the entire spectrum of mTBI, and the use of complementary models or embracing the heterogeneity within a single model may be beneficial.

Although animal models of mTBI can provide insight and guidance to human mTBI, ultimately the findings from animal model studies must be translated and validated in the clinical setting whenever possible. Such translational and interdisciplinary research strategies require major efforts and collaboration between clinicians and scientists, and can be challenging to achieve. However, considering that mTBI is common and affects individuals regardless of age, sex, or race worldwide, it is imperative that this research is conducted to improve the understanding of these injuries and facilitate evidence-based clinical practice.

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