Molecular and Cellular Neuroscience 66 (2015) 103–113

Contents lists available at ScienceDirect

Molecular and Cellular Neuroscience

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

Neuroimaging and traumatic brain injury: State of the field and voids in translational knowledge

Erica D. Bruce [a], Sneha Konda [b], Dana D. Dean [c], Ernest W. Wang [c], Jason H. Huang [c], Deborah M. Little [b,c,*]

[a] Baylor University, Department of Environmental Science, Institute of Biomedical Studies, The Institute of Ecological, Earth, and Environmental Science, One Bear Place #97266, Waco, TX 76798-7266, United States
[b] Texas A&M Health Science Center College of Medicine, Neuroscience Institute, 5701 Airport Road, MS AR D120, Temple, TX 76508, United States
[c] Baylor Scott and White Healthcare, Neuroscience Institute, 5701 Airport Road, MS AR D120, Temple, TX 76508, United States

ARTICLE INFO

Article history:
Received 25 January 2015
Revised 24 March 2015
Accepted 25 March 2015
Available online 27 March 2015

Keywords:
Traumatic brain injury (TBI)
Neuroimaging
Biomarkers
Magnetic resonance imaging (MRI)

ABSTRACT

Traumatic brain injury (TBI) is a leading cause of death and disability in every developed country in the world and is believed to be a risk factor in the later development of depression, anxiety disorders and neurodegenerative diseases including chronic traumatic encephalopathy (CTE), Alzheimer's Disease (AD), Parkinson's Disease (PD), and amyotrophic lateral sclerosis (ALS). One challenge faced by those who conduct research into TBI is the lack of a verified and validated biomarker that can be used to diagnose TBI or for use as a prognostic variable which can identify those at risk for poor recovery following injury or at risk for neurodegeneration later in life. Neuroimaging continues to hold promise as a TBI biomarker but is limited by a lack of clear relationship between the neuropathology of injury/recovery and the quantitative and image based data that is obtained. Specifically lacking is the data on biochemical and biologic changes that lead to alterations in neuroimaging markers. There are multiple routes towards developing the knowledge required to more definitively link pathology to imaging but the most efficient approach is expanded leveraging of in vivo human blood, serum, and imaging biomarkers with both in vivo and ex vivo animal findings.

This review describes the current use and limitations of imaging in TBI including a discussion of currently used animal injury models and the available animal imaging data and extracted markers that hold the greatest promise for helping translate alterations in imaging back to injury pathology. Further, it reviews both the human and animal TBI literature supporting current standards, identifies the remaining voids in the literature, and briefly highlights recent advances in molecular imaging. This article is part of a Special Issue entitled 'Traumatic Brain Injury'.

Contents

* Corresponding author at: Section on Veterans Biomedical Research, Neuroscience Institute, Baylor Scott & White Health, 5701 Airport Road, Mailbox MS-AR-D120, Temple, Texas 76502, United States.
E-mail address: deborahmlittle@gmail.com (D.M. Little).

http://dx.doi.org/10.1016/j.mcn.2015.03.017
1044-7431/

1. Introduction and scope of the problem

As reviewed in other articles in this special issue, TBI is a major public health problem and one that still lacks objective diagnostic tools, neurobiological predictors of outcomes, and allows the bounding criteria to identify those at greatest risk of poor long term outcomes including progression to neurodegenerative disease. What has clearly emerged from the recent literatures in military and sports medicine is that rapid and appropriate clinical management — ranging from rest to monitoring of intracranial pressure to neurosurgical intervention in more severe cases — can significantly alter the patient outcome particularly when started within 48 h of the injury. However, for such intervention and management to occur the injury must first be identified. For ensuring appropriate use of clinical resources, objective diagnostic studies and biomarkers of injury must be identified and validated. Neuroimaging, either alone or in combination with blood based biomarkers, is ideal in this role as it is still a clinical standard in cases with progression of behavioral or neurologic status to rule out contusion or hemorrhage. Beyond use to rule out emergent conditions that may require immediate neurosurgical intervention, the goal of neuroimaging should also include a role in identification of treatable injuries, to prevent secondary damage, and to provide useful prognostic information. Neuroimaging can provide important information for long-term treatment of TBI, identifying chronic sequelae, determining prognosis, and guiding rehabilitation for TBI patients.

Although TBI has long been known to be a major public health concern, the attention paid to TBI has increased recently in part due to the prevalence and incidence of injury among service members supporting the Global War on Terror and increased civilian awareness of the risk of sports concussions. The Armed Forces Health Surveillance Center (AFHSC) reported that during a 10-year period (January 1997–December 2006), 110,392 military members had at least one TBI-related medical encounter, and there were 15,732 hospitalizations with TBI-related diagnoses (Cameron et al., 2012; Cernak and Noble-Haeusslein; Lange et al., 2012). The prevalent use of improvised explosive devices (IEDs) increases the likelihood that American military personnel will be more frequently exposed to incidents that can cause TBI resulting in repeated TBIs in the same veteran increasing the risk for poorer long term outcomes.

In civilians, TBI is commonly caused by motor vehicle accidents, pedestrian versus motor vehicle accidents, sports, falls, and assaults. Within this list it seems prudent to separate out TBIs caused by athletic participation as the causes of injury are somewhat unique as is the risk for repeated concussions and repeated sub-concussive blows to the head. The question of the prevalence and risk caused by repeated concussions is still somewhat unknown as the bounding conditions for risk of later neurodegenerative disease have yet to be defined. However the risk of poor outcome and later neurodegeneration disease secondary to concussion is likely defined by some interaction between genetic factors, number of concussions, severity of injury, latency between concussions, age of injury and adherence to an appropriate clinical management protocol. Survivors of TBI are often left with significant cognitive, behavioral, and communicative disabilities, and some patients develop long-term medical complications, such as epilepsy and Alzheimer's disease (Centers for Disease Control and Prevention (CDC) et al., 2013; Gilbert et al., 2014; Pitkanen and Immonen, 2014; Prince et al., 2012; Sivanandam and Thakur, 2012; Yeh et al., 2013). Given the prevalence of sports concussions (300,000 sports-related concussions each year in the United States (Gessel et al., 2007)) and the high profile of those with exceptionally bad outcomes, public concern has become focused on the long term risk of repeated concussions and the associated long-term consequences. Similarly, those in occupations at high risk for repeated exposure (such as veterans) and repeated concussive injury have also driven not only public concern but also federal funding into the validation and development of diagnostic and prognostic markers as identification of a TBI is the first critical step towards risk reduction.

The challenge for diagnostics among those suffering a TBI is of greatest concern in the mildest form of injury. A traumatic brain injury (TBI) can be classified as mild if loss of consciousness and/or confusion and disorientation is shorter than 30 min (Hirtz et al., 2007; Vos et al., 2012). Mild TBI is not only the most prevalent severity of injury but it is often missed at the time of initial injury (McAllister et al., 2001; Mechtler et al., 2014; Vos et al., 2012). The challenge is exacerbated by usually normal MRI (magnetic resonance imaging) and CT (computerized tomography) scans. In the acute phase following injury, mild TBI is associated with a 10% risk for intracranial abnormalities like contusion, subdural or epidural hematoma, brain swelling, or subarachnoid hemorrhage (Vos et al., 2012). There is a very low risk (1%) of life-threatening intracranial hematoma and a very low mortality of 0.1% in adults and in children in mild TBI (although children have a lower risk) (Bigler and Maxwell, 2012; Eierud et al., 2014; McAllister et al., 2001; Mendez et al., 2005; Vos et al., 2012). Even in the absence of the severe consequences listed above and in the presence of normal neuroimaging, the concussed individual can experience cognitive problems such as headache, difficulty thinking, memory loss, attention deficits, mood swings and frustration and may be at an increased risk of poor outcomes if clinical management is ignored or a second injury occurs within some critical window. But, for the majority of those with a mild TBI, recovery and return to pre-injury baseline represents the gross majority (Bigler and Maxwell, 2012; Eierud et al., 2014). However, in 10 – 20% (approximately) of people with mild TBI, symptoms remain (Bazarian and Atabaki, 2001) and the factors that contribute to this minority are not well understood but likely include acute injury management, previous injury, genetic contributions and damage to the brain that is below the threshold for identification on standard clinical imaging.

2. Role of imaging in TBI

Neuroimaging can and should have a significant role in defining the bounding criteria and risk prediction model to identify those at increased risk of neurodegeneration in acute and chronic TBI. It is one of the few methods that allow in vivo and non-invasive assessments of neuropathology. The challenge with defining the role of imaging in TBI is that we do not have a single imaging modality that meets all of the following criteria: (1) accessible and safe for use in acute injury in those with altered consciousness; (2) equally sensitive to all injury severities, (3) equally sensitive to the acute through chronic time course, and (4) appropriate for identification of the earliest of pathological changes in the transition to neurodegenerative disease. Practically, this means that instead of assessment of the injury as a continuum (or continuous variable), we triage and segregate our imaging tools in large part by injury severity (to be treated as categorical). This is a challenge in terms of identifying factors that predict who will be at greater risk for neurodegeneration and the precipitating cause for increased concern as these factors likely can be found in all stages of injury (for example, less than full recovery in mild without acute imaging, delayed recovery in repeated TBI and MRI in the chronic stage only with less than full recovery). Further complicating this challenge is that there is an understandable disconnect between the clinical need and motivation for imaging and the lack of sensitivity of that imaging across our continuum.

Neuroimaging does provide some degree of diagnostic value in TBI (for example, identification by computed tomography (CT) scan of blood product or swelling following moderate to severe injury), characterization of acute reaction to injury (for example, PET ligands for inflammation), quantification of injury severity (for example, quantification of degree of white matter damage assessed via diffusion tensor imaging), assessment of degree of alteration of functional networks (for example, resting state functional magnetic resonance imaging), and chronic progressive alterations (for example, changes in cortical thickness, atrophy, alterations in biochemistry of high risk brain regions and the growing promise of imaging tau and amyloid pathology).

These tools, taken together with changes in screening and management of brain injury, and ongoing studies in high risk populations can inform risk for neurodegeneration. Further, incorporating appropriate neuroimaging modalities into animal studies serves to inform an iterative, translational, study design that will provide valuable data for developing therapeutics and management strategies for treating TBI.

In human applications, traditional neuroimaging has a role in acute diagnosis, monitoring changes in cognitive status, and assessments of progression of atrophy. We focus herein on the two neuroimaging methods most commonly used including computerized tomography (CT) and magnetic resonance imaging (MRI). At its simplest, CT involves the use of rotating x-ray equipment where strength of the x-ray is measured after it passes through biologic tissue. Residual x-ray beams are weaker in bone and dense tissue as compared to the residual after it has passed through soft tissue. This information is reconstructed in space and as a function of tissue density. CT imaging is the standard of care in patients with acute injury and altered consciousness and following acute changes in neurologic status. Although it does bring exposure to radiation, it does not require medical history to assess safety (compared to risk of MRI), is sensitive to blood which is critical for acute management (again, compared to MRI), offers reasonable clarity of different tissue and bone, and can be carried out and interpreted rapidly. At present, the major neurologic clinical application of CT is in the acute assessment of blood and blood products and also offers information on potential skull and spine injury. CT is the primary neuroimaging modality in acute assessment of combat injury for the specific assessment of hematoma, hemorrhage, and contusions (Marshall and Riechers, 2012). CT also offers the best option for assessment of penetrating brain injury which may or may not involve ferromagnetic objects.

In addition to standard CT, CT perfusion allows quantification and assessment of cerebral perfusion. CT perfusion relies upon the repeated collection of a series of images to characterize tissue transit times of contrast agent. CT perfusion is not commonly included in assessment of acute TBI but does offer significant clinical utility in both primary hypoxic — ischemic brain injury (Hill and Volpe, 1981; Taylor, 1994) and hypoxic — ischemic injury secondary to neurosurgical intervention in penetrating brain injury (Fujita et al., 2014), holds potential for detection of significant blood–brain barrier disruption (Dankbaar et al., 2009).

These strengths support the role of CT as the preferred method of acute injury assessment in moderate to severe TBI to rule out blood as CT is quick to acquire, requires comparatively little patient compliance, and is cost effective for ruling out hemorrhage (Stein et al., 2006). There are limited uses in outcome prediction for mild TBI but it does appear to have limited predictive validity in severe TBI including the reports that acute lesions observed on CT are associated with one year functional outcome (Wardlaw, Easton, & Statham, 2002).

CT however is limited in its usefulness in the detection of diffuse axonal injury in all but the most significant injuries. CT has a limited role in chronic assessment and is not sensitive to progressive changes in volume, tissue integrity, or pathologic hallmarks of the most common dementias. Other than gross predictive validity (for example, identification of major bleeds and skull fractures) it does not relate to the spectrum of outcomes in mild to moderate TBI.

Magnetic resonance-based imaging (MRI) is useful both in acute and subacute injury and multiple types of MRI have demonstrated usefulness in TBI. These uses include structural imaging for identification of lesions, blood and atrophy, perfusion based MRI which allows an investigation of blood flow, diffusion tensor imaging which allows assessment of white matter tracts and connectivity, spectroscopy which allows a biochemical assessment in vivo and arterial spin labeling. Briefly, MRI involves the interaction between a static magnetic field, local magnetic fields, and radio waves. MRI is exceptionally sensitive to hydrogen but can be used to measure any atom which has an odd number of protons and is abundant in the human body. Such atoms include hydrogen, carbon-13, sodium, and phosphorus. These advanced imaging targets are not widely available and are underdeveloped in TBI but may prove to be important in populations believed to be at greatest risk for conversion into neurodegenerative disease.

Simply, six main factors contribute to MRI. These include the properties of nuclear spin, the properties of the radio frequency (RF) excitation, properties of tissue relaxation, the strength of the static magnet field, the timing of RF pulses and the sensitivity of signal detection. The total MR signal is a combination of the sums of proton density reduced by T1, T2, and T2* relaxation. As such, each relaxation component offers distinct information about the character of tissue. The value of MRI in TBI is significant both clinically and for research into the chronic effects of TBI and risk factors for progression to neurodegeneration. First, unlike traditional CT, MRI is appropriate for clinical triage across the spectrum of injury severity and in all stages of chronicity. However, like CT, standard structural MRI is less sensitive to the milder range of injury severity. In this range standard T1-weighted structural sequences, T2-weighted sequences, sequences sensitized to blood, and those sensitive to acute changes in local water content have limited roles in milder injury in the absence of micro-bleeds and lesions. However, MRI, even with this caveat, is still far more sensitive to structural alterations than CT.

2.1. T1 weighted structural imaging

For imaging brain structure and volume, T1-weighted images are generally the standard both in clinical and research applications. The MRI T1 images are more spatially sensitive than CT making them potentially useful as markers of progression of injury to disease. Structural volume assessments also provide us the area of greatest overlap between TBI and measures of tissue atrophy in the common neurodegenerative diseases with numerous reports of both global and regional atrophy and reports of cortical thinning in early and late stage Alzheimer's disease (for example, (Barnes et al., 2009; Shi et al., 2009), Parkinson's disease (for example, (Ibarretxe-Bilbao et al., 2012)), ALS (for example, (Ellis et al., 2001)) and almost every other neurodegenerative disease. Similar to these diseases, there are reports of atrophy in the subacute and early chronic period following moderate to severe TBI (Trivedi et al., 2007) and also in chronic TBI (Orrison et al., 2009). There is also data to suggest that injury severity is associated with greater observations of tissue loss (Levine et al., 2008). Most interesting is the report of measures of atrophy in the acute and subacute phase following experimental models of TBI being predictive of chronic outcome (Immonen et al., 2009). But again, as with CT, these findings are heavily biased by injury severity. Further, atrophy is a gross non-specific observation with no pre-injury data currently available. Without that data it is unclear if measures and reports of global atrophy and cortical thinning are simply measures of injury severity or whether they are indicators of a pathological process. Also unknown is whether a history of single mild TBI is sufficient to increase risk of atrophy.

2.2. Proton magnetic resonance spectroscopy (^{1}H MRS)

MRS allows the examination of neuronal intracellular metabolic status and provides information about neuronal integrity, hypoxia, inflammation, and axonal injury. Common metabolites in MRS include myo-inositol (mI) a marker of the integrity of cell membranes, choline (Cho) which is associated with glial cell membrane integrity, creatine (Cr) a marker for ATP, glutamate (Glx), a marker of the neurotransmitter, N-acetyl aspartate (NAA) which is a marker for neuronal or dendrite integrity, lactate, which is a measure of hypoxia, and lipids which are an indicator of tissue necrosis.

The strength of MRS is in the strong relationship between measures of metabolism and cognition in TBI (Babikian et al., 2006; Hunter et al., 2005; Nakabayashi et al., 2007) and both MCI and AD (Ackl et al., 2005; Falini et al., 2005; Garcia Santos et al., 2008; Jones and Waldman, 2004; Kantarci et al., 2002a,b, 2007; Modrego, 2006). Within the MCI

literature, there is a suggestion, similar to MR perfusion, that MRS may offer a method to predict those who may decline into dementia (Kantarci et al., 2007; Modrego, 2006) and may correlate with genetic risk (Kantarci et al., 2002a) Further, there is a suggestion in the literature that NAA may correlate with post-concussive symptoms (Kirov et al., 2013). A final hint of the potential of MRS in TBI is also the use in examination of alterations in biochemistry in the brain with recovery (Nakabayashi et al., 2007). However, even with the potential promise, very little research in MRS as applied to TBI is available.

The greatest limitation of MRS is that its value at low field strengths is limited because of the signal-to-noise ratio required to characterize the quantities of each chemical and challenge of conducting high quality studies without on-site expertise in MRS. Additionally, unless carried out in a center with expertise in this area, the quality of the study can be compromised by scanner quality and artifacts caused by structures in and around the brain.

2.3. Diffusion tensor magnetic resonance imaging (DTI)

DTI has arguably had the greatest influence to date of neuroimaging modalities in chronic TBI. DTI is a special form of diffusion-weighted imaging that allows the assessment and visualization of white matter and nerve fibers on a millimeter-level scale (Le Bihan et al., 2001). Although white and gray matter can be visualized and differentiated with standard MRI pulse sequences, standard MRI does not allow for the examination of the integrity or directionality of white matter tracts. DTI takes advantage of the diffusivity of water and the restrictions imposed on the diffusion of water by the myelin and axonal bodies ssociated with white matter fiber tracts. When fiber tracts are dense, for example, the restriction imposed by their density leads to directionally dependent or anisotropic diffusion. In well organized and intact white matter fiber tracts, the shape of water diffusion will occur preferentially along those tracts (i.e., more anisotropic). When there is less organization or a lack of aligned and organized fiber structures (i.e., gray matter, cerebrospinal fluid, axonal loss or demyelination) the shape of water diffusion will be more isotropic and most commonly measured as fractional anisotropy (FA). The FA values are dependent not only upon the shape of diffusion (eigenvalues) but also the primary direction of diffusion (eigenvectors). These values can be combined in various methods to provide estimates of the axial and radial diffusivity in addition to more standard measures of water diffusion. Axonal diffusivity reflects the integrity of axonal bodies while radial diffusivity is a measure of the degree of myelination (Kraus et al., 2007). The last 15 years has seen a dramatic increase in the use of DTI to characterize the effects of trauma on brain structure as DTI does appear to be sensitive to diffuse axonal injury.

Although the specifics are still not well understood, FA is believed to reflect many factors including the degree of myelination and axonal density and/or integrity (Arfanakis et al., 2002a,b; Harsan et al., 2006; Song et al., 2002a, 2003). More discrete analysis of the axial (λ) and radial diffusivity (λ) also provide potential measures of the mechanisms that underlie changes in white matter (Pierpaoli et al., 2001; Song et al., 2002b). λ reflects diffusivity parallel to axonal fibers. Increases in λ are thought to reflect pathology of the axon itself. λ reflects diffusivity perpendicular to axonal fibers and appears to be more strongly correlated with myelin abnormalities, either dysmyelination or demyelination. DTI has also recently been used to characterize neuronal integrity in gray matter structures and may provide additional information about tissue integrity including the potential for associated markers of dopamine (D. Vaillancourt et al., 2009).

In the late period following TBI, the most common finding is reduced FA that is proportional to the injury severity (Nakayama et al., 2006; Tisserand et al., 2006; Xu et al., 2007). There is not yet a consensus as to what these changes mean in terms of specific underlying neuropathology nor is there consensus on how they relate to functional impairment.

The most promising DTI applications appear in the form of multimodal imaging studies. In at least one study using both magnetic resonance spectroscopy and DTI, outcome was more strongly predicted by the combination of FA and NAA/Cr ratios than either FA or NAA/Cr alone (Tollard et al., 2009). Another recent study combined DTI and magnetoencephalography (MEG) to characterize the relationship between integrity of white matter and the ability of MEG to assess neuronal activation with high temporal resolution. Although a very small sample size was used ($n = 10$) the results are promising. In regions with reduced integrity of FA, there was also slowing of MEG waves suggesting that the lack of connectivity affected local neuronal function. Interestingly none of the 10 patients had lesions present on standard neuroimaging (Huang et al., 2009). Studies utilizing multimodal MRI to include DTI and MR Spectroscopy, DTI and PET, or DTI and SPECT will likely prove immensely valuable for characterizing individual differences in recovery from or damage due to TBI and for characterizing the downstream effects of reductions in white matter tract integrity. In addition to the value in TBI, there is evidence to suggest alterations in white matter may also be one of the earlier signs of pathology in MCI (Selnes et al., 2013; Teipel et al., 2010; Wee et al., 2011, 2012; Zhuang et al., 2010), AD (Damoiseaux et al., 2009; Stebbins and Murphy, 2009; Ukmar et al., 2008; Zhou et al., 2008), and PD (Gallagher et al., 2013; Planetta et al., 2013; Prodoehl et al., 2013; Reimao et al., 2011; D.E. Vaillancourt et al., 2009; Zhang et al., 2011) and progression of disease (Fellgiebel et al., 2006; van Bruggen et al., 2012) which could increase the value of MRI as a screening tool or a prognostic marker.

2.4. Arterial spin labeling (ASL)

ASL, an alternative to the BOLD method of neuroimaging, combines fMRI's ability to measure cerebral blood flow with the benefits of exogenous contrast agents, while remaining a noninvasive technique. ASL allows for the characterization of blood flow within brain tissue, but allows for direct visualization, rather than the indirect measure provided by the BOLD method. Perfusion is quantified by measuring the magnetic state of inflowing blood in relation to the magnetic state of static tissue. ASL is, in particularly relevant to the study of the acute and long term effects of TBI in the brain because it is potentially not affected by differential vasodilatation effects which can be complicated by acute medication usage.

ASL allows for rapid quantitative measurements of perfusion in the brain (van Laar et al., 2008). Much like PET, ASL takes advantage of the principles of exogenous tracers. Instead of invasive radiotracer injection, however, in ASL arterial blood water is first magnetized or 'labeled', then imaged via MRI. Arterial blood water is labeled immediately below the region of interest via a 180-degree radiofrequency inversion pulse. The application of this pulse to the region below the slice of interest results in inversion of the net magnetization of the blood water; that is, the water molecules in the blood are now magnetically labeled and can be detected via MR imaging. After a period of time known as the 'transit time,' the magnetically labeled (i.e. paramagnetic) blood water travels to the region of interest and exchanges with the unmagnetized water present in the tissue altering total tissue magnetization. During this inflow of the inverted spin water molecules, total tissue magnetization is reduced, thereby reducing the MR signal and image intensity. At this point, an image (known as the 'tag image') is taken. The experiment is then repeated without labeling the arterial blood to create another image (known as the 'control image'). To produce an image showing blood perfusion, the tag image is subtracted from the control image. The resulting image reflects the total amount of arterial blood delivered to each voxel in the region of interest within the transit time (University of Michigan Functional MRI Laboratory, 2007).

Several methods of ASL perfusion imaging exist. In continuous ASL (CASL), a continuous radiofrequency pulse is applied to the targeted region below the slice of interest, resulting in continuous inversion of

the magnetization of arterial blood water. Because of this continuous inversion, a steady-state develops in which regional magnetization in the brain is directly related to cerebral blood flow (Calamante et al., 1999). In pulsed ASL (PASL), a short (approximately 10 milliseconds) radiofrequency pulse is used to label blood water spins over a very specific area (University of Michigan Functional MRI Laboratory, 2007), which allows for minimization of the distance between the labeling region and the imaging slice (Calamante et al., 1999). Both have advantages and disadvantages.

There is very promising data to suggest a role for measures of perfusion in acute TBI as a potential predictor of atrophy to follow. As with stroke, experimental models of controlled cortical impact have shown an initial decrease in cerebral blood flow after severe TBI in rats (Hendrich et al., 1999). Importantly, the reduction in blood flow was observed not only in the area surrounding the impact but bilaterally. This reduction in blood flow may represent one mechanism by which pathology can be triggered. Further adding potential in this area is the report of use of ASL to predict conversion from mild cognitive impairment into Alzheimer's (Chao et al., 2010).

3. Animal models

The translation from bench to bedside in TBI relies significantly upon the value and applicability of the model used to cause injury. We briefly review the most commonly used experimental models of TBI including fluid percussion, controlled cortical impact, and closed head mechanisms of injury.

3.1. Fluid percussion injury

The fluid percussion injury (FPI) model is favored for the diffuse, global damage it is capable of generating by way of transferring energy in a fluid waveform directly to the surface of the brain. This is accomplished by having a weighted pendulum at a set height fall and strike a stopper at one end of a fluid-filled cylinder in order to displace the fluid through a transducer at the opposite end impacting the brain (open head model) of an animal (Cernak, 2005; Petraglia et al., 2014; Xiong et al., 2013a). In open head models, the dura is exposed by a craniotomy, and traditionally left intact. But with any open-head models there is experimental challenge of ensuring that surgical procedures do not generate undesired effects in addition to the simulated injury. Keeping the dura intact is difficult in small rodents, particularly in mice, which have a skull thickness as thin as ~200 nm (Choi et al., 2007; Lin et al., 2011). Damage may not only result in infection, or other conditions leading to cell death, but it may also confound results when examining pathophysiological aspects of TBI, such as dynamics surrounding the blood–brain barrier. However, the most cited limitation of FPI is the inconsistency in the delivery of injuries (Cernak, 2005; Xiong et al., 2013a). Variability in desired peak pressure may be as much as ± 0.4 atm. This inconsistency may be attributed to the change in volume of the cylinder with each additional pendulum strike. In theory, the fluid should stay within the closed system of the cylinder and transducer, but in actuality, some fluid is lost between the transducer and the head of the animal. Additionally, the preparative surgery and angle of impact require a high level of skill to produce replicable injuries. Currently, a closed head repetitive FPI (rFPI) model (Petraglia et al., 2014) has been developed increasing the utility of this model for translational studies of chronic traumatic encephalopathy (CTE). This model could prove invaluable for research investigating the mechanisms that lead to CTE witnessed in athletes and military personnel after multiple concussive events.

3.2. Controlled cortical impact

The controlled cortical impact (CCI) model, where a solid impact device is used to deliver a focal injury to the exposed dura, is also a commonly utilized injury model. Numerous studies have evaluated both cognitive and motor outcomes across a spectrum of injury severities, as well as under mixed conditions including closed head injury (CHI), hypovolemic shock, and hypoxemia (Bennett et al., 2012; Dapul et al., 2013; Foley et al., 2013). Like FPI, CCI allows for stereotactic control over the impact site, but has certain advantages over FPI, primarily the ability to accurately calibrate injury parameters, such as velocity and duration of impact, and the relatively minimal deviation of these parameters between animals (Cernak, 2005; Xiong et al., 2013a). CCI is also frequently cited as better suited for biomechanical studies of TBI versus FPI. However, the injuries are focal in nature, unlike FPI, and there is considerable risk of penetrating the dura when using high impact velocities. CCI produces a set of well-characterized pathological sequelae, useful in the study of the early and intermediate phases of TBI, but the method of injury raises doubts as to its clinical relevance. Recent advances that enlist repetitive brain injury, mixed methods of TBI, as well as comorbidities such as hypoxemia, hypovolemic shock, and polytrauma (Probst et al., 2012), such as bone fracture hold much promise for accurately reproducing injuries and sequelae that more closely simulate those encountered in clinical settings. Likewise, these more clinically relevant studies provide a more robust model with which to evaluate therapeutic interventions.

3.3. Closed-head models

There are a number of other closed-head impact models used in TBI research that attempt to better simulate concussive injuries sustained by humans. The variations on the weight drop model leave the skull intact. Many still use the well-established method of positioning the animal on a foam pad so that the head immediately rebounds after being depressed by the weight to generate coup–coutrecoup injuries (Kane et al., 2012; Marmarou et al., 1994). CCI devices can also be used to recreate this effect (Petraglia et al., 2014). A recent study used a novel “hit and run” model where mice were suspended by their incisors and struck by a horizontally positioned CCI device (Ren et al., 2013). These closed-head models are advantageous in that animals can be injured multiple times, which is not appropriate for the FPI and CCI models. This allows for investigators to study effects of repetitive TBI, clinically relevant in contact sports, where chronic traumatic encephalopathy has been a major issue (Kane et al., 2012; Petraglia et al., 2014). However, closed-head models lack the stereotactic precision of CCI and FPI. While great care is made to ensure that weights and impactors strike the skull at specific sites, deviations occur. This is a risk in studies where the head is displaced, or allowed to freely rotate or spin, as in the “hit and run” model. But when animals are struck multiples times over multiple days as in some studies, accuracy may be less of a concern when the goal is to recreate an overall effect of repetitive brain injury.

A considerable caveat in the majority of TBI research is the use of anesthesia. Anesthesia is necessary for FPI and CCI, where it may confer certain neuroprotective effects, or generate unwanted physiological changes, such as elevated cerebral blood flow and intracranial pressure (Kawaguchi et al., 2005; Statler et al., 2006). Studies continue to anesthetize animals, and while this certainly allows for greater control over the experimental model, and is acceptable when examining biomechanical effects of trauma, anesthesia may confound both behavioral measures and the biochemical dynamics of the injury cascade. When the goal is to evaluate TBI from a system-based outlook, anesthesia may be a serious limitation. With a closed-head approach, a conscious animal model is possible if the animal is successfully restrained, as has been demonstrated in a recent mouse study (Petraglia et al., 2014).

In all impact studies, whether open- or closed-head, the inherent differences in human and animal physiology should also be considered. As the majority of studies use rodents, scale and relative dimensions are a factor, as are structural differences that may yield complex shear forces (Cernak, 2005). An obvious disparity is that in most animal

models the cerebrum is impacted superiorly, whereas many humans sustain injuries to anterior or posterior regions of the brain, especially in sports or in whiplash injuries.

Over the past decade, a plethora of animal models have been developed in an attempt to elucidate the multi-faceted nature of TBI and access the broad scope of application neuroimaging may hold in understanding the neural substrates and complex molecular cascades for this process of injuries. These models offer a paradigm in which to study the underlying biological, mechanical and cellular frameworks of TBI, for use in characterizing and assessing therapeutic modalities.

Rodents have been the dominant animal of choice in TBI research though they differ greatly from humans in terms of brain size, brain anatomy, and complexity as well as limit the direct experimental testing of major clinical problems manifested in TBI such as higher cognition, emotion, and speech (Zhang et al., 2014). These shortcomings of rodent models are outweighed by its advantages of availability, reproducibility, affordability, and ease of manipulation, both genetically and physiologically (Longhi et al., 2001). Thus, rodent models are favored over other animal models although they may be closer to the physiology and size of humans. Four specific models, controlled cortical injury (CCI) model (Washington et al., 2012), fluid percussion injury (FPI) model (Zhao et al., 2014), closed head injury (CHI) model, and blast injury model will be discussed later on in this article along with the subsequent limitations and advantages of each. Further testing and experimental trials are warranted on larger animals before being applied in a clinical setting (Prins and Hovda, 2003).

Initially, the goal of animal models was targeted towards understanding and addressing the biomechanics of brain injury e.g. cranial lesions, tissue strain, pressure variations, shear, and tensile force (Cernak and Noble-Haeusslein, 2009). Current animal models have shifted towards attempting to define the detrimental molecular sequelae that are initiated by this trauma (Marklund and Hillered, 2011). While the ability to manipulate these models can advance our understanding of TBI beyond what can be discerned clinically, limitations exist. Improvements are underway to obtain more accurate models that more closely replicate the biological context of human TBI to bridge the gap between preclinical laboratory findings and patient intervention.

TBI consists of mainly two disease processes, a primary process which is the immediate response to trauma, and a secondary process which consists of a complex cascade of physiological perturbations largely dependent on varying factors such as age, gender, and genetic makeup. The majority of animal models thus far have been designed to reflect a relatively homogenous type of injury, confined and referable to a specific neuroanatomical and observational criterion, with the above parameters well controlled (Milman et al., 2005; Morales et al., 2005; Xiong et al., 2013b) While this experimental approach aids in delineating key injury mechanisms in isolation, the simplicity of these models does not factor in or reflect the clinical complexity and heterogeneity of clinical TBI (Morganti-Kossmann et al., 2010). Thus, no single model is capable of fully replicating all aspects of TBI. To address this limitation, models have been refined, modified, and even combined to more accurately emulate the pathophysiological heterogeneity observed in the clinical realm to ensure translational applicability (Zhang et al., 2014) of outcome measurements and therapeutic interventions. Likewise, parameters such as gender, age, genetics, species/strain differences, and effect of standardized treatment strategies such as neurorehabilitation have also been largely unexplored in many animal models (Doppenberg et al., 2004; Esopenko and Levine, 2014; Flanagan et al., 2005) even though these factors bear a crucial role in the progression of the secondary injury cascade and comprise viable, central targets for optimal TBI management and long-term patient outcomes.

4. Application of Neuroimaging in Experimental TBI Models

Neuroimaging is a key component to detecting changes in brain activity and morphology as related to the functional and cognitive impairment manifested in TBI. Imaging has been used in conjunction with animal models to identify unique biochemical, neural and genetic biomarkers to reflect different injury severities and patterns of injuries (Schneider et al., 2002). While the scope of neuroimaging in evaluation of severity and outcomes of TBI has been broadened by the advent of revolutionary technological advances, accurate and early prediction of short and long term outcomes is limited by the identification of these biomarkers. It remains unknown if these biomarkers are in any way clinically relevant or can be used translationally to facilitate treatment outcomes. It is therefore paramount that the search for sensitive and reliable biomarkers be shifted towards being clinically relevant to traverse the gap between laboratory findings and patient medical care.

There is a paucity of literature highlighting neuroimaging techniques in studies utilizing animal models of TBI. This is not surprising due to the fact that the dedication of imaging facilities for animal research purposes is less common. Since imaging techniques are the mainstay of diagnosis, progression, and prognosis of TBI in the clinical scenario (Hunter et al., 2012b) it is of paramount importance that animal TBI models employ the same imaging modalities when possible. Recent animal studies have shown encouraging results using various advanced imaging modalities proving their value in translational research. The use of diffusion tensor imaging (DTI) in a repetitive injury model of mild TBI (Bennett et al., 2012) demonstrated the ability to detect differences in axonal integrity as a reduction in mean diffusivity and radial diffusivity without concomitant changes in amyloid precursor protein (APP). This study revealed that axonal integrity changed from 24-hr to 7 days post-injury and that DTI could be used to track such changes. Functional MRI (fMRI) was used in a lateral FPI model to track recovery in the S1 cortex (Niskanen et al., 2013). Results showed that a decrease in blood-oxygen-level dependent (BOLD) responses could be demonstrated without abnormalities on T2 weighted MRI images being present. Thus, this work encourages the use of BOLD as a tool for use clinically to aid in prognostic outcomes and therapeutic evaluation. Another promising study using proton magnetic resonance spectroscopy (MRS) combined with DTI explored the use of these two imaging modalities to probe the progression of microstructural and metabolic profiles following CCI (Xu et al., 2011). Researchers found changes in metabolic and structural profiles within two hours of injury and resolution of metabolic perturbations within four hours after injury. Thus, a treatment window of opportunity of around 3 h was given as a plausible time point for intervention strategies before secondary insults ensue. These studies reveal the ability of neuroimaging, applied in translational scenarios to reveal promising insights into disease progression and treatment monitoring. Future use of such imaging modalities are encouraged to further the correlation between animal studies and clinical application.

Most animal imaging studies have been short term in nature, focusing on outcomes and survival times from hours to at most one month beyond injury (Luo et al., 2014). These short-term studies have been invaluable in analyzing disease manifestations and pathologies of acute TBI, but do not provide valid assessments about long-term injury responses or whether short-term mechanical changes result in long-term histological and behavioral impairments (Morales et al., 2005). It has been shown that structural and functional changes occur up to one year after TBI (Pierce et al., 1998), meaning that the time period of secondary damage as well as window for therapeutic intervention is longer than initially presumed. This necessitates the need for a shift towards longer term animal models and a broader range of time points with which to evaluate the full extent of morphological, cellular, molecular, and behavioral changes in TBI to more accurately reflect the clinical scenario (Doppenberg et al., 2004). The establishment of animal models in synergy with imaging methods has been integral in understanding the primary and secondary sequelae following TBI, thus providing additional insight for translation to human studies. We first review the imaging methods and then discuss the application of each in TBI. We do not distinguish between mechanisms of injury such as blast versus

sports concussion as it is unclear if these actually result in changes in neuropathology. We then review animal models most commonly used and then discuss the limited animal imaging literature.

5. Discussion

Several limitations of the previously mentioned animal models exist and represent a void in the current knowledge that hinders translation from animals to humans. Notable physiological differences between rodent and human brain structure and function include, geometry, white-to-gray matter ratios, gyral complexity, and craniospinal angle (Laurer and McIntosh, 1999; Morales et al., 2005; Xiong et al., 2013a). These differences can lead to substantially different responses to comparable trauma among similar species, thus complicating the translational nature of the data collected (Cernak, 2005; Povlishock et al., 1994; Xiong et al., 2013a). Differences in response between male and female rodents, namely, pre-injury comorbidities, sex hormone secretion, brain function and metabolism, may affect outcomes (Bazarian et al., 2010; Crandall, 2011; Farace and Alves, 2000). Measurements of injury severity also provide a stumbling block for translating data from animal models to humans and is critically important for diagnosis, treatment, and long term prognosis of TBI in humans. The Glasgow coma scale (GCS) is the primary means for patient selection in TBI clinical trials, and the Glasgow outcome scale (GOS), or its eight-point extended version (GOSe), remains a primary method for assessing outcomes (Lu et al., 2008, 2010). However, there has been no consensus of a communal scoring system for injury severity in animal models of TBI that correlates to a brief neurological examination such as the GCS. Complicating things further are the laboratory specific scoring systems that are based on specific, custom equipment and scenarios making comparison of experimental findings challenging.

Neuroimaging, particularly MRI, provides a useful tool for non-invasive detection of white matter reorganization following TBI (Jiang et al., 2011; Li et al., 2012). Many advanced MRI technology can detect subtle changes in brain activity as well as morphological changes that are related to impairments in cognitive, motor, and behavioral functioning (Benson et al., 2007; Kou et al., 2010; Shenton et al., 2012). The applicability of advanced MRI techniques has been applied to human cases of mild clinical TBI (Hunter et al., 2012a) as well as animal models of TBI (Budde et al., 2011; Foley et al., 2009; Jiang et al., 2011; Li et al., 2012) and provides notable advances to the field. With these advanced MRI techniques, researchers now have a tool with which to measure potential biomarkers of TBI.

Focus should be given to developing distinct biochemical, genetic and neuroimaging biomarkers specific to particular injury severities and types. An effective approach for developing these biomarkers must be an integrated and iterative method using animal models as well as human clinical cases of TBI to influence the next generation of testing. Biomarkers measured in animal models must genuinely reflect the sequelae of TBI in humans and likewise, biomarkers measured in human cases of TBI should inform translational research efforts. If the advanced neuroimaging modalities previously mentioned are used in conjunction with an iterative research paradigm to develop biomarkers (genetic, biochemical, and neuroimaging) this will facilitate translation of results from the laboratory to clinical use.

Some neuroimaging methods still lack the individual patient-level sensitivity and specificity to serve as a diagnostic tool, especially in mTBI. Heterogeneity of injury, the evolution of technology, and the lack of available biomarkers (biochemical, genetic, neuroimaging) are challenges to developing diagnostic tools as well as predictors of recovery in mTBI. Motivations for further neuroimaging work and the combined efforts with animal models is evident with these critical voids in knowledge. Future efforts should focus on both acute and chronic stage clinical diagnosis as well as a synergistic improvement with neuropsychological assessments and rehabilitation strategies. Iterative and integrative (animal and human studies) preclinical testing paradigms that are focused on providing data to predict an individual's recovery will provide critical translational data. Neuroimaging strategies that help to inform the next iteration of animal experiments to measure transient and persistent cognitive deficits, measure the success of cognitive and pharmacologic interventions and provide stronger correlative understanding between neuroimaging and neurobehavioral outcomes is critical in improving the translational potential of animal studies.

A plethora of short-term studies has provided abundant information on the pathophysiology and functional outcomes during the acute stage following TBI. However, long term studies (2 months–1 year after injury) are needed to correlate acute behavioral data with long-term clinical outcomes. Therapies that are based on short-term studies need to be validated over longer periods of time to assess clinical relevance for long term efficacy. Perhaps the therapy that is available to TBI patients prophylactically or shortly after injury (neuroprotective) is not the appropriate therapy for long-term (neurorestorative) treatment. Neuroimaging integrated into these long term studies will provide a database with which long-term prognosis can be evaluated. Limited studies have evaluated outcomes within longer time frames but have shown that there are considerable functional and structural changes that can occur even up to a year after a TBI (Babikian et al., 2006; Benz et al., 1999; Irimia et al., 2014; Mahmood et al., 2006; Sandry et al., 2015). These longer term studies have a potential to provide researchers and clinicians with the imaging, cognitive, and behavioral data needed to design treatment strategies promoting long-term recovery. This is especially useful for patients with TBI that don't receive immediate care due to logistical or facility insufficiencies like those encountered in the combat theater.

The heterogeneous nature of TBI occurrence with additional comorbidities, like in polytrauma cases, further complicates the translational data that can be gathered from animal models. In order to develop a neuroimaging paradigm that facilitates diagnosis and prognosis of polytrauma TBI cases, animal models must begin to integrate comorbidities similar to those encounter in human cases. Some studies have evaluated TBI in animal models with comorbidities such as hypoxia, hypotension, femur fractures, shock and repetitive injury (Dapul et al., 2013; Foley et al., 2013; Hellewell et al., 2010; Kane et al., 2012; Maegele et al., 2007; Petraglia et al., 2014; Probst et al., 2012; Robertson et al., 2000). These studies reveal that systemic perturbations occur morphologically, behaviorally, cognitively, and immunologically thus illustrating a complex pathophysiology. The translation of data collected in these mixed polytrauma animal models is crucial to the development of a neuroimaging paradigm for diagnosis and prognosis. Further, developing therapies for the complex human pathobiology of TBI will be dependent on data collected from these mixed polytrauma studies. The nature of polytrauma can change the efficacy and toxicity of a potential therapy by effecting, via organ insult or injury, the biotransformation, absorption, distribution, metabolism or excretion of a drug. The toxicology involved in drug delivery for polytrauma cases can be dependent on unique neurochemical mediators and mechanisms that are specific to polytrauma (Arand et al., 2001; Ray et al., 2002). Further, advanced neuroimaging modalities be useful in evaluating potential therapeutics in this regard (Mayer and Bellgowan, 2014; McAllister et al., 2006, 2011).

6. Future perspective

Recent advances in neuroimaging have undoubtedly changed the way that scientist and clinicians evaluate and study human brain function, dysfunction, and rehabilitation. These complex methods of image analysis lend themselves to complementary assessment of behavioral, cognitive, and morphologic outcomes of TBI. In addition, these advanced imaging modalities have changed the way scientist and clinicians approach treatment strategies and rehabilitation paradigms. While much of the early work in neuroimaging focused on the diagnostic significance, the prognostic value of neuroimaging biomarkers is

gaining attention. However, as summarized in a recent report to congress, this research has not yet moved beyond the value-added of group descriptive studies. Until neuroimaging markers in human imaging can be translated into their biochemical or biologic etiology these studies will remain descriptive. Animal studies that incorporate in vivo imaging, in vivo physiology, appropriate models of TBI, and ex vivo translation back to the neuroimaging findings, the field will be limited to show movement forward. Of critical importance, neuroimaging data can and must prove valuable in efforts to identify mechanisms underlying dysfunction and those mediating therapeutic efficacy. Significant research funding is being devoted to the needs of TBI patients, particularly for soldiers that have returned from deployment in the Iraq and Afghanistan over the past decade, as well as increased attention to civilian concussion and stroke. Surprisingly, stroke, multiple sclerosis (MS), and TBI are of particularly critical importance based on economic impact and rehabilitation needs, as each condition is among the leading causes of disability in adulthood worldwide (World Health Organization, 2011).

New genetic, molecular, biochemical, and neuroimaging biomarkers should be a focus of translational research efforts as they have the potential to contribute to filling significant voids in the knowledge base. Iterative and integrated (animal and human with neuroimaging) studies will provide researchers and clinicians with the highest quality of translational capacity. Recent advances in the field of positron emission tomography (PET) likely offer the most potential as a near term solution for identifying progression of neurodegeneration. The molecular imaging potential afforded by PET has already provided significant advances in neurodegenerative diseases and early applications to TBI provide significant promise. The two most relevant advances for TBI have been in amyloid and tau imaging with amyloid being significantly more developed than tau imaging. Three FDA approved tracers for amyloid imaging, as they apply to patients with suspected Alzheimer's disease, include flutemetamol, florbetapir, and florbetaben F18. While these agents are approved for application in Alzheimer's disease, the natural translation to TBI in patients at greatest risk for poor outcomes (high rates of repeated TBI for example) has already begun (for example, (Provenzano et al., 2010)). In addition to amyloid imaging, there are increased reports of success in the development of agents that bind to tau. These include ligands ^{18}F-T807 and ^{18}F-T808, ^{18}F-FDDNP, and (18)F-THK-5105. Both (18)F-THK-5105 and (18)F-THK-5117 have shown initial promise for selective binding to tau in mouse models of Alzheimer's (Okamura et al., 2013) and initial promise in vivo in patients with Alzheimer's disease (Okamura et al., 2014). Initial applications of ^{18}F-T807 and ^{18}F-T808 also show promise for having a higher affinity for tau and do show correlations with post-mortem pathology (Chien et al., 2013, 2014). ^{18}F-FDDNP also showed early promise for selective binding to tau but recent reports support a less selective binding to include amyloid (Small et al., 2006).

Further, incorporating polytrauma to animal models of TBI will more accurately represent the complex pathophysiology seen in human cases. Animal studies are of critical importance for addressing complex physiological and pathophysiological mechanisms associated with TBI, testing potential therapeutics prior to clinical trials. Thus, it is critically important not only to incorporate polytrauma into animal studies but furthermore, to use higher species with correlative features to that of humans (i.e., upright walkers, anatomically correlative, functionally correlative with human brain). When researchers and clinicians take these novel, iterative and integrative approaches into study consideration we will begin to more effectively develop neuroprotective/neuroregenerative therapeutics that have been rigorously tested in appropriate models, and are truly translational. Perhaps our failure to achieve a breakthrough therapeutic for treating TBI is not solely contributed to inadequate animal models, rather it is our lack of integrative and iterative approaches using basic research as well as clinical observations (behavioral, cognitive and neuroimaging) to fills gaps in translational knowledge. Thus, the importance of the translation of new discoveries from bench to bedside and then back to the bench will ultimately be the means by which scientists and clinicians make an ultimate breakthrough. Neuroimaging and other complementary tools, both preclinical and clinical, as discussed herein are facilitating the personalized treatment, rehabilitation diagnostics and therapeutics of the future for TBI patients.

References

Ackl, N., Ising, M., Schreiber, Y.A., Atiya, M., Sonntag, A., Auer, D.P., 2005. Hippocampal metabolic abnormalities in mild cognitive impairment and Alzheimer's disease. Neurosci. Lett. 384, 23–28.

Arand, M., Melzner, H., Kinzl, L., Brückner, U., Gebhard, F., 2001. Early inflammatory mediator response following isolated traumatic brain injury and other major trauma in humans. Langenbeck's Arch. Surg. 386, 241–248.

Arfanakis, K., Cordes, D., Haughton, V.M., Carew, J.D., Meyerand, M.E., 2002a. Independent component analysis applied to diffusion tensor MRI. Magn. Reson. Med. 47, 354–363.

Arfanakis, K., Haughton, V.M., Carew, J.D., Rogers, B.P., Dempsey, R.J., Meyerand, M.E., 2002b. Diffusion tensor MR imaging in diffuse axonal injury. Am. J. Neuroradiol. 23, 794–802.

Babikian, T., Freier, M.C., Ashwal, S., Riggs, M.L., Burley, T., Holshouser, B.A., 2006. MR spectroscopy: predicting long-term neuropsychological outcome following pediatric TBI. J. Magn. Reson. Imaging 24, 801–811.

Barnes, J., Bartlett, J.W., van de Pol, L.A., Loy, C.T., Scahill, R.I., Frost, C., Thompson, P., Fox, N.C., 2009. A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. Neurobiol. Aging 30, 1711–1723.

Bazarian, J.J., Atabaki, S., 2001. Predicting postconcussion syndrome after minor traumatic brain injury. Acad. Emerg. Med. 8, 788–795.

Bazarian, J.J., Blyth, B., Mookerjee, S., He, H., McDermott, M.P., 2010. Sex differences in outcome after mild traumatic brain injury. J. Neurotrauma 27, 527–539.

Bennett, R.E., Mac Donald, C.L., Brody, D.L., 2012. Diffusion tensor imaging detects axonal injury in a mouse model of repetitive closed-skull traumatic brain injury. Neurosci. Lett. 513, 160–165.

Benson, R.R., Meda, S.A., Vasudevan, S., Kou, Z., Govindarajan, K.A., Hanks, R.A., Millis, S.R., Makki, M., Latif, Z., Coplin, W., Meythaler, J., Haacke, E.M., 2007. Global white matter analysis of diffusion tensor images is predictive of injury severity in traumatic brain injury. J. Neurotrauma 24, 446–459.

Benz, B., Ritz, A., Kiesow, S., 1999. Influence of age-related factors on long-term outcome after traumatic brain injury (TBI) in children: a review of recent literature and some preliminary findings. Restor. Neurol. Neurosci. 14, 135–141.

Bigler, E.D., Maxwell, W.L., 2012. Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. Brain Imaging Behav. 6, 108–136.

Budde, M.D., Janes, L., Gold, E., Turtzo, L.C., Frank, J.A., 2011. The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: validation in the rat using Fourier analysis of stained tissue sections. Brain 134, 2248–2260.

Calamante, F., Thomas, D.L., Pell, G.S., Wiersma, J., Turner, R., 1999. Measuring cerebral blood flow using magnetic resonance imaging techniques. J. Cereb. Blood Flow Metab. 19, 701–735.

Cameron, K.L., Marshall, S.W., Sturdivant, R.X., Lincoln, A.E., 2012. Trends in the incidence of physician-diagnosed mild traumatic brain injury among active duty U.S. military personnel between 1997 and 2007. J. Neurotrauma 29, 1313–1321.

Centers for Disease Control and Prevention (CDC), The National Institutes of Health (NIH), The Department of Defense (DoD), The Department of Veterans Affairs (VA) Leadership Panel, 2013. Report to Congress on Traumatic Brain Injury in the United States: Understanding the Public Health Problem among Current and Former Military Personnel.

Cernak, I., 2005. Animal models of head trauma. NeuroRx 2, 410–422.

Cernak, I., Noble-Haeusslein, L.J., 2009. Traumatic brain injury: an overview of pathobiology with emphasis on military populations. J. Cereb. Blood Flow Metab. 30, 255–266.

Cernak, I., Noble-Haeusslein, L.J., Traumatic brain injury: an overview of pathobiology with emphasis on military populations. J. Cereb. Blood Flow Metab. 30, 255–266.

Chao, L.L., Buckley, S.T., Kornak, J., Schuff, N., Madison, C., Yaffe, K., Miller, B.L., Kramer, J.H., Weiner, M.W., 2010. ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. Alzheimer Dis. Assoc. Disord. 24, 19–27.

Chien, D.T., Bahri, S., Szardenings, A.K., Walsh, J.C., Mu, F., Su, M.Y., Shankle, W.R., Elizarov, A., Kolb, H.C., 2013. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. J. Alzheimers Dis. 34, 457–468.

Chien, D.T., Szardenings, A.K., Bahri, S., Walsh, J.C., Mu, F., Xia, C., Shankle, W.R., Lerner, A.J., Su, M.Y., Elizarov, A., Kolb, H.C., 2014. Early clinical PET imaging results with the novel PHF-tau radioligand [F18]-T808. J. Alzheimers Dis. 38, 171–184.

Choi, J.J., Pernot, M., Brown, T.R., Small, S.A., Konofagou, E.E., 2007. Spatio-temporal analysis of molecular delivery through the blood–brain barrier using focused ultrasound. Phys. Med. Biol. 52, 5509–5530.

Crandall, M., 2011. Sex differences for traumatic brain injury outcomes: comment on "protection from traumatic brain injury in hormonally active women vs men of a similar age". Arch. Surg. 146, 442–443.

Damoiseaux, J.S., Smith, S.M., Witter, M.P., Sanz-Arigita, E.J., Barkhof, F., Scheltens, P., Stam, C.J., Zarei, M., Rombouts, S.A., 2009. White matter tract integrity in aging and Alzheimer's disease. Hum. Brain Mapp. 30, 1051–1059.

Dankbaar, J.W., Hom, J., Schneider, T., Cheng, S.C., Lau, B.C., van der Schaaf, I., Virmani, S., Pohlman, S., Wintermark, M., 2009. Age- and anatomy-related values of blood–brain barrier permeability measured by perfusion-CT in non-stroke patients. J. Neuroradiol. 36, 219–227.

Dapul, H.R., Park, J., Zhang, J., Lee, C., DanEshmand, A., Lok, J., Ayata, C., Gray, T., Scalzo, A., Qiu, J., Lo, E.H., Whalen, M.J., 2013. Concussive injury before or after controlled cortical impact exacerbates histopathology and functional outcome in a mixed traumatic brain injury model in mice. J. Neurotrauma 30, 382–391.
Doppenberg, E.M., Choi, S.C., Bullock, R., 2004. Clinical trials in traumatic brain injury: lessons for the future. J. Neurosurg. Anesthesiol. 16, 87–94.
Eierud, C., Craddock, R.C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., LaConte, S.M., 2014. Neuroimaging after mild traumatic brain injury: review and meta-analysis. Neuroimage Clin. 4, 283–294.
Ellis, C.M., Suckling, J., Amaro Jr., E., Bullmore, E.T., Simmons, A., Williams, S.C., Leigh, P.N., 2001. Volumetric analysis reveals corticospinal tract degeneration and extramotor involvement in ALS. Neurology 57, 1571–1578.
Esopenko, C., Levine, B., 2014. Aging, neurodegenerative disease and traumatic brain injury: the role of neuroimaging. J. Neurotrauma 32, 209–220.
Falini, A., Bozzali, M., Magnani, G., Pero, G., Gambini, A., Benedetti, B., Mossini, R., Franceschi, M., Comi, G., Scotti, G., Filippi, M., 2005. A whole brain MR spectroscopy study from patients with Alzheimer's disease and mild cognitive impairment. NeuroImage 26, 1159–1163.
Farace, E., Alves, W.M., 2000. Do women fare worse: a metaanalysis of gender differences in traumatic brain injury outcome. J. Neurosurg. 93, 539–545.
Fellgiebel, A., Dellani, P.R., Greverus, D., Scheurich, A., Stoeter, P., Muller, M.J., 2006. Predicting conversion to dementia in mild cognitive impairment by volumetric and diffusivity measurements of the hippocampus. Psychiatry Res. 146, 283–287.
Flanagan, S.R., Hibbard, M.R., Gordon, W.A., 2005. The impact of age on traumatic brain injury. Phys. Med. Rehabil. Clin. N. Am. 16, 163–177.
Foley, L.M., Hitchens, T.K., Ho, C., Janesko-Feldman, K.L., Melick, J.A., Bayir, H., Kochanek, P.M., 2009. Magnetic resonance imaging assessment of macrophage accumulation in mouse brain after experimental traumatic brain injury. J. Neurotrauma 26, 1509–1519.
Foley, L.M., Iqbal O'Meara, A.M., Wisniewski, S.R., Hitchens, T.K., Melick, J.A., Ho, C., Jenkins, L.W., Kochanek, P.M., 2013. MRI assessment of cerebral blood flow after experimental traumatic brain injury combined with hemorrhagic shock in mice. J. Cereb. Blood Flow Metab. 33, 129–136.
Fujita, Y., Algarra, N.N., Vavilala, M.S., Prathep, S., Prapruettham, S., Sharma, D., 2014. Intraoperative secondary insults during extracranial surgery in children with traumatic brain injury. Childs Nerv. Syst. 30, 1201–1208.
Gallagher, C., Bell, B., Bendlin, B., Palotti, M., Okonkwo, O., Sodhi, A., Wong, R., Buyan-Dent, L., Johnson, S., Willette, A., Harding, S., Ninman, N., Kastman, E., Alexander, A., 2013. White matter microstructural integrity and executive function in Parkinson's disease. J. Int. Neuropsychol. Soc. 19, 349–354.
Garcia Santos, J.M., Gavrila, D., Antunez, C., Tormo, M.J., Salmeron, D., Carles, R., Jimenez Veiga, J., Parrilla, G., Torres del Rio, S., Fortuna, L., Navarro, C., 2008. Magnetic resonance spectroscopy performance for detection of dementia, Alzheimer's disease and mild cognitive impairment in a community-based survey. Dement. Geriatr. Cogn. Disord. 26, 15–25.
Gessel, L.M., Fields, S.K., Collins, C.L., Dick, R.W., Comstock, R.D., 2007. Concussions among United States high school and collegiate athletes. J. Athl. Train. 42, 495–503.
Gilbert, M., Snyder, C., Corcoran, C., Norton, M.C., Lyketsos, C.G., Tschanz, J.T., 2014. The association of traumatic brain injury with rate of progression of cognitive and functional impairment in a population-based cohort of Alzheimer's disease: the Cache County Dementia Progression Study. Int. Psychogeriatr. 26, 1593–1601.
Harsan, L., Poulet, P., Guignard, B., Steibel, J., Parizel, N., de Sousa, P., Boehm, N., Grucker, D., Ghandour, M., 2006. Brain dysmyelination and recovery assessment by noninvasive in vivo diffusion tensor magnetic resonance imaging. J. Neurosci. Res. 83, 392–402.
Hellewell, S.C., Yan, E.B., Agyapomaa, D.A., Bye, N., Morganti-Kossmann, M.C., 2010. Post-traumatic hypoxia exacerbates brain tissue damage: analysis of axonal injury and glial responses. J. Neurotrauma 27, 1997–2010.
Hendrich, K.S., Kochanek, P.M., Williams, D.S., Schiding, J.K., Marion, D.W., Ho, C., 1999. Early perfusion after controlled cortical impact in rats: quantification by arterial spin-labeled MRI and the influence of spin–lattice relaxation time heterogeneity. Magn. Reson. Med. 42, 673–681.
Hill, A., Volpe, J.J., 1981. Seizures, hypoxic–ischemic brain injury, and intraventricular hemorrhage in the newborn. Ann. Neurol. 10, 109–121.
Hirtz, D., Thurman, D.J., Gwinn-Hardy, K., Mohamed, M., Chaudhuri, A.R., Zalutsky, R., 2007. How common are the "common" neurologic disorders? Neurology 68, 326–337.
Huang, M., Theilmann, R.J., Robb, A., Angeles, A., Nichols, S., Drake, A., Dandrea, J., Levy, M., Holland, M., Song, T., Ge, S., Hwang, E., Yoo, K., Cui, L., Baker, D.G., Trauner, D., Coimbra, R., Lee, R.R., 2009. Integrated imaging approach with MEG and DTI to detect mild traumatic brain injury in military and civilian patients. J. Neurotrauma 26, 1213–1226.
Hunter, J.V., Thornton, R.J., Wang, Z.J., Levin, H.S., Roberson, G., Brooks, W.M., Swank, P.R., 2005. Late proton MR spectroscopy in children after traumatic brain injury: correlation with cognitive outcomes. AJNR Am. J. Neuroradiol. 26, 482–488.
Hunter, J.V., Wilde, E.A., Tong, K.A., Holshouser, B.A., 2012a. Emerging imaging tools for use with traumatic brain injury research. J. Neurotrauma 29, 654–671.
Hunter, J.V., Wilde, E.A., Tong, K.A., Holshouser, B.A., 2012b. Emerging Imaging Tools for Use with Traumatic Brain Injury Research. J. Neurotrauma 29, 654–671.
Ibarretxe-Bilbao, N., Junque, C., Segura, B., Baggio, H.C., Marti, M.J., Valldeoriola, F., Bargallo, N., Tolosa, E., 2012. Progression of cortical thinning in early Parkinson's disease. Mov. Disord. 27, 1746–1753.
Immonen, R.J., Kharatishvili, I., Grohn, H., Pitkanen, A., Grohn, O.H., 2009. Quantitative MRI predicts long-term structural and functional outcome after experimental traumatic brain injury. NeuroImage 45, 1–9.
Irimia, A., Goh, S.Y., Torgerson, C.M., Vespa, P., Van Horn, J.D., 2014. Structural and connectomic neuroimaging for the personalized study of longitudinal alterations in cortical shape, thickness and connectivity after traumatic brain injury. J. Neurosurg. Sci. 58, 129–144.
Jiang, Q., Qu, C., Chopp, M., Ding, G.L., Nejad-Davarani, S.P., Helpern, J.A., Jensen, J.H., Zhang, Z.G., Li, L., Lu, M., Kaplan, D., Hu, J., Shen, Y., Kou, Z., Li, Q., Wang, S., Mahmood, A., 2011. MRI evaluation of axonal reorganization after bone marrow stromal cell treatment of traumatic brain injury. NMR Biomed. 24, 1119–1128.
Jones, R.S., Waldman, A.D., 2004. 1H-MRS evaluation of metabolism in Alzheimer's disease and vascular dementia. Neurol. Res. 26, 488–495.
Kane, M.J., Angoa-Perez, M., Briggs, D.I., Viano, D.C., Kreipke, C.W., Kuhn, D.M., 2012. A mouse model of human repetitive mild traumatic brain injury. J. Neurosci. Methods 203, 41–49.
Kantarci, K., Smith, G.E., Ivnik, R.J., Petersen, R.C., Boeve, B.F., Knopman, D.S., Tangalos, E.G., Jack Jr., C.R., 2002a. 1H magnetic resonance spectroscopy, cognitive function, and apolipoprotein E genotype in normal aging, mild cognitive impairment and Alzheimer's disease. J. Int. Neuropsychol. Soc. 8, 934–942.
Kantarci, K., Xu, Y., Shiung, M.M., O'Brien, P.C., Cha, R.H., Smith, G.E., Ivnik, R.J., Boeve, B.F., Edland, S.D., Kokmen, E., Tangalos, E.G., Petersen, R.C., Jack Jr., C.R., 2002b. Comparative diagnostic utility of different MR modalities in mild cognitive impairment and Alzheimer's disease. Dement. Geriatr. Cogn. Disord. 14, 198–207.
Kantarci, K., Weigand, S.D., Petersen, R.C., Boeve, B.F., Knopman, D.S., Gunter, J., Reyes, D., Shiung, M., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Tangalos, E.G., Jack Jr., C.R., 2007. Longitudinal 1H MRS changes in mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 28, 1330–1339.
Kawaguchi, M., Furuya, H., Patel, P.M., 2005. Neuroprotective effects of anesthetic agents. J. Anesth. 19, 150–156.
Kirov, I.I., Tal, A., Babb, J.S., Reaume, J., Bushnik, T., Ashman, T.A., Flanagan, S., Grossman, R.I., Gonen, O., 2013. Proton MR spectroscopy correlates diffuse axonal abnormalities with post-concussive symptoms in mild traumatic brain injury. J. Neurotrauma 30, 1200–1204.
Kou, Z., Wu, Zhen, Tong, Karen A., Holshouser, Barbara, Benson, Randall R., Hu, Jiani, Haacke, Mark E., 2010. The role of advanced MR imaging findings as biomarkers of traumatic brain injury. J. Head Trauma Rehabil. 25, 267–282.
Kraus, M., Susmaras, T., Caughlin, B., Walker, C., Sweeney, J., Little, D., 2007. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain 130, 2508–2519.
Lange, R.T., Brickell, T.A., French, L.M., Merritt, V.C., Bhagwat, A., Pancholi, S., Iverson, G.L., 2012. Neuropsychological Outcome from uncomplicated mild, complicated mild, and moderate traumatic brain injury in US military personnel. Arch. Clin. Neuropsychol. 27, 480–494.
Laurer, H.L., McIntosh, T.K., 1999. Experimental models of brain trauma. Curr. Opin. Neurol. 12, 715–721.
Le Bihan, D., Mangin, J.F., Poupon, C.P., Clark, C.A., Pappata, S., Molko, N., Chabriat, H., 2001. Diffusion tensor imaging: concepts and applications. J. Magn. Reson. Imaging 13, 534–543.
Levine, B., Kovacevic, N., Nica, E.I., Cheung, G., Gao, F., Schwartz, M.L., Black, S.E., 2008. The Toronto traumatic brain injury study: injury severity and quantified MRI. Neurology 70, 771–778.
Li, L., Chopp, M., Ding, G.L., Qu, C.S., Li, Q.J., Lu, M., Wang, S.Y., Nejad-Davarani, S.P., Mahmood, A., Jiang, Q., 2012. MRI measurement of angiogenesis and the therapeutic effect of acute marrow stromal cell administration on traumatic brain injury. J. Cereb. Blood Flow Metab. 32, 2023–2032.
Lin, A.J., Koike, M.A., Green, K.N., Kim, J.G., Mazhar, A., Rice, T.B., LaFerla, F.M., Tromberg, B.J., 2011. Spatial frequency domain imaging of intrinsic optical property contrast in a mouse model of Alzheimer's disease. Ann. Biomed. Eng. 39, 1349–1357.
Longhi, L., Saatman, K.E., Raghupathi, R., Laurer, H.L., Lenzlinger, P.M., Riess, P., Neugebauer, E., Trojanowski, J.Q., Lee, V.M., Grady, M.S., Graham, D.I., McIntosh, T.K., 2001. A review and rationale for the use of genetically engineered animals in the study of traumatic brain injury. J. Cereb. Blood Flow Metab. 21, 1241–1258.
Lu, J., Murray, G.D., Steyerberg, E.W., Butcher, I., McHugh, G.S., Lingsma, H., Mushkudiani, N., Choi, S., Maas, A.I.R., Marmarou, A., 2008. Effects of Glasgow outcome scale misclassification on traumatic brain injury clinical trials. J. Neurotrauma 25, 641–651.
Lu, J., Marmarou, A., Lapane, K., Turf, E., Wilson, L., 2010. A method for reducing misclassification in the extended Glasgow outcome score. J. Neurotrauma 27, 843–852.
Luo, J., Nguyen, A., Villeda, S., Zhang, H., Ding, Z., Lindsey, D., Bieri, G., Castellano, J.M., Beaupre, G.S., Wyss-Coray, T., 2014. Long-term cognitive impairments and pathological alterations in a mouse model of repetitive mild traumatic brain injury. Front. Neurol. 5, 12.
Maegele, M., Sauerland, S., Bouillon, B., Schäfer, U., Trübel, H., Riess, P., Neugebauer, E.A.M., 2007. Differential immunoresponses following experimental traumatic brain injury, bone fracture and "two-hit"-combined neurotrauma. Inflamm. Res. 56, 318–323.
Mahmood, A., Lu, D., Qu, C., Goussev, A., Chopp, M., 2006. Long-term recovery after bone marrow stromal cell treatment of traumatic brain injury in rats. J. Neurosurg. 104, 272–277.
Marklund, N., Hillered, L., 2011. Animal modelling of traumatic brain injury in preclinical drug development: where do we go from here? Br. J. Pharmacol. 164, 1207–1229.
Marmarou, A., Foda, M.A., van den Brink, W., Campbell, J., Kita, H., Demetriadou, K., 1994. A new model of diffuse brain injury in rats. Part I: pathophysiology and biomechanics. J. Neurosurg. 80, 291–300.
Marshall, S.A., Riechers II, R.G., 2012. Diagnosis and management of moderate and severe traumatic brain injury sustained in combat. Mil. Med. 177, 76–85.
Mayer, A., Bellgowan, P.F., 2014. Functional magnetic resonance imaging in mild traumatic brain injury. In: Slobounov, S.M., Sebastianelli, W.J. (Eds.), Concussions in Athletics. Springer, New York, pp. 249–270.
McAllister, T.W., Sparling, M.B., Flashman, L.A., Saykin, A.J., 2001. Neuroimaging findings in mild traumatic brain injury. J. Clin. Exp. Neuropsychol. 23, 775–791.
McAllister, T.W., Flashman, L.A., McDonald, B.C., Saykin, A.J., 2006. Mechanisms of working memory dysfunction after mild and moderate TBI: evidence from functional MRI and neurogenetics. J. Neurotrauma 23, 1450–1467.

McAllister, Thomas W., McDonald, Brenna C., Ferrell, Richard B., Tosteson, Tor D., Yanofsky, Norman N., Grove, Margaret R., Saykin, Andrew J., 2011. Dopaminergic challenge with bromocriptine one month after mild traumatic brain injury: altered working memory and BOLD response. J. Neuropsychiatry Clin. Neurosci. 23, 277–286.
Mechtler, L.L., Shastri, K.K., Crutchfield, K.E., 2014. Advanced neuroimaging of mild traumatic brain injury. Neurol. Clin. 32, 31–58.
Mendez, C.V., Hurley, R.A., Lassonde, M., Zhang, L., Taber, K.H., 2005. Mild traumatic brain injury: neuroimaging of sports-related concussion. J. Neuropsychiatry Clin. Neurosci. 17, 297–303.
Milman, A., Rosenberg, A., Weizman, R., Pick, C.G., 2005. Mild traumatic brain injury induces persistent cognitive deficits and behavioral disturbances in mice. J. Neurotrauma 22, 1003–1010.
Modrego, P.J., 2006. Predictors of conversion to dementia of probable Alzheimer type in patients with mild cognitive impairment. Curr. Alzheimer Res. 3, 161–170.
Morales, D.M., Marklund, N., Lebold, D., Thompson, H.J., Pitkanen, A., Maxwell, W.L., Longhi, L., Laurer, H., Maegele, M., Neugebauer, E., Graham, D.I., Stocchetti, N., McIntosh, T.K., 2005. Experimental models of traumatic brain injury: do we really need to build a better mousetrap? Neuroscience 136, 971–989.
Morganti-Kossmann, M.C., Yan, E., Bye, N., 2010. Animal models of traumatic brain injury: is there an optimal model to reproduce human brain injury in the laboratory? Injury 41 (Suppl. 1), S10–S13.
Nakabayashi, M., Suzaki, S., Tomita, H., 2007. Neural injury and recovery near cortical contusions: a clinical magnetic resonance spectroscopy study. J. Neurosurg. 106, 370–377.
Nakayama, N., Okamura, A., et al., 2006. Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. J. Neurol. Neurosurg. Psychiatry 77, 850–855.
Niskanen, J.P., Airaksinen, A.M., Sierra, A., Huttunen, J.K., Nissinen, J., Karjalainen, P.A., Pitkanen, A., Grohn, O.H., 2013. Monitoring functional impairment and recovery after traumatic brain injury in rats by FMRI. J. Neurotrauma 30, 546–556.
Okamura, N., Furumoto, S., Harada, R., Tago, T., Yoshikawa, T., Fodero-Tavoletti, M., Mulligan, R.S., Villemagne, V.L., Akatsu, H., Yamamoto, T., Arai, H., Iwata, R., Yanai, K., Kudo, Y., 2013. Novel 18F-labeled arylquinoline derivatives for noninvasive imaging of tau pathology in Alzheimer disease. J. Nucl. Med. 54, 1420–1427.
Okamura, N., Furumoto, S., Fodero-Tavoletti, M.T., Mulligan, R.S., Harada, R., Yates, P., Pejoska, S., Kudo, Y., Masters, C.L., Yanai, K., Rowe, C.C., Villemagne, V.L., 2014. Non-invasive assessment of Alzheimer's disease neurofibrillary pathology using 18F-THK5105 PET. Brain 137, 1762–1771.
Orrison, W.W., Hanson, E.H., Alamo, T., Watson, D., Sharma, M., Perkins, T.G., Tandy, R.D., 2009. Traumatic brain injury: a review and high-field MRI findings in 100 unarmed combatants using a literature-based checklist approach. J. Neurotrauma 26, 689–701.
Petraglia, A.L., Plog, B.A., Dayawansa, S., Chen, M., Dashnaw, M.L., Czerniecka, K., Walker, C.T., Viterise, T., Hyrien, O., Iliff, J.J., Deane, R., Nedergaard, M., Huang, J.H., 2014. The spectrum of neurobehavioral sequelae after repetitive mild traumatic brain injury: a novel mouse model of chronic traumatic encephalopathy. J. Neurotrauma 31, 1211–1224.
Pierce, J.E., Smith, D.H., Trojanowski, J.Q., McIntosh, T.K., 1998. Enduring cognitive, neurobehavioral and histopathological changes persist for up to one year following severe experimental brain injury in rats. Neuroscience 87, 359–369.
Pierpaoli, C., Barnett, A., Pajevic, S., Chen, R., Penix, L., Virta, A., Basser, P., 2001. Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. NeuroImage 13, 1174–1185.
Pitkanen, A., Immonen, R., 2014. Epilepsy related to traumatic brain injury. Neurotherapeutics 11, 286–296.
Planetta, P.J., Schulze, E.T., Geary, E.K., Corcos, D.M., Goldman, J.G., Little, D.M., Vaillancourt, D.E., 2013. Thalamic projection fiber integrity in de novo Parkinson disease. AJNR Am. J. Neuroradiol. 34, 74–79.
Povlishock, J.T., Hayes, R.L., Michel, M.E., McIntosh, T.K., 1994. Workshop on animal models of traumatic brain injury. J. Neurotrauma 11, 723–732.
Prince, D.A., Parada, I., Graber, K., 2012. Traumatic brain injury and posttraumatic epilepsy. In: Noebels, J.L., Avoli, M., Rogawski, M.A., Olsen, R.W., Delgado-Escueta, A.V. (Eds.), Jasper's Basic Mechanisms of the Epilepsies, 4th ed. (Bethesda (MD)).
Prins, M.L., Hovda, D.A., 2003. Developing experimental models to address traumatic brain injury in children. J. Neurotrauma 20, 123–137.
Probst, C., Mirzayan, M.J., Mommsen, P., Zeckey, C., Tegeder, T., Geerken, L., Maegele, M., Samii, A., van Griensven, M., 2012. Systemic inflammatory effects of traumatic brain injury, femur fracture, and shock: an experimental murine polytrauma model. Mediat. Inflamm. 2012, 136020.
Prodoehl, J., Li, H., Planetta, P.J., Goetz, C.G., Shannon, K.M., Tangonan, R., Comella, C.L., Simuni, T., Zhou, X.J., Leurgans, S., Corcos, D.M., Vaillancourt, D.E., 2013. Diffusion tensor imaging of Parkinson's disease, atypical parkinsonism, and essential tremor. Mov. Disord. 28, 1816–1822.
Provenzano, F.A., Jordan, B., Tikofsky, R.S., Saxena, C., Van Heertum, R.L., Ichise, M., 2010. F-18 FDG PET imaging of chronic traumatic brain injury in boxers: a statistical parametric analysis. Nucl. Med. Commun. 31, 952–957.
Ray, S.K., Dixon, C.E., Banik, N.L., 2002. Molecular mechanisms in the pathogenesis of traumatic brain injury. Histol. Histopathol. 17, 1137–1152.
Reimao, S., Morgado, C., Neto, L., Ferreira, J., Coelho, M., Rosa, M., Campos, J., 2011. Diffusion tensor imaging in movement disorders: review of major patterns and correlation with normal brainstem/cerebellar white matter. Neuroradiol. J. 24, 177–186.
Ren, Z., Iliff, J.J., Yang, L., Yang, J., Chen, X., Chen, M.J., Giese, R.N., Wang, B., Shi, X., Nedergaard, M., 2013. 'Hit & Run' model of closed-skull traumatic brain injury (TBI) reveals complex patterns of post-traumatic AQP4 dysregulation. J. Cereb. Blood Flow Metab. 33, 834–845.
Robertson, C.L., Clark, R.S., Dixon, C.E., Alexander, H.L., Graham, S.H., Wisniewski, S.R., Marion, D.W., Safar, P.J., Kochanek, P.M., 2000. No long-term benefit from hypothermia after severe traumatic brain injury with secondary insult in rats. Crit. Care Med. 28, 3218–3223.
Sandry, J., DeLuca, J., Chiaravalloti, N., 2015. Working memory capacity links cognitive reserve with long-term memory in moderate to severe TBI: a translational approach. J. Neurol. 262, 59–64.
Schneider, G., Fries, P., Wagner-Jochem, D., Thome, D., Laurer, H., Kramann, B., Mautes, A., Hagen, T., 2002. Pathophysiological changes after traumatic brain injury: comparison of two experimental animal models by means of MRI. MAGMA 14, 233–241.
Selnes, P., Aarsland, D., Bjornerud, A., Gjerstad, L., Wallin, A., Hessen, E., Reinvang, I., Grambaite, R., Auning, E., Kjaervik, V.K., Due-Tonnessen, P., Stenset, V., Fladby, T., 2013. Diffusion tensor imaging surpasses cerebrospinal fluid as predictor of cognitive decline and medial temporal lobe atrophy in subjective cognitive impairment and mild cognitive impairment. J. Alzheimers Dis. 33, 723–736.
Shenton, M.E., Hamoda, H.M., Schneiderman, J.S., Bouix, S., Pasternak, O., Rathi, Y., Vu, M.A., Purohit, M.P., Helmer, K., Koerte, I., Lin, A.P., Westin, C.F., Kikinis, R., Kubicki, M., Stern, R.A., Zafonte, R., 2012. A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. Brain Imaging Behav. 6, 137–192.
Shi, F., Liu, B., Zhou, Y., Yu, C., Jiang, T., 2009. Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: meta-analyses of MRI studies. Hippocampus 19, 1055–1064.
Sivanandam, T.M., Thakur, M.K., 2012. Traumatic brain injury: a risk factor for Alzheimer's disease. Neurosci. Biobehav. Rev. 36, 1376–1381.
Small, G.W., Kepe, V., Ercoli, L.M., Siddarth, P., Bookheimer, S.Y., Miller, K.J., Lavretsky, H., Burggren, A.C., Cole, G.M., Vinters, H.V., Thompson, P.M., Huang, S.C., Satyamurthy, N., Phelps, M.E., Barrio, J.R., 2006. PET of brain amyloid and tau in mild cognitive impairment. N. Engl. J. Med. 355, 2652–2663.
Song, S.K., Sun, S.W., Ramsbottom, M., Chang, C., Russell, J., Cross, A., 2002a. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. NeuroImage 17, 1429–1436.
Song, S., Sun, S., Ramsbottom, M., Chang, C., Russell, J., Cross, A., 2002b. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. NeuroImage 17, 1429–1436.
Song, S., Sun, S., Ju, W., Lin, S., Cross, A., Neufeld, A., 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. NeuroImage 20, 1714–1722.
Statler, K.D., Alexander, H., Vagni, V., Dixon, C.E., Clark, R.S., Jenkins, L., Kochanek, P.M., 2006. Comparison of seven anesthetic agents on outcome after experimental traumatic brain injury in adult, male rats. J. Neurotrauma 23, 97–108.
Stebbins, G.T., Murphy, C.M., 2009. Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. Behav. Neurol. 21, 39–49.
Stein, S.C., Burnett, M.G., Glick, H.A., 2006. Indications for CT scanning in mild traumatic brain injury: a cost-effectiveness study. J. Trauma 61, 558–566.
Taylor, G.A., 1994. Alterations in regional cerebral blood flow in neonatal stroke: preliminary findings with color Doppler sonography. Pediatr. Radiol. 24, 111–115.
Teipel, S.J., Meindl, T., Wagner, M., Stieltjes, B., Reuter, S., Hauenstein, K.H., Filippi, M., Ernemann, U., Reiser, M.F., Hampel, H., 2010. Longitudinal changes in fiber tract integrity in healthy aging and mild cognitive impairment: a DTI follow-up study. J. Alzheimers Dis. 22, 507–522.
Tisserand, D., Staanisz, G., Lobaugh, N., Gibson, E., Li, T., Black, S., 2006. Diffusion tensor imaging for the evaluation of white matter pathology in traumatic brian injury. Brain Cogn. 60, 216–217.
Tollard, E., Galanaud, D., Perlbarg, V., Sanchez-Pena, P., Le Fur, Y., Abdennour, L., Cozzone, P., Lehericy, S., Chiras, J., Puybasset, L., 2009. Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: preliminary results. Crit. Care Med. 37, 1448–1455.
Trivedi, M.A., Ward, M.A., Hess, T.M., Gale, S.D., Dempsey, R.J., Rowley, H.A., Johnson, S.C., 2007. Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: relationship with duration of coma. J. Neurotrauma 24, 766–771.
Ukmar, M., Makuc, E., Onor, M.L., Garbin, G., Trevisiol, M., Cova, M.A., 2008. Evaluation of white matter damage in patients with Alzheimer's disease and in patients with mild cognitive impairment by using diffusion tensor imaging. Radiol. Med. 113, 915–922.
University of Michigan Functional MRI Laboratory, 2007. Arterial Spin Labeling.
Vaillancourt, D., Spraker, M., Prodoehl, J., Abraham, I., Corcos, D., Zhou, X., Comella, C., Little, D., 2009. High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease. Neurology 72, 1378–1384.
Vaillancourt, D.E., Spraker, M.B., Prodoehl, J., Abraham, I., Corcos, D.M., Zhou, X.J., Comella, C.L., Little, D.M., 2009. High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease. Neurology 72, 1378–1384.
van Bruggen, T., Stieltjes, B., Thomann, P.A., Parzer, P., Meinzer, H.P., Fritzsche, K.H., 2012. Do Alzheimer-specific microstructural changes in mild cognitive impairment predict conversion? Psychiatry Res. 203, 184–193.
van Laar, P.J., van der Graaf, Y., Mali, W.P.T.M., van der Grond, J., Hendrikse, J., 2008. Effect of cerebrovascular risk factors on regional cerebral blood flow. Radiology 246, 196–204.
Vos, P.E., Alekseenko, Y., Battistin, L., Ehler, E., Gerstenbrand, F., Muresanu, D.F., Potapov, A., Stepan, C.A., Traubner, P., Vecsei, L., von Wild, K., 2012. Mild traumatic brain injury. Eur. J. Neurol. 19, 191–198.
Wardlaw, J.M., Easton, V.J., Statham, P., 2002. Which CT features help predict outcome after head injury? J. Neurol. Neurosurg. Psychiatry 72, 188–192.
Washington, P.M., Forcelli, P.A., Wilkins, T., Zapple, D.N., Parsadanian, M., Burns, M.P., 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, 2283–2296.

Wee, C.Y., Yap, P.T., Zhang, D., Denny, K., Wang, L., Shen, D., 2011. Identification of individuals with MCI via multimodality connectivity networks. Medical Image Computing and Computer-assisted Intervention: MICCAI — International Conference on Medical Image Computing and Computer-Assisted Intervention 14, pp. 277–284.

Wee, C.Y., Yap, P.T., Zhang, D., Denny, K., Browndyke, J.N., Potter, G.G., Welsh-Bohmer, K.A., Wang, L., Shen, D., 2012. Identification of MCI individuals using structural and functional connectivity networks. NeuroImage 59, 2045–2056.

World Health Organization, 2011. World Report on Disability. 978 92 4 068636 6 (ePUB).

Xiong, Y., Mahmood, A., Chopp, M., 2013a. Animal models of traumatic brain injury. Nat. Rev. Neurosci. 14, 128–142.

Xiong, Y., Mahmood, A., Chopp, M., 2013b. Animal models of traumatic brain injury. Nat. Rev. Neurosci. 14, 128–142.

Xu, J., Rasmussen, I.-A., Lagopoulos, J., Haberg, A., 2007. Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. J. Neurotrauma 24, 753–765.

Xu, S., Zhuo, J., Racz, J., Shi, D., Roys, S., Fiskum, G., Gullapalli, R., 2011. Early microstructural and metabolic changes following controlled cortical impact injury in rat: a magnetic resonance imaging and spectroscopy study. J. Neurotrauma 28, 2091–2102.

Yeh, C.C., Chen, T.L., Hu, C.J., Chiu, W.T., Liao, C.C., 2013. Risk of epilepsy after traumatic brain injury: a retrospective population-based cohort study. J. Neurol. Neurosurg. Psychiatry 84, 441–445.

Zhang, K., Yu, C., Zhang, Y., Wu, X., Zhu, C., Chan, P., Li, K., 2011. Voxel-based analysis of diffusion tensor indices in the brain in patients with Parkinson's disease. Eur. J. Radiol. 77, 269–273.

Zhang, Y., Cai, J., Shields, L.E., Liu, N., Xu, X.-M., Shields, C., 2014. Traumatic brain injury using mouse models. Transl. Stroke Res. 5, 454–471.

Zhao, J., Chen, Z., Xi, G., Keep, R.F., Hua, Y., 2014. Deferoxamine attenuates acute hydrocephalus after traumatic brain injury in rats. Transl. Stroke Res. 5, 586–594.

Zhou, Y., Dougherty Jr., J.H., Hubner, K.F., Bai, B., Cannon, R.L., Hutson, R.K., 2008. Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. Alzheimers Dement. 4, 265–270.

Zhuang, L., Wen, W., Zhu, W., Trollor, J., Kochan, N., Crawford, J., Reppermund, S., Brodaty, H., Sachdev, P., 2010. White matter integrity in mild cognitive impairment: a tract-based spatial statistics study. NeuroImage 53, 16–25.