Brain Imaging and Behavior (2017) 11:591–610
DOI 10.1007/s11682-017-9684-0

REVIEW ARTICLE

Structural imaging of mild traumatic brain injury may not be enough: overview of functional and metabolic imaging of mild traumatic brain injury

Samuel S. Shin[1] · **James W. Bales**[2] · **C. Edward Dixon**[3] · **Misun Hwang**[4]

Published online: 13 February 2017

Abstract A majority of patients with traumatic brain injury (TBI) present as mild injury with no findings on conventional clinical imaging methods. Due to this difficulty of imaging assessment on mild TBI patients, there has been much emphasis on the development of diffusion imaging modalities such as diffusion tensor imaging (DTI). However, basic science research in TBI shows that many of the functional and metabolic abnormalities in TBI may be present even in the absence of structural damage. Moreover, structural damage may be present at a microscopic and molecular level that is not detectable by structural imaging modality. The use of functional and metabolic imaging modalities can provide information on pathological changes in mild TBI patients that may not be detected by structural imaging. Although there are various differences in protocols of positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) methods, these may be important modalities to be used in conjunction with structural imaging in the future in order to detect and understand the pathophysiology of mild TBI. In this review, studies of mild TBI patients using these modalities that detect functional and metabolic state of the brain are discussed. Each modality's advantages and disadvantages are compared, and potential future applications of using combined modalities are explored.

Keywords Mild traumatic brain injury · TBI · Concussion · Imaging · Diffusion tensor imaging; DTI

✉ Misun Hwang
mhwang11@jhmi.edu

[1] Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2] Department of Neurological Surgery, University of Washington School of Medicine, Seattle, WA, USA

[3] Department of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

[4] Russel H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, 1800 Orleans St Zayed Tower 4174, Baltimore, MD 21287, USA

Introduction

Background

Traumatic brain injury (TBI) occurs from numerous mechanisms including motor vehicle accidents (MVA), military blast injury, blunt object trauma, falls, and repetitive sports-related concussion. Due to the fact that each injury may have completely different pathophysiology from another and the numerous molecular mechanisms involved in TBI, it has been difficult to develop therapeutic strategies (Laskowski et al. 2015; Saatman et al. 2008; Bramlett and Dietrich 2015). Moreover, optimal imaging technique has been a subject of debate over the last few decades due to difficulty in consistent and accurate detection of injury (McCrory et al. 2009; Yuh et al. 2014).

In a clinical setting, conventional neuroimaging methods typically involve computed tomography (CT) and magnetic resonance imaging (MRI). Although these methods are useful in detecting gross pathology such as skull fractures, large hemorrhage, cerebral edema, and mass shifts in brain tissue, they are limited by the resolution of imaging (Honce et al. 2016; Delouche et al. 2016). Specifically for mild TBI (mTBI) patients where neural injury can occur at a microscopic scale, conventional imaging methods may commonly yield no significant findings. Due to this limited sensitivity of injury

detection in TBI, there have been further developments of neuroimaging techniques such as susceptibility-weighted imaging (SWI) which is sensitive to small areas of traumatic hemorrhage, and diffusion imaging which is based on detection of differences in diffusion properties of water molecules at each voxel of the image (Hunter et al. 2012).

Of particular interest is diffusion tensor imaging (DTI), which has been gaining interest in the TBI community due to its ability to detect axonal injury (Niogi et al. 2008; Aoki et al. 2012; Lipton et al. 2009; Rutgers et al. 2008; Koerte et al. 2016). In a structurally intact axon, water molecules have higher degree of diffusion in the axial direction compared to radial direction as they are bounded by the membrane. Using diffusion weighted images, diffusion tensor matrix can be calculated and three eigenvalues can be derived that characterizes the magnitude of diffusion and their directionality (Wheeler-Kingshott and Cercignani 2009; Alexander et al. 2007). Among the three eigenvalues, one of the eigenvalues describes water diffusion in an axial direction (parallel to the axon), termed "axial diffusivity". The other two eigenvalues can be used to derive "radial diffusivity" which characterizes the diffusion in a direction perpendicular to the axon (Song et al. 2002). An intact axon will have predominantly high axial diffusivity, but structural damage to the axon by trauma will result in reduction of this value. Additionally, "fractional anisotropy" (FA) can be calculated from the three eigenvalues to assess the degree of diffusion in a specific direction. It is a measurement of how ellipsoidal a diffusion tensor of water molecules is compared to that of a sphere ranging between 0 and 1. Whereas a value of 1 indicates diffusion only in one axis, a value of 0 indicates equal diffusion in all directions similar to a sphere. Thus, compromise in the structural integrity of axons may be detected by DTI using these parameters.

While changes in DTI parameters such as FA can be due to injury of white matter compromising myelin integrity, many neuropathologic conditions such as edema, neuronal death, inflammation, and gliosis can cause it (O'Donnell and Pasternak 2015). In addition, many nonpathologic properties of the brain parenchyma can alter FA values such as crossing of white matter fibers or proximity to the body of cerebrospinal fluid, adding to the lack of specificity of changes in FA. While DTI has limitations in its specificity, the last decade has seen an emergence of interest and numerous research efforts to use DTI and other diffusion imaging modalities to detect markers of mTBI.

Axonal injury and imaging

Various studies show the sensitivity of DTI in white matter damage as well as correlation of this finding with cognitive deficits (Niogi et al. 2008; Kennedy et al. 2009; Kraus et al. 2007). A great interest in diffusion imaging has been its ability to detect areas of injury even in mTBI (Messe et al. 2011; Inglese et al. 2005; Smits et al. 2011; Cubon et al. 2011; Ware et al. 2016; Jorge et al. 2012; Wilde et al. 2008).

Although there has been much debate on the optimal settings and parameters for diffusion imaging of TBI, much of the cellular damage in TBI resulting in functional deficits may not be detected even with DTI. For example, DTI studies have shown no significant differences even when post concussive symptoms and verbal memory deficits are present (Levin et al. 2010). Efforts to correlate DTI results with functional imaging such as functional MRI (fMRI) showed inconsistent results (Zhang et al. 2010b). These findings may be due to the fact that DTI is limited in detecting small areas of injury in tortuous white matter pathways as well as high angle turns of axons (S. S. Shin et al. 2014; S. S. Shin et al. 2012). While it is a very powerful tool for detection of damage in large fiber tracks that are largely linear, axonal injury in areas of high angular turns may be less detectable (Hagmann et al. 2006; Jbabdi and Johansen-Berg 2011). Moreoever, in areas of high interstitial fluid content, DTI may be compromised (Yokoyama et al. 2008).

Biochemical events underlying TBI

Early studies of TBI patients who had no intracranial hemorrhage found diffuse white matter injury which was believed to be due to distortion and rupture of axons at the time of impact (Peerless and Rewcastle 1967; Strich 1956). Although severe TBI can directly induce shearing of axonal fibers as well as vascular structures, it was found more recently that much of the axonal injury in TBI occurs over a broad range of time from minutes to weeks via molecular pathology that eventually leads to severing of the axons. At the time of impact, alignment of the neurofilament is disrupted and there is development of focal swelling along the axonal tract (Grady et al. 1993; Povlishock 1993). Structural damage of the axon is accompanied by influx of calcium, which activates calcium activated proteases and subsequently leads to further cytoskeletal injury over minutes to hours (Povlishock et al. 1997; Buki et al. 1999; Krishnamurthy and Laskowitz 2016; MacFarlane and Glenn 2015; Yang et al. 2015). With continued neurofilament degradation and cytoskeletal injury over period of days to weeks, there is impaired axonal transport and eventual disconnection at the injury site along the axon.

Axonal injury occurs in cases of mTBI (Blumbergs et al. 1994, 1995), and the pathological events in mTBI may be more noticeable at the microscopic and molecular level (Fig. 1). Detection of these changes by biochemical assays or histological analysis of brain tissue have been commonly used in animal models of TBI (Thelin et al. 2016; Mouzon et al. 2014). However, for clinical scenario where noninvasive or minimally invasive detection is needed, such methods are not feasible. Noninvasive detection as well as spatial and temporal information of the injury at microscopic and molecular

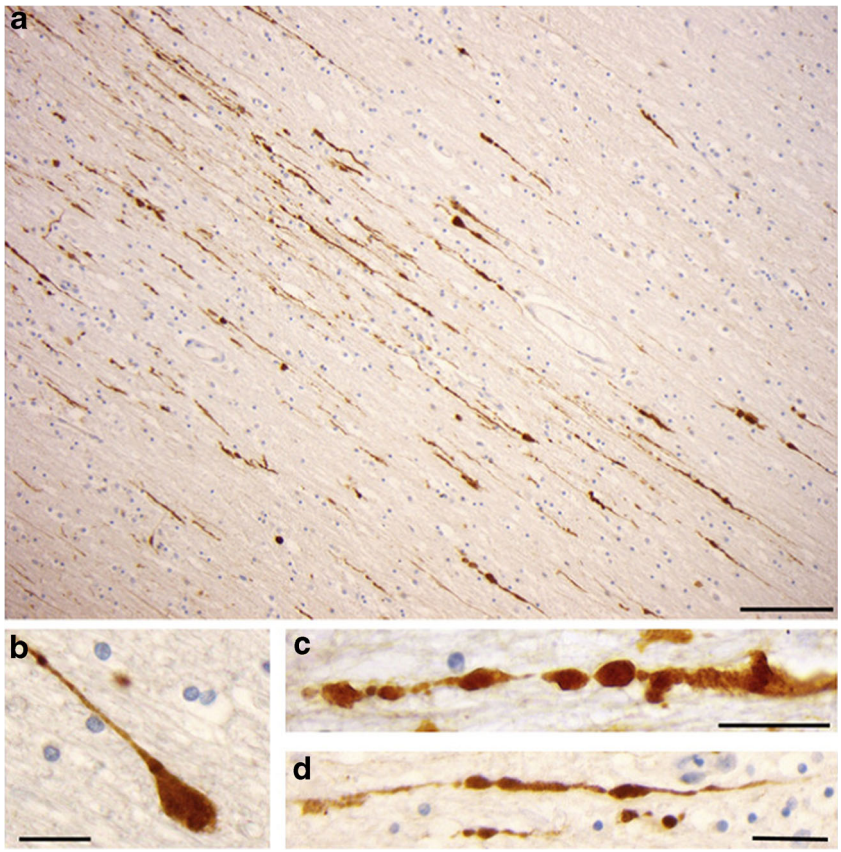

Fig. 1 Histological detection of axonal injury. Markers of axonal pathology can be detected at a microscopic scale using immunohistochemical techniques sensitive for amyloid precursor protein. **a** shows low magnification axonal injury (scale bar: 100 μm). **b** shows high magnification with axonal bulb formation (scale bar: 15 μm) and (c-d) show high magnification with axonal accumulation of amyloid precursor protein (scale bar: 30 μm). This figure is reproduced from Johnson et al., (Johnson et al. 2013) with permission

level for mTBI presents a serious challenge to the community of neurotrauma researchers and clinicians. With advancements in noninvasive imaging techniques, complex changes in metabolism and neurotransmitter levels occurring after TBI may be further characterized in the future (Van Horn et al. 2016).

Since neuronal dysfunction may be present in mTBI without overt damage or disconnection of axonal tracts, the sole use of diffusion imaging to assess for the level of injury after mTBI may not be accurate. Well characterized areas of axonal damage in TBI are the superior longitudinal fasciculus, cingulum, corona radiata, and corpus callosum (Bigler and Maxwell 2012; Gentry et al. 1988). However, much of this information has been based on structural imaging reports. Microstructural damage to the neuronal axolemma as well as neuronal dysfunction that has been posited to contribute to cognitive and behavioral impairment in mTBI patients may not be detected by current structural imaging methods such as DTI. Axonal injury leading to eventual disconnection may take period of days to weeks, but neuronal dysfunction leading up to the time of disconnection may not be detected by these methods.

In this review, we discuss the results of several functional imaging techniques that have been used in the recent years for detection of TBI. The general interpretation of the results as well as the advantages and disadvantages are outlined in (Table 1). Moreover, we discuss the possibility of using both structural and functional imaging in future mTBI studies. Some prior studies have successfully used the integration of structural information using diffusion imaging techniques and functional information using electroencephalography (EEG) or fMRI to investigate connectivity of brain regions (Jarbo and Verstynen 2015; Skudlarski et al. 2008; van den Heuvel et al. 2008), Alzheimer's disease (using EEG and DTI) (Vecchio et al. 2015), and autism (using fMRI and diffusion weighted imaging) (Fishman et al. 2015; Barbeau et al. 2015). Such integrated approach may be more sensitive and help us gain further insight into the pathophysiology of TBI. In several sections, results of functional imaging on severe TBI patients will be discussed in addition to results from mTBI patients for comparison. As TBI can be a very heterogeneous entity, comprehensive understanding of the findings from different types, severity, and time points after injury will be important in gaining a useful insight into the pathophysiology of mTBI.

Nuclear medicine imaging

Detection of metabolic changes

Positron emission tomography (PET) can be used to detect either increased or decreased rate of metabolism.

Table 1 Summary of widely used metabolic or functional imaging modalities for mTBI. A brief summary of general findings are represented in the table. Although there have been numerous papers showing the use of each of these modalities in TBI, they are limited by the differences in protocols resulting in variable results as well as the limitation in understanding of how these techniques work

Modality	Physiological Change detected	Timecourse of findings	Advantages	Disadvantages	Clinical considerations
PET (FDG)	Glucose metabolism	Acute – Increased metabolism Chronic – Reduced metabolism	Less motion sensitive than MRI	Lower spatial resolution/ more expensive than MRI	Requires injection ofradioisotope
SPECT	Cerebral blood flow	Acute and chronic – Reductions in CBF in clinically relevant areas	Relatively inexpensive compared to PET	Lengthy protocols	Requires injection ofradioisotope
fMRI	Oxygen consumption	Acute/subacute –Decreased DMN connectivity, increased frontal/parietal activation with demanding task Chronic – DMN hypoconnectivity persists, hyper/hypoconnectivity in other networks	Virtually no risks, fully noninvasive	More expensive than MRI; Requires patient to tolerate MRI; extremely motion sensitive	Cannot use in patients with metal implants
EEG - Conventional	Electrical potential change by neuronal current	Acute –Alterations in underlying EEG in first 24 h associated with worse functional outcome in mild TBI Chronic – Unclear if any utility beyond patients with suspected seizure activity clinically	Can be used for longer timeframe than other modalities (several days); Well characterized methods of interpretation; Inexpensive compared to MRI; high temporal resolution	Limited evidence of how it can be applied clinically; Low spatial resolution	EEG is widely used in clinical setting
EEG - Quantitative	Electrical potential change by neuronal current	Acute and chronic – Can detect alterations in alpha and theta wave patterns not apparent on conventional EEG.	More sensitive than conventional EEG; Inexpensive compared to MRI; High temporal resolution; Portable	Inexpensive compared to MRI; Low spatial resolution	EEG is widely used in clinical setting
MEG	Magnetic field change by neuronal current	Chronic – Low frequency wave in injured patients	High temporal resolution	Expensive and time intensive; Requires use of MRI in conjunction	Requires a dedicated shielded room and MEG set up

DMN default mode network, *CBF* cerebral blood flow

Metabolic imaging by PET is based on using a radioactive labeling agent termed a tracer such as F-2-fluro-2-deoxyglucose (FDG). When FDG is injected systemically, it accumulates in the target tissue. Since FDG emits positron and the emission can be measured by a detector, higher accumulation of the label will result in higher signal. For example, in a human or animal subject with increased level of neuronal activity and metabolism, FDG composed of glucose is uptaken. This can result from an increased cerebral metabolic rate glucose (CMR_{glc}) of the target region of the brain. However, loss of neurons or reduced activity of neurons will result in a reduced consumption of glucose, leading to a decrease in CMR_{glc}. In addition, the detection of glucose metabolism via PET is heavily dependent on glucose uptake by astrocytes. Since glucose uptake is predominantly done by astrocytes in response to glutamate release (Magistretti et al. 1999; Magistretti and Pellerin 1996), alteration in FDG-PET signal is a combined result of metabolic disruption of both neurons and astrocytes. Often in conjunction with glucose metabolic rate, cerebral metabolic rate of oxygen ($CMRO_2$) is also assessed by MRI based information. Along with cerebral blood flow (CBF) and metabolic ratio ($CMRO_2$/CMR_{glu}), these values provide overall details about the metabolic activity level of the brain following injury. Thus, PET imaging provides valuable insight into the metabolic derangements that occur after TBI.

Metabolic changes at acute time points

The PET imaging studies on TBI subjects show that metabolic rate of glucose is time dependent after injury. The results have generally shown that CMR_{glu} is increased early after injury (Sunami et al. 1989; Yamaki et al. 1996; Bergsneider et al. 1997) and decreased at later time points (Zhang et al. 2010a; Humayun et al. 1989; Gross et al. 1996; Chen et al. 2003).

Earlier studies of PET imaging on TBI subjects focused on acute and subacute metabolic changes that occur in the order of hours to days after the insult. A rat study using

autoradiographic methods demonstrated hypermetabolism of glucose in one to two hours following TBI, possibly due to cortical spreading depression (Sunami et al. 1989). However, others suggested that mechanism underlying increased glucose metabolism is excitatotoxic activity: excessive activation of glutamate receptors, ionic influx, and depolarization subsequently leads to increase in glucose consumption to reestablish ionic gradients (Yamaki et al. 1996; Bergsneider et al. 1997). These studies performed FDG-PET imaging on patients that had severe injury, and found increased cerebral metabolic rate of glucose (CMR_{glc}) at 10 days (Yamaki et al. 1996) and 8 days or prior (Bergsneider et al. 1997).

In addition to changes in glucose metabolism, some of the patients had reduced cerebral metabolic rate of oxygen ($CMRO_2$) (Yamaki et al. 1996; Bergsneider et al. 1997). This indicated that they were in hyperglycolitic state where glucose consumption occurs along with diminished oxidative metabolism. In another study of moderate to severe injury subjects at days 0–9, there was a slight reduction in glucose metabolism and severe reduction in oxygen metabolism (Glenn et al. 2003). Although both were reduced, a much greater reduction of oxygen metabolism resulted in relatively anaerobic condition. Similarly, PET imaging of the regions at varying distances from the contusion core at days 0–5 after injury showed decreasing CBF, $CMRO_2$, CMR_{glc}, and oxygen extraction fraction, indicating anaerobic metabolism. These results were in agreement with earlier studies showing hyperglycolysis for severe TBI at 4 days or prior (Wu et al. 2013).

Although much of the PET imaging studies have shown hyperglycolysis following TBI, it should be noted that pentose phosphate cycle is another pathway of glucose metabolism that had been described at early time points following TBI. Patients with TBI have increased glucose metabolism via pentose phosphate cycle peaking at 48 h after injury (Dusick et al. 2007). Various cellular functions important at the time of injury are activated by pentose phosphate cycle. Pentose phosphate cycle supports the generation of glutathione which reduces oxidative stress, and it produces ribose which is an important component of mRNA synthesis that leads to protein synthesis. As novel PET imaging markers develop in the future, these other aspects of glucose metabolism can be further characterized.

Most for the PET imaging studies for mTBI patients evaluated the subjects at chronic time points between months to years following the insult, and shorter timescale PET imaging for mTBI are less common. A report of single case of MVA at 2 days following injury showed no significant alteration in cerebral glucose metabolism (Abu-Judeh et al. 1998). Other mTBI studies using PET imaging were performed at chronic time points, and most studies commonly found reduced glucose metabolism in various regions of the brain.

Metabolic changes at chronic timepoints

At chronic timepoints, the metabolic changes are reversed and reduced glucose metabolism is reported. A case report of a severe TBI patient at 2 years following the MVA showed bilateral reduction in hippocampal and anterior cingulate cortex glucose metabolism (Mattioli et al. 1996). These regions along with bilateral thalami, left inferior frontal gyrus, and left superior temporal gyrus were also identified to have reduced glucose metabolism in 36 patients (mean time after injury: 16.7 months, range: 6–38 months). Also a study with patients divided into groups of different severities of injury (including minimally conscious and vegetative patients) identified reduced glucose metabolic rate in areas such as thalamus, cingulate gyrus, lingual gyrus, parahippocampal gyrus, and hypothalamus, at chronic timepoints after injury (Nakayama et al. 2006). These reductions in glucose metabolism are in agreement with the hemodynamic compromise seen in areas of contusion following injury. Reduction in CBF as well as flow to volume ratio (FVR), which is calculated by the ratio of CBF to cerebral blood volume, has been shown in contusional and pericontusional areas after TBI (Hattori et al. 2003).

The studies mentioned thus far show changes in glucose metabolism for severe TBI patients over time. In most of the severe TBI studies described here, conventional neuroimaging can identify gross injuries. For mTBI subjects however, the injury may only be apparent at a microscopic level and easily missed by CT and MRI. An important value of metabolic imaging can be recognized in its ability to detect abnormal physiology after mTBI where conventional neuroimaging may miss detection.

Wide regions of the brain have been described to be reduced in glucose metabolism at chronic timepoints: at 3–12 months post injury, 3 mTBI patients subjected to FDG-PET imaging showed decreased regional glucose metabolism despite unchanged global glucose metabolism (Humayun et al. 1989). There were local reductions in medial temporal, posterior temporal, posterior frontal cortices, in addition to caudate nucleus. These patients also showed memory and attention deficits. .Similarly, another report of 20 mTBI patients who were subjected to FDG-PET imaging 1–5 years after injury compared neuropsychological test results with alterations in glucose metabolism (Gross et al. 1996). Most commonly reported cognitive deficits were in memory and executive function. In contrast to the study by Humayun, this study also reported increased glucose metabolic rate in some regions. Temporal gray and frontal white matter regions were specifically reported to be hypermetabolic. Additionally, no significant difference in regional glucose metabolism of frontal and temporal regions has also been reported (Chen et al. 2003). These patients were assessed by FDG-PET at a mean of 16.6 months after injury (range: 5–35 months).

In several studies of military personnel who were exposed to mTBI from a blast, PET was performed at chronic time points. All revealed decreased metabolic state chronically in varying regions throughout the brain ranging from frontal and temporal cortex to cerebellum and brainstem (Mendez et al. 2013; Petrie et al. 2014; Peskind et al. 2011; Stocker et al. 2014). A study of 34 blast mTBI veterans scanned at mean of 3.8 years after injury (range: 1.2–7.1 years) detected reduction of glucose metabolism in parietal, somatosensory, and visual cortices (Petrie et al. 2014). Similarly, in 12 blast mTBI patients at a range of 22–78 months after injury, reduced metabolism in right superior parietal region was detected (Mendez et al. 2013).

A study of 12 veterans with mean time from injury: 3.5 and range: 2–5 years showed decreased cerebral metabolic rate of glucose in cerebellum, vermis, pons, medial temporal lobe when compared to normal controls (Peskind et al. 2011). Moreover, these subjects had functional deficits in several measures such as attention, working memory, verbal fluency, and processing speed which was consistent with the areas of damage. A larger and more recent study specifically looking at patients who suffered from mTBI as a result of blast injury has suggested even longer and permanent deficit following TBI. Combat related blast injury patients underwent PET imaging at a mean of 42.6 months (range: 15–86 months). Among the subjects who finished all the PET scans of the study ($n = 25$), there was reduced glucose metabolism at both awake and REM sleep even after injury (Stocker et al. 2014). Specific regions of reduced cerebral glucose metabolism were in the right hemisphere: olfactory gyrus, caudate, putamen, amygdala, hippocampus, and parahippocampal gyrus. Midline structures such as the cingulate gyrus were also included in the areas of decreased glucose metabolism. These blast mTBI studies using PET at chronic timepoints all indicate reduced metabolism.

Although there have been numerous studies using PET imaging in TBI patients, it is difficult to draw a comprehensive conclusion given the differences in imaging protocols, subject population, and multiple factors that can contribute to PET signals. Despite such differences in studies and some reports showing no significant differences, it should be noted that reports of acute TBI commonly show hypermetabolic findings whereas reports of chronic TBI commonly show hypometabolic findings. In a setting where macroscopic injury cannot be identified by structural imaging, PET study may be a sensitive method of detection of metabolic dysfunction.

When DTI was performed in addition to FDG-PET for blast mTBI patients, there were differences in the location of significant injury detected by each modality (Petrie et al. 2014). Whereas reduction of diffusion parameters indicating axonal damage were detected at only the genu of the corpus callosum, FDG-PET identified reduced CMR_{glu} at wide regions of parietal, somatosensory, and visual cortices. Given that these patients had numerous positive findings in neurobehavioral assessment tests such as postconcussive symptoms, post traumatic stress disorder, depression, sleep disturbance, and alcohol use, corpus callosum injury alone is not likely to be responsible for all of these symptoms. Thus, metabolic imaging provides important information regarding the location of pathology that structural imaging modality may not pick up. Since some DTI studies on mTBI have even resulted in no significant or inconsistent results when compared to the neurobehavioral symptoms or functional imaging studies (Levin et al. 2010; Zhang et al. 2010b), using the combination of diffusion imaging along with functional imaging will provide a more complete understanding of injury.

Detection of neuroinflammation and neurodegenerative changes

Neuroinflammation can be prolonged for months to years following TBI, and PET imaging of this change can be a sensitive marker to monitor the effects of initial injury. Various ligands which target 18-kDA translocator protein (TSPO) have been used for PET imaging of post TBI neuroinflammation, since TPSO is upregulated in activated microglia (Wang et al. 2014; Israel et al. 2016; Folkersma et al. 2011; Ramlackhansingh et al. 2011; Coughlin et al. 2015). The time course of inflammation has been characterized in animal models of TBI: In a closed head injury model of mice looking at labeling at 1, 7, and 16 days after injury, [^{18}F]DPA-714 labeled activated microglia at 7 and 16 days (Israel et al. 2016).

Similarly, a [^{18}F]DPA-714 PET imaging of controlled cortical impact model of rats showed peak labeling at 6 days after injury which gradually reduced to original levels by 28 days after injury (Wang et al. 2014).

However, human studies showed a much longer timecourse of inflammation. A PET ligand [^{11}C](R)PK11195 that binds to activated microglia has been effective in detecting significant elevation in areas of inflammation following TBI at 6 months (Folkersma et al. 2011) and upto 17 years (Ramlackhansingh et al. 2011). However, the findings in these studies cannot be generalized to mTBI patients since they also included moderate and severe TBI patients.

Metabolic, neuroinflammatory, and neurodegenerative changes in sports related mTBI

Similar to the preclinical studies showing metabolic and neuroinflammatory changes, patients who suffered multiple mTBI had detectable changes in cerebral glucose metabolism. Among boxers who experienced chronic and repetitive subconcussive injury, decreased cerebral glucose metabolism was found in posterior cingulate cortex, parieto-occipital lobe,

frontal lobe, and the cerebellum (Provenzano et al. 2010). It should be noted that multiple subconcussive TBI may be considered a unique entity separate from concussion. Although there are no obvious neurological deficits that are apparent among athletes who suffer from these injuries, injury models of subconcussive TBI shows that there are cumulative effects in axonal injury and damage to cytoskeletal proteins (Bailes et al. 2013).

Another study using a different ligand [^{11}C]DPA-713 showed significant increase in microglia activity among only mTBI patients: this study imaged former National Football League (NFL) players who were subjected to repetitive subconcussive injury and concussions throughout their careers (Coughlin et al. 2015). In this study, comparison of 9 NFL players to 9 age-matched healthy controls showed significantly higher binding in supramarginal gyrus and amygdala.

Positron emission tomography imaging can also be useful in detection of neurodegenerative changes after TBI such as protein aggregate formation. Case report of an NFL athlete who underwent [^{18}F]-T807 PET imaging showed labeling of striatal and nigral structures consistent with tauopathy in these regions (Mitsis et al. 2014). Also a case series of in NFL players who received PET imaging using [^{18}F]FDDNP which shows fibrillary insoluble protein aggregates (e.g. tau and Aβ) resulted in significant patterns of detection consistent with tau deposition (Barrio et al. 2015) **(**Fig. 2**)**. Other ligands such as ^{11}C–Pittsburgh compound B and ^{18}F–AV-45 which are specific to Aβ aggregates have demonstrated significant pathology in moderate to severe TBI patients (Scott et al. 2016; Hong et al. 2014; Gatson et al. 2016) but not in mTBI thus far. Future PET imaging studies should utilize the numerous arsenal of novel ligands in order to detect protein aggregates or neuroinflammatory changes among mTBI patients.

Single photon emission computed tomography: SPECT studies

There have been a number of recent studies using single photon emission computed tomography (SPECT) which detects CBF by using gamma ray emitting isotope such as ^{99m}Tc. Agents such as ^{99m}Tc-hexamethylpropleneamine oxime (^{99m}Tc-HMPAO), ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD), and iomazenil are commonly used for injection in SPECT imaging (Andersen 1989; Leveille et al. 1992). These radioactive tracers are injected in the subjects for uptake by the brain tissue, and uptake of this agent is proportional to the CBF. Photons are emitted by a process termed gamma emission during the decay of the ray emitting isotope, and these photons are detected by gamma-cameras. The level of CBF can be measured since the level of gamma emission is proportional to CBF. As a cost effective imaging method, SPECT has been initially regarded as a strong candidate for widespread clinical use. However, the positive and negative predictive value of this test has been the matter of debate for many neurological pathologies.

The utility of using SPECT in the detection of TBI is based on its sensitivity even in the absence of anatomical damage especially in mTBI. In a report of 43 mTBI patients at a mean interval of 1.3 years (range: 0.1–5.4 years), 53% of patients using SPECT had abnormal results, whereas 9% of patients using MRI and 4.6% of patients using CT scans had abnormal

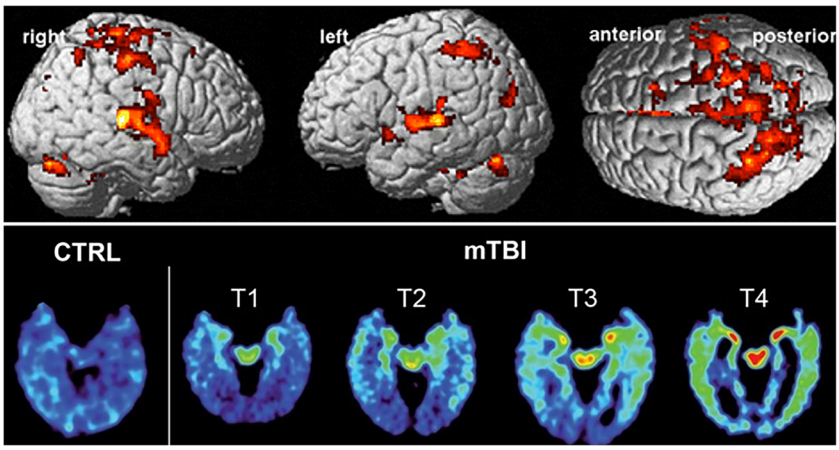

Fig. 2 Functional and metabolic imaging examples. (*above*) Functional MRI study showing BOLD signals among subjects who experienced blast mTBI: modified from (Scheibel et al. 2012; Wilde et al. 2015) with permission. Activation of specific cortical areas such as anterior cingulate cortex and medial prefrontal cortex are clearly portrayed by this imaging modality. (below) PET imaging using [F-18]FDDNP, a tracer specific to fibrillar protein aggregates which are markers of neurodegenerative changes after a lifetime of repetitive mTBI: modified from (Barrio et al. 2015) with permission, Copyright (2015) National Academy of Sciences. Control subjects were compared to retired American football players in this study, and 4 types of distribution patterns of fibrillar protein aggregates were found (T1-T4). CTRL = control

results (Kant et al. 1997). This sensitivity of SPECT compared to conventional imaging was shown even for severe TBI patients. In a study of 19 patients with severe head injury, SPECT between 3 to 36 months after injury (no mean interval was given) detected more lesions than CT or MRI as well as significantly reduced CBF (Newton et al. 1992).

Detection of cerebral ischemia

Areas of hypoperfusion have been identified using SPECT imaging at as early as 24 h after injury upto 3 years after injury (Abdel-Dayem et al. 1998; Abu-Judeh et al. 1998; Romero et al. 2015). Most of the mTBI studies have reported hypoperfusion patterns in frontal, parietal, and temporal lobes. In an early case report by Abu-Judeh et al., bilateral frontal and parietal regions have been identified as areas of hypoperfusion (Abu-Judeh et al. 1998). In a prospective study with 92 mTBI patients (64 adults and 28 children), hypoperfusion in frontal lobes and temporal lobes was reported within 72 h after injury (Gowda et al. 2006). There was an association with higher degree of injury, since more number of abnormalities were detected among patients with posttraumatic amnesia and loss of consciousness. This reduction in CBF in the frontal lobes was also noted in another study comparing mTBI patients to controls (Marks et al. 2006). However, no difference in CBF was found in the temporal lobes, different from the results by Gowda et al. Occipital and parietal lobes as well as thalami and basal ganglia also had notable reduction in CBF in this study. Another study using automated algorithm to analyze SPECT data after ^{99m}Tc-ECD uptake showed reduced CBF in anterior cingulate gyrus, as well as medial frontal gyrus, hippocampus, and parahippocampal gyrus at a mean of 13 days after injury (Y. B. Shin et al. 2006).

In addition to studies at early time points after injury, SPECT has also been used for imaging of mTBI at subacute to chronic time points. In a SPECT study comparing patients at less then 3 months to between 3 months upto 3 years after injury, subcortical hypoperfusion was noted: basal ganglia and thalami were reported as most commonly found hypoperfused areas, followed by frontal lobes (Abdel-Dayem et al. 1998). Widespread hypoperfusion including frontal and subcortical hypoperfusion was detected among patients who experienced mTBI at a mean of 5.2 years ago (Bonne et al. 2003). These regions included head of caudate nucleus, bilateral medial frontal, superior and medial temporal, and left pre-central regions.

As previously reviewed, it is well known that CBF is reduced immediately after severe TBI and remains low for extended period (Len and Neary 2011). Metabolic imaging studies for mTBI characterized changes in glucose and oxygen consumption as well as CBF. Future efforts in metabolic imaging will not only be focused on increasing sensitivity of detection of injury, but also exploring the mechanism of mTBI induced metabolic derangements.

Correlation to symptoms and functional deficits

Some studies have found group associations between hypoperfusion in a given region and post concussive symptoms. Among pediatric patients who had persistent post concussion syndrome, medial temporal hypoperfusion was noted at 3 months after injury (Agrawal et al. 2005). Another prospective study analyzing 136 patients showed that persistent abnormalities in SPECT signals over 12 months were associated with post concussive symptoms (Jacobs et al. 1996). Specifically, frontal cortex hypoperfusion was associated with post concussive symptoms.

Using a complex cognitive test and comparing the activation of CBF to the resting state, 15 mTBI patients were compared to normal control subjects (Hattori et al. 2009). This led to the finding of different activation patterns between TBI and controls: mTBI patients had larger area of supratentorial activation but smaller area of cerebellar activation, suggesting dissociation of frontocerebellar connection. Another study using a Stroop test which assesses executive function showed that hypoperfusion of right superior frontal and middle frontal gyri predicted worse executive function in mTBI patients (Romero et al. 2015). Using a newly developed software, a quantitative index was calculated to identify specific regions of brain associated with neuropsychological impairments in patients with mTBI and diffuse axonal injury compared to controls (Uruma et al. 2013). There was low regional ^{99m}Tc-ECD uptake indicating low CBF in the left anterior cingulate gyrus associated with neuropsychological impairment such as problems in memory, attention, and executive function.

Comorbidities associated with TBI can make interpretation of SPECT difficult. For example, presence of migraine or psychiatric conditions such as depression or post traumatic stress disorders may result in alteration in SPECT imaging. In addition, if there is an underlying neurobehavioral condition prior to TBI, the abnormal cerebral perfusion detected by SPECT can be falsely attributed to be due to TBI. Interpretation of SPECT data to explain clinical symptoms in mTBI patients can be complicated by overlapping pathology of TBI and psychiatric conditions.

Functional MRI studies

Function magnetic resonance imaging techniques are based on detection of changes in vascular activity of the brain [Figure 2]. With increased activity of neurons, there is increased vascular flow due to increased metabolic demand for oxygen (Attwell et al. 2010). Additionally there is increased release of oxygen from red blood cells, where oxyhemoglobin

changes to deoxyhemoglobin. Since there are differences in magnetic properties of oxyhemoglobin and deoxyhemoglobin, this change can be detected by a method named blood-oxygen level dependent (BOLD) contrast imaging (Buxton et al. 2004; Buxton et al. 1998). Thus, fMRI studies use this principle to detect activity changes in different regions of the brain at either resting state or with specific task assigned to the subject.

Hemodynamic changes have been studied using fMRI in healthy subjects as well as various pathological states including neurodegenerative diseases and acquired brain injury. Although specific areas of the brain can be activated with a given task, there is brain activity even if no specific task is given to the patient. Thus, resting state fMRI can reveal how different regions of the brain interact with each other to form networks even at rest (Buckner et al. 2008; Greicius et al. 2009). The categorization of fMRI studies can be broadly divided into two types: 1. Task-based paradigms and 2. Resting state measurements.

Activation during task-based paradigms

Among the task-based fMRI paradigms, assessment of working memory is found in many TBI studies. A commonly used working memory task named n-back task has been performed in mTBI patients in conjunction to functional imaging of the brain (McAllister et al. 2001; McAllister et al. 1999). Briefly, n-back task involves the subjects listening to a series of letters and identifying a repetition of the letter that was previously heard. In a 2-back task, the subject is required to identify if there has been a repetition of the same letter from 2 steps ago. Similarly in a 3-back task, they must identify a repetition from 3 steps ago. The initial study using fMRI in mTBI patients compared 12 mTBI patients and 11 control subjects at one month after injury (McAllister et al. 1999). In this study, while the task performance of auditory n-back task did not differ significantly between mTBI patients and control subjects activation patterns on fMRI differed. The mTBI patients had significantly higher activation in the right parietal and dorsolateral frontal regions during the increases in working memory load.

Another study was performed by the same group using a the 2-back task as well as a more difficult 3-back task and fMRI at one month after injury (McAllister et al. 2001). It identified again a higher level of activation at bilateral frontal and parietal regions for mTBI patients compared to controls, but a much higher increase in activation was found in fMRI during moderate processing load compared to fMRI during highest processing load. This indicated that activation of brain regions in TBI patients may not follow a linear curve with increasing working memory load. Another report by the same group showed that with increasing working memory load, there is a change in the pattern of activation: there is increased activation specifically in right parietal and right dorsolateral prefrontal cortex (McAllister et al. 1999).

A study with n-back testing using larger population of mTBI patients (n = 43) showed that there was no difference in activation at any region between mTBI patients and controls (Stulemeijer et al. 2010). However when comparing medial temporal lobe activation and post traumatic amnesia duration, a significant negative correlation was found. Thus, this implicated that memory deficits following mTBI may be partially contributed to medial temporal lobe dysfunction. The differences in activation of bilateral frontal and parietal regions found by Mcallister et al. (McAllister et al. 2001) was not detected by Stulemeijer et al., explained to be due to the differences in study design. In addition to Mcallister's study, another report compared activation patterns between TBI subjects and controls with increasing demand in working memory task (Turner et al. 2011). Turner et al., showed that with increasingly demanding verbal working memory task, there is increased recruitment of related networks within left and right prefrontal cortex in TBI patients compared to controls. However, there was discrepancy between this result compared to a prior study (McAllister et al. 2001): higher recruitment with higher working memory load was found by Turner et al., but not by Mcallister et al. These differences may be attributed to the different severity of injury between the two studies. Whereas Turner et al., reported fMRI results of moderate to severely injured TBI patients, Mcallister et al., reported fMRI results of mTBI patients. Although it is difficult to make a simple conclusion from these reports, the overlapping information among them suggest that there is increased activation in prefrontal cortex and medial temporal lobes with increasing working memory load.

However, alteration in activity level following mTBI is not unidirectional across various regions of the brain. Hypoactivation of language areas have also been reported in football players with concussions: left sided language areas such as inferior frontal gyrus, middle frontal gyrus, as well as angular gyrus had hypoactivation compared to control subjects during verbal learning paradigm (Terry et al. 2015). Despite the imaging findings, there was no significant difference in verbal memory paradigm performance between the TBI group and control subjects showing that the hypoactivity of language areas may be a result of a compensatory change. Thus, region dependent and task dependent hyperactivation or hypoactivation results after mTBI, and this has been reported in wide regions of frontal, temporal, parietal cortex among many others. Since discrepancy of results shown by these studies may be due to heterogeneity of the patient population, data acquisition, and imaging analysis, changes in activation patterns during task based fMRI needs further clarification

with larger number of subjects and various working memory load tasks.

Resting state fMRI and changes in network connectivity following TBI

Default mode network (DMN) is a set of brain regions composed of the following nodes: rostral anterior cingulate gyrus (rACC), superior temporal and supramarginal gyrus (SMG), posterior cingulate gyrus (PCC), and ventromedial prefrontal cortex (Greicius et al. 2003; Buckner et al. 2008). Known as a resting state network, they are more active at rest than during attention demanding tasks. It represents internal thought process and self-reflective mental activity, whereas task positive network (TPN) reviewed in the prior section has the opposite function and is activated during goal directed activity. The functional connectivity of DMN has been shown to be reduced in minimally conscious patients (Boly et al. 2009; Boly et al. 2008). Specifically, the level of connectivity correlates with the level of consciousness when comparing healthy control subjects, locked-in patients, and minimally conscious patients (Vanhaudenhuyse et al. 2010). Disruption of normal DMN function after TBI has been associated with cognitive dysfunction, as TBI patients were unable to deactivate DMN and showed impairment of inhibitory control (Bonnelle et al. 2012).

In studies of mTBI patients, hypoconnectivity of DMN has been demonstrated at early time points. In mTBI patients, reduced connectivity at major nodes of DMN such as PCC and precuneus were reported when scanned at a median time of 13 h (range: 3 h-7 days) (Iraji et al. 2015). Hypoconnectivity within the DMN was also shown at less than 3 weeks after injury, along with the finding of significant hyperconnectivity between DMN and lateral prefrontal cortex (Mayer et al. 2011).

Similarly, mTBI patients with postraumatic symptoms had reduced functional connectivity in the cingulate cortex and medial prefrontal cortex at a mean interval time of 22 days (range: 3–53 days) (Zhou et al. 2012). As a measure of global connectivity, modular organization of the network was previously analyzed in mTBI patients with a median interval time of 14 days (range: 0–90 days) (Han et al. 2014). Modularity is a parameter based on graph theory, in which high level of modularity denotes networks with stronger community structure, with higher level of connectivity than is expected by random chance. The subjects in this study were military personnel exposed to concussive blast injury, and there was reduced resting state functional connectivity between modules at 90 days after injury (Han et al. 2014).

Other networks were also reported to have altered connectivity after TBI. Reduced interhemispheric functional connectivity was shown in athletes with mTBI at 10 days after injury (Slobounov et al. 2011) and patients with mild to severe TBI (mean GCS 8, range unspecified) with apparent traumatic axonal injury visualized on MRI at a mean follow up time of 7.1 months (range unspecified) (Marquez de la Plata et al. 2011). Furthermore, this reduced interhemispheric functional connectivity was associated with deficits in cognitive performance at 1 month follow up (Sours et al. 2015). Another study showed reduced connectivity of bilateral primary somatosensory and motor cortices in soldiers who experienced mostly mTBI (only 5 of 139 had severe or moderate TBI, with a mean interval time since deployment of 31.9 ± 26.2 months) (Robinson et al. 2015). This connectivity was significantly reduced only among soldiers who were exposed to a blast at a close range only (less than 10 m away), likely due to the fact that pressure waves in a blast is highly variable depending on what obstacles are present in the nearby setting. Although these studies show wide range of follow up and injury severity, they show similarly reduced connectivity of emotion related network, motor network, and interhemispheric network at chronic time points.

Not only decreased connectivity after injury, but also increased connectivity in various regions following TBI has been reported. Among mTBI patients at 35 days after injury, there was increased functional connectivity between TPN and DMN during rest, which was associated with reduced memory function (Sours et al. 2013). There was also an increased connectivity between TPN and salience network (SN), which includes anterior insula, presupplementary motor area, and cingulate cortex. The SN has a crucial role in coordinating and regulating dynamic changes of other networks, such as shifting between internal state (such as DMN) and attentional networks (such as TPN) (Menon and Uddin 2010). This increased connectivity between TPN and SN showed that there is a disruption of segregation of DMN and TPN. Since functional connectivity between DMN and TPN increases with difficulty of a cognitive task (Bluhm et al. 2011), increased connectivity between these networks even at rest in TBI patients may indicate a pathological process. The inability to deactivate DMN even during goal oriented tasks likely contributes to cognitive dysfunction.

Functional hypoconnectivity for athletes with multiple subconcussive injuries

Similar findings of hypoconnectivity have been made among subjects who were exposed to multiple subconcussive mTBI. As previously mentioned in PET imaging sections, subconcussive mTBI is a unique entity separate from single mTBI event. Unlike patients who suffered a concussion or a single incidence of mTBI, many of the athletes who had no visible signs of neurological dysfunction may accrue hundreds to over a thousand subconcussive injuries resulting in significant functional impairment (Bailes et al. 2013). Analysis of resting state fMRI showed that football athletes, when

compared to non-collision sport athletes, had hyperconnection prior to the beginning of the practice and game schedules (Abbas et al. 2015).

It is hypothesized that multiple prior traumas strengthened collateral projections for pathways for these athletes. However, during the season, there is hypoconnectivity at 1 month and 4 months into the season, possibly due to subconcussive trauma producing reduction in neurophysiological function exceeding the compensatory response. At the post season time point, hyperconnectivity is detected again, supporting the idea of compensatory recruitment of collateral projections. Development of hypoconnectivity over time was also seen in another longitudinal analysis of football players spanning from 24 h to 30 days after a single concussion. This study demonstrated a significant DMN hypoconnectivity at 7 days, which is followed by a partial recovery at 30 days (Zhu et al. 2015).

Functional and structural connectivity

Asides from solely functional connectivity studies, several studies to date have compared the results of the functional imaging to structural imaging analysis. With the intention of validating each imaging modality, complementary information from fMRI and structural MRI such as DTI can be compared. These prior studies demonstrated functional connectivity at resting state correlating with structural connectivity (Skudlarski et al. 2008; van den Heuvel et al. 2008). Although structural connectivity and functional connectivity are interrelated, presence of one does not necessitate the presence of the other. For example, medial temporal lobe and medial prefrontal cortex have functional connectivity but no structural connectivity (Greicius et al. 2009). Such relationship is possible since indirect structural connections between the two structures will allow functional coordination of activity without direct structural link between the two regions.

Only a few studies have compared the functional and structural connectivity in the mTBI subjects. In a task related report where controls and moderate to severe TBI patients were subjected to switching motor task, there was no significant correlation between alterations in various functional connectivity parameters (connection strength, connectivity degree, regional efficiency, etc) and structural connectivity assessed by DTI (Caeyenberghs et al. 2013). This example demonstrates that functional imaging may have an important complementary role to structural imaging, since it can be more sensitive to a pathological process of mTBI than structural imaging.

Combined studies using both structural and functional modalities have only started to appear in the literature recently, but with further developments in each modality they may serve complementary roles and validate each other. Furthermore as most of the axonal injury in TBI result from subacute to chronic degeneration following the initial stretch injury and not due to the initial severing event, studies of relationships of functional connectivity and structural integrity may be performed at various timepoints following mTBI in the future studies.

In summary, mTBI leads to numerous functional changes that can be detected by fMRI studies that evaluate the functional status of the brain either during rest or during active task based paradigms. Task based paradigms showed higher activation of multiple areas, including parietal and frontal regions as well as medial temporal lobes in fMRI. However, hypoactivation of language areas such as inferior frontal, middle frontal, as well as angular gyrus has also been reported. When resting state network was evaluated, multiple regions' hypoconnectivity was noted among patients with mTBI. However, there is increased connectivity in some other studies that showed that TPN and DMN has a higher connectivity. These results imply that at mTBI causes dysregulations in connectivity at both resting and active state. Functional imaging with fMRI gives crucial insight into some of the specific measures by which mTBI leads to altered brain function: communication between regions, activation levels of various regions, and shifting between resting and active states is impaired.

Electrophysiological studies

Although EEG is not an imaging modality, it is discussed in the review due to its widespread use as a electrophyiological assessment tool and its relationship to the imaging modality magnetoencephalography. Clinical electrophysiological techniques employ technologies allowing for noninvasive examination of cerebral function and are commonly used in the setting of a TBI. Electroencephalography measures differences in electrical potential between two points where electrodes are placed. Conventional EEG in the clinical setting uses data collected from 21 scalp electrodes arranged according to the international 10–20 system (Nuwer 1997) and was the first tool which allowed characterization of cerebral physiology in post TBI patients (Sjaardema and Glaser 1942). The utilization of conventional EEG often depends upon the severity of brain injury seen in the neurocritical care assessment. Often employed in the analysis of moderate to severe TBI (Abend et al. 2010) it has only been sparingly used in patients with mTBI (Fontaine et al. 1999).

Characteristic findings of conventional EEG on TBI patients include generalized or focal slowing and attenuated alpha response (7.5–12.5 Hz frequency band). The information that is provided during these recordings allows detection of abnormal electrical patterns and has been used in prognostication in severe TBI (Leon-Carrion et al. 2008a). Although there may be a limited number of findings in mTBI, there is an association with worse recovery from TBI in patients who

have pathological findings on EEG within the first 24 h after mTBI (Hessen and Nestvold 2009). However, correlation between EEG and clinical symptoms is inconsistent in mTBI patients (Arciniegas 2011), unlike the robust correlation seen in severe TBI (Vespa et al. 2002). For this reason conventional EEG has fairly limited clinical use in patients with a mTBI without a clinical concern for underlying electrophysiological alteration such as seizures.

Using conventional EEG as a starting point there has been considerable development of tools which may provide more sophisticated analysis of physiologic parameters after injury. These include quantitative EEG (qEEG) which utilizes higher density EEG with more robust data analytical techniques. The other notable tool is magnetoencephalogram (MEG) which applies EEG to detect magnetic fields. These methods have been studied for their utility in mTBI and may have more important roles in the future with advancements in EEG technology.

As previously reviewed, older studies in 1940s–1960s found EEG changes in about half of the boxers studied, especially when EEG was performed immediately after the matches (Loosemore et al. 2007). Another review of the literature looking at studies prior to 1980s also showed inconsistent EEG findings among boxers, with the occurrence of significant EEG abnormality varying between 20 and 60% of the subjects (Haglund and Eriksson 1993). This lack of correlation between EEG abnormalities and effect of TBI from boxing has been attributed to the fact that EEGs are mainly sensitive to cortical dysfunction, leaving out the detection of much of the encephalopathy occurring in the subcortical system.

The study designs vary widely across many of these prior EEG studies on boxers. An older study of 53 boxers compared to 53 football players found no significant differences in EEG (Thomassen et al. 1979). Also, another report of 47 boxers showed no significant EEG abnormality when compared to control groups of different sport athletes (Haglund and Persson 1990). Additionally when there is an EEG abnormality, they tend to be very specific findings not reported by other EEG studies. McLatchie et al., reported regional slow activity and 7 Hz dominant discharges among a few other findings (McLatchie et al. 1987), whereas Breton et al., reported changes in electrical potentials responding to auditory stimulus (Breton et al. 1991). Consistent findings are difficult to identify among these earlier studies likely due to the differences in study designs.

Quantitative electroencephalography

Computer assisted EEG analysis allows for a more quantitative evaluation of EEG data provided. In general, qEEG refers to a number of different analytic paradigms. This includes spectral analysis (frequency over a given time), coherence (evaluation of the consistency of amplitude and phase), phase (timing of activity between channels), amplitude, and symmetry of activity (Tebano et al. 1988; Coutin-Churchman et al. 2003). Using the more robust techniques available with qEEG allows for a more detailed analysis of potential disruptions in electrophysiological activity after TBI and abnormal findings have been reported consistently in the literature (Fenton 1996; Johnstone and Thatcher 1991). This includes alterations in theta and alpha frequencies which have been utilized in statistical paradigms to identify patients with even mTBI (Randolph and Miller 1988).

To date most of the qEEG literature has focused on the utilization of specific analytical packages to provide a program capable of distinguishing patients who have experienced a TBI to those who have not (Leon-Carrion et al. 2008a; Leon-Carrion et al. 2008b). The reported accuracy of some of these methods which employ an analysis of frontal and frontal-temporal coherence and phase alterations is close to 95% (Thatcher et al. 1989; Thatcher et al. 2001). However, using the same parameters as Thatcher et al. on a qEEG, a lower values of 88% (Trudeau et al. 1998) and 79% (Thornton 1999) were also reported. Combination of more than one function analysis can increase the accuracy of mTBI detection, since using both the analysis developed by Thatcher et al. with another method resulted in 100% accuracy (Thornton 1999). Asides from using optimal analytical methods, another major challenge in mTBI detection using qEEG is the fact that many of the described disturbances are seen across a spectrum of other pathological conditions. Many of the neuropsychiatric disorders including mood disorders, dementia, and a drug abuse history may result in qEEG abnormalities, making the use of qEEG to diagnose mTBI difficult (Coutin-Churchman et al. 2003; Coburn et al. 2006).

The future of qEEG as a promising analytical technique in the TBI population lies within recent efforts to use qEEG abnormalities as a way of predicting post TBI neuropsychological performance (Thatcher et al. 2001). Some studies have also suggested that qEEG may be more sensitive to injury in mTBI than even neurocognitive testing: whereas postconcussive symptoms and neurocognitive abnormalities resolved between the time of injury and day 3 in post concussion football players, the alterations on qEEG continued up to day 8 (McCrea et al. 2010; Barr et al. 2012). There are also unique advantages of EEG which makes it a promising technique to be used in TBI management when technological advancements overcome some of the hurdles presented here. Compared to other functional detection methods, EEG also provides a very high temporal resolution information. It also allows for a continuous monitoring of brain activity for an extended period of time if necessary, unlike imaging studies which are performed in the order of seconds to minutes. The utility of qEEG as an analytical tool in mTBI patients will likely improve in the future as it may provide clinicians with

a tool for prognostication of patients and distinguish those who may need a higher level of post injury rehabilitation from those who may benefit less.

Magnetoencephalography studies

Magnetoencephalography is a functional imaging technique that detects magnetic fields emitted by activity in the brain. It can be used to detect pathological slow-waves (delta wave: 1-4 Hz frequency band) that indicate axonal injury. Based upon the principle that electrical currents generated by neural elements create weak magnetic fields, MEG is a complimentary analytical technique to EEG that may allow for analysis of larger cumulative effects of cerebral dysfunction.

Prior results of MEG at a chronic timepoint after injury (range: 2–38 months) showed that it can detect abnormal activities in mTBI patients who had no MRI findings (Lewine et al. 1999). Another study using MEG in mTBI patients at a mean time of 8.2 months (range: 4 weeks-3 years) showed that MEG can reveal regions of injury with high detection rates of 87% (Huang et al. 2012). Moreover, detection of slow waves by MEG in prefrontal areas correlated with neurobehavioral changes seen after concussion (Huang et al. 2014). However, there are many directions of research that is needed for the use MEG in mTBI patients. How MEG activity changes over the time course of recovery is unclear. Furthermore, what these alterations acutely mean for long term recovery is yet to be clearly identified. Currently the state of the technology for MEG requires cost similar to that of a high field MRI scanner. A dedicated shielded room is also required since MEG is measured by a superconducting quantum interference device (SQUID) which is a costly equipment to purchase and maintain. This makes MEG an expensive correlate to other imaging and electrophysiological modalities available. Despite the costs and many aspects of the technique that are currently unknown, MEG may have a role in future research for mTBI subjects due to its complimentary function to EEG and unique parameter that is monitored: magnetic field generated by neural activity (Lee and Huang 2014).

Limitations of current metabolic imaging

The most important limitations that invegstigators must be aware of prior to using the information gained from previously reported studies is the importance of timing of the study after injury. The cellular cascade of events and metabolic changes are highly dependent on the exact timing after injury as these metabolic disruptions are constantly changing within the timeline of hours to days to weeks. Moreoever, these changes can vary in their timeline across different regions of the brain, making generalizations immensely difficult. Although we divided the studies by broad categories of acute and chronic, further studies and analysis are warranted in the future to fully characterize functional and metabolic changes after TBI.

Differences in injury types should also be considered when comparing studies. It has been well known that the trauma from motor vehicle accident, fall, sports injury, and combat blast injury all have different biomechanical loading pattern. For example, several studies of blast injury have been cited here in this review (Han et al. 2014; Huang et al. 2012; Levin et al. 2010; Robinson et al. 2015), but biomechanical effect of a blast were described to be different than that of blunt trauma as previously reviewed (Courtney and Courtney 2015). For example, unlike blunt injury which is mainly due to translational or rotational acceleration of the brain leading to axonal injury and damage to the vasculature, blast injury also entails direct cranial entry of the pressure wave and increased thoracic pressure propagating to the brain directly or via increased blood pressure. Morever, blast injury does not occur in isolation and is often accompanied by body injury from other projectiles at the time of the blast. Due to the unique differences between these injury modalities, the results of metabolic imaging from blast injury compared to blunt injury may have important differences that have not yet been well characterized.

Additionally while most of the studies included in this review focus on adult population and only a few have studied pediatric population (Gowda et al. 2006; Agrawal et al. 2005), metabolic derangements following TBI cannot be directly compared between adults and children. Given that neurogenesis is influenced by exposure to sex hormones (Spritzer and Galea 2007; Galea et al. 2013), throughout sexual maturation and during adolescence the process of cerebral maturation differ between the two sexes. Moreover, cerebral maturation has been shown to continue well into the second decade of life making (Paus 2005). Comparison of various studies and formulation of conclusion is difficult given numerous variables described in this report that can influence the metabolic changes following TBI.

As previously mentioned in a SPECT section, comorbidities that often occur with TBI make interpretation of metabolic imaging difficult. Headache, depression, post traumatic sleep disorder (PTSD), psychiatric disorders are often found in TBI patients (Alway et al. 2016; Roy et al. 2015; Amen et al. 2015; Davenport et al. 2016). In addition to TBI, these pathological states result in abnormal cerebral perfusion, glucose or oxygen metabolism, as well as functional connectivity making it difficult to distinguish if the imaging findings are a result of TBI or its associated comordities. However, this is not a limitation specific to metabolic imaging as structural imaging methods such as DTI have also shown to be affected by comorbidities such as PTSD, confounding its interpretation (Davenport et al. 2016).

In metabolic imaging using PET, the quantification of radiolabeled tracers such as FDG is based on mathematical kinetic modeling which makes several assumptions. When the PET tracer is initially injected, the concentration of tracer will be different between the blood and tissue due to plasma clearance. However, constant infusion of the tracer is performed to achieve steady state of the tracer and the tracer is assumed to be freely diffusible. These assumptions in a pathological state such as TBI may have limitations given the alterations in permeability of blood brain barrier as well as changes in electrolyte, fluid, and cellular contents between blood and parenchymal compartments.

Also in a pathological setting such as stroke, parameters such as lumped constant can be variable and non-uniform over the whole brain (Gjedde et al. 1985). Lumped constant, a number that is used to describe the relationship between FDG and glucose in terms of transport and phosphorylation, may similarly be very different depending on the site, severity, and time course of injury following TBI. Various factors such as neoplasia, ischemia, or hypoglycemia have all shown to result in variety of lumped constants (Spence et al. 1998; Crane et al. 1981), further bringing into question that PET imaging in TBI may need more robust body of evidence in the future for validation.

One unique feature of PET studies is that they are performed with the subjects' eyes open, which means that any electrophysiologic changes due to physiologic neuronal activity or seizures can increase the ligand uptake, not only the pathophysiological change after TBI such as increased blood brain barrier permeability. Imaging studies using PET with the subjects' eyes open can thus be influenced by these additional factors unlike fMRI.

Although fMRI studies are useful tools in indirect assessment of cerebral blood flow and connectivity in different brain regions following TBI, it suffers from the fact that TBI can result in uncoupling of cerebral blood flow to neuronal firing. In normal physiology, the linear relationship between BOLD signal and neural activity has been robustly demonstrated (Logothetis et al. 2001). However, following TBI there are various alterations in regional CBF (Giza and Hovda 2001; Jantzen et al. 2004) which is partially due to uncoupling of CBF from neuronal firing (Toth et al. 2016). An animal study with rat model of TBI demonstrated that recovery of BOLD response is associated with density of myelinated fibers, indicating that uncoupling of CBF to neural signals may be due to destruction of signaling pathways to enhance blood flow to a particular area (Niskanen et al. 2013). Thus, fMRI changes seen in TBI subjects may be a combination of pathological or compensatory changes in blood flow, as well as the effect of uncoupling.

Conclusions

Detection of injury in mTBI is a challenge that has recently been brought to the attention of TBI researchers and clinicians. Cellular and molecular basis of injury can be overlooked when only structural abnormalities are searched using either conventional imaging (CT, MRI) or DTI. Integration of both structural and functional imaging data will likely increase the accuracy of detection. While one imaging modality may have a strength in detection of particular pathology (e.g. DTI for white matter injury), there are disadvantages of each modality such as false positive connections detected by DTI at crossing fibers and large vessel effects in fMRI. There are also high regional and time dependent metabolic changes which must be taken into account when interpreting the studies as mentioned in this review, given that metabolic change occurring after TBI is a dynamic process and also greatly differs depending on the region. However, these problems arise from the fact that many of these techniques have not been well characterized yet in the setting of mTBI.

Since mTBI imaging has been a very strong interest in the TBI community in the last 10 to 15 years, many of the studies still require validation. Prior TBI research has focused heavily on clinical management of severe TBI, as well as preclinical research on pathological mechanisms and therapeutic agents for TBI. Structural imaging with MRI and CT became accepted and widespread through the 80 and early 90s, and afterwards PET, fMRI, SPECT have been reported in larger presence through the 90s (Hutton 2014; Paans 1997; Walker et al. 2004). Their use in mTBI have become more common in the literature since the early 2000s. Newer promising techniques such as qEEG has advantages of high temporal resolution and MEG has advantage of high sensitivity to injury, but the body of literature is not large enough to make assessments about the insight they provide. These techniques may also require further development and characterization prior to generalized use in large population of mTBI patients.

Despite the heterogeneity of some of the protocols and reported data in the literature, important information is gathered from the review of the broad spectrum of functional and metabolic imaging literature in mTBI. Nuclear imaging with PET and SPECT has shown valuable insights into metabolic changes in mTBI: SPECT studies have generally shown hypoperfusion of various regions mostly in the frontal lobe at both acute and chronic time points. Although PET imaging on acute mTBI is underreported in the literature, chronic studies have shown decreased glucose metabolism at wide range of areas that are both cortical and subcortical. There is also a wide body of literature on chronic changes among athletes who were subjected to repetitive mTBI. These studies demonstrate there are extensive neurodegenerative and neuroinflammatory changes over time. In fMRI studies, resting state imaging has generally shown reduced functional

connectivity. However, fMRI studies with task based paradigms showed that there is region dependent hyper- or hypoactivity after mTBI. Since spatial and temporal resolution of each imaging modality will likely improve over the next few decades with advancing technology, the sensitivity and specificity for detecting small and subtle areas of injury will naturally improve. Additionally, combining structural and functional imaging methods will increase the detection of injury in the clinical setting and help in understanding of mTBI. With advancements in metabolic and functional imaging, these techniques used in combination with structural imaging will lead to exciting new insights on pathological mechanisms as well as novel treatment regimen for millions of patients currently suffering from mTBI.

Compliance with ethical standards

Funding This study was not funded my any agency.

Conflict of interest The authors report no conflict of interest in this study.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Abbas, K., Shenk, T. E., Poole, V. N., Breedlove, E. L., Leverenz, L. J., Nauman, E. A., et al. (2015). Alteration of default mode network in high school football athletes due to repetitive subconcussive mild traumatic brain injury: a resting-state functional magnetic resonance imaging study. *Brain Connectivity, 5*(2), 91–101.

Abdel-Dayem, H. M., Abu-Judeh, H., Kumar, M., Atay, S., Naddaf, S., El-Zeftawy, H., et al. (1998). SPECT brain perfusion abnormalities in mild or moderate traumatic brain injury. *Clinical Nuclear Medicine, 23*(5), 309–317.

Abend, N. S., Dlugos, D. J., Hahn, C. D., Hirsch, L. J., & Herman, S. T. (2010). Use of EEG monitoring and management of non-convulsive seizures in critically ill patients: a survey of neurologists. *Neurocritical Care, 12*(3), 382–389.

Abu-Judeh, H. H., Singh, M., Masdeu, J. C., & Abdel-Dayem, H. M. (1998). Discordance between FDG uptake and technetium-99 m-HMPAO brain perfusion in acute traumatic brain injury. *Journal of Nuclear Medicine, 39*(8), 1357–1359.

Agrawal, D., Gowda, N. K., Bal, C. S., Pant, M., & Mahapatra, A. K. (2005). Is medial temporal injury responsible for pediatric postconcussion syndrome? A prospective controlled study with single-photon emission computerized tomography. *Journal of Neurosurgery, 102*(2 Suppl), 167–171.

Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics, 4*(3), 316–329.

Alway, Y., McKay, A., Gould, K. R., Johnston, L., & Ponsford, J. (2016). Factors associated with posttraumatic stress disorder following moderate to severe traumatic brain injury: a prospective study. *Depression and Anxiety, 33*(1), 19–26.

Amen, D. G., Raji, C. A., Willeumier, K., Taylor, D., Tarzwell, R., Newberg, A., et al. (2015). Functional neuroimaging distinguishes posttraumatic stress disorder from traumatic brain injury in focused and large community datasets. *PloS One, 10*(7), e0129659.

Andersen, A. R. (1989). 99mTc-D,L-hexamethylene-propyleneamine oxime (99mTc-HMPAO): basic kinetic studies of a tracer of cerebral blood flow. *Cerebrovascular and Brain Metabolism Reviews, 1*(4), 288–318.

Aoki, Y., Inokuchi, R., Gunshin, M., Yahagi, N., & Suwa, H. (2012). Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis. *Journal of Neurology, Neurosurgery, and Psychiatry, 83*(9), 870–876.

Arciniegas, D. B. (2011). Clinical electrophysiologic assessments and mild traumatic brain injury: state-of-the-science and implications for clinical practice. *International Journal of Psychophysiology, 82*(1), 41–52.

Attwell, D., Buchan, A. M., Charpak, S., Lauritzen, M., Macvicar, B. A., & Newman, E. A. (2010). Glial and neuronal control of brain blood flow. *Nature, 468*(7321), 232–243.

Bailes, J. E., Petraglia, A. L., Omalu, B. I., Nauman, E., & Talavage, T. (2013). Role of subconcussion in repetitive mild traumatic brain injury. *Journal of Neurosurgery, 119*(5), 1235–1245.

Barbeau, E. B., Lewis, J. D., Doyon, J., Benali, H., Zeffiro, T. A., & Mottron, L. (2015). A greater involvement of posterior brain areas in interhemispheric transfer in autism: fMRI, DWI and behavioral evidences. *Neuroimage Clin, 8*, 267–280.

Barr, W. B., Prichep, L. S., Chabot, R., Powell, M. R., & McCrea, M. (2012). Measuring brain electrical activity to track recovery from sport-related concussion. *Brain Injury, 26*(1), 58–66.

Barrio, J. R., Small, G. W., Wong, K. P., Huang, S. C., Liu, J., Merrill, D. A., et al. (2015). In vivo characterization of chronic traumatic encephalopathy using [F-18]FDDNP PET brain imaging. *Proceedings of the National Academy of Sciences of the United States of America, 112*(16), E2039–E2047.

Bergsneider, M., Hovda, D. A., Shalmon, E., Kelly, D. F., Vespa, P. M., Martin, N. A., et al. (1997). Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *Journal of Neurosurgery, 86*(2), 241–251.

Bigler, E. D., & Maxwell, W. L. (2012). Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. *Brain Imaging and Behavior, 6*(2), 108–136.

Bluhm, R. L., Clark, C. R., McFarlane, A. C., Moores, K. A., Shaw, M. E., & Lanius, R. A. (2011). Default network connectivity during a working memory task. *Human Brain Mapping, 32*(7), 1029–1035.

Blumbergs, P. C., Scott, G., Manavis, J., Wainwright, H., Simpson, D. A., & McLean, A. J. (1994). Staining of amyloid precursor protein to study axonal damage in mild head injury. *Lancet, 344*(8929), 1055–1056.

Blumbergs, P. C., Scott, G., Manavis, J., Wainwright, H., Simpson, D. A., & McLean, A. J. (1995). Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. *Journal of Neurotrauma, 12*(4), 565–572.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T. T., et al. (2008). Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? *Annals of the New York Academy of Sciences, 1129*, 119–129.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., et al. (2009). Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping, 30*(8), 2393–2400.

Bonne, O., Gilboa, A., Louzoun, Y., Kempf-Sherf, O., Katz, M., Fishman, Y., et al. (2003). Cerebral blood flow in chronic symptomatic mild traumatic brain injury. *Psychiatry Research, 124*(3), 141–152.

Bonnelle, V., Ham, T. E., Leech, R., Kinnunen, K. M., Mehta, M. A., Greenwood, R. J., et al. (2012). Salience network integrity predicts default mode network function after traumatic brain injury.

Proceedings of the National Academy of Sciences of the United States of America, 109(12), 4690–4695.

Bramlett, H. M., & Dietrich, W. D. (2015). Long-term consequences of traumatic brain injury: current status of potential mechanisms of injury and neurological outcomes. *Journal of Neurotrauma, 32*(23), 1834–1848.

Breton, F., Pincemaille, Y., Tarriere, C., & Renault, B. (1991). Event-related potential assessment of attention and the orienting reaction in boxers before and after a fight. *Biological Psychology, 31*(1), 57–71.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124*, 1–38.

Buki, A., Okonkwo, D. O., & Povlishock, J. T. (1999). Postinjury cyclosporin a administration limits axonal damage and disconnection in traumatic brain injury. *Journal of Neurotrauma, 16*(6), 511–521.

Buxton, R. B., Wong, E. C., & Frank, L. R. (1998). Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. *Magnetic Resonance in Medicine, 39*(6), 855–864.

Buxton, R. B., Uludag, K., Dubowitz, D. J., & Liu, T. T. (2004). Modeling the hemodynamic response to brain activation. *NeuroImage, 23*(Suppl 1), S220–S233.

Caeyenberghs, K., Leemans, A., Leunissen, I., Michiels, K., & Swinnen, S. P. (2013). Topological correlations of structural and functional networks in patients with traumatic brain injury. *Frontiers in Human Neuroscience, 7*, 726.

Chen, S. H., Kareken, D. A., Fastenau, P. S., Trexler, L. E., & Hutchins, G. D. (2003). A study of persistent post-concussion symptoms in mild head trauma using positron emission tomography. *Journal of Neurology, Neurosurgery, and Psychiatry, 74*(3), 326–332.

Coburn, K. L., Lauterbach, E. C., Boutros, N. N., Black, K. J., Arciniegas, D. B., & Coffey, C. E. (2006). The value of quantitative electroencephalography in clinical psychiatry: a report by the committee on research of the American neuropsychiatric association. *The Journal of Neuropsychiatry and Clinical Neurosciences, 18*(4), 460–500.

Coughlin, J. M., Wang, Y., Munro, C. A., Ma, S., Yue, C., Chen, S., et al. (2015). Neuroinflammation and brain atrophy in former NFL players: an in vivo multimodal imaging pilot study. *Neurobiology of Disease, 74*, 58–65.

Courtney, A., & Courtney, M. (2015). The complexity of biomechanics causing primary blast-induced traumatic brain injury: a review of potential mechanisms. *Frontiers in Neurology, 6*, 221.

Coutin-Churchman, P., Anez, Y., Uzcategui, M., Alvarez, L., Vergara, F., Mendez, L., et al. (2003). Quantitative spectral analysis of EEG in psychiatry revisited: drawing signs out of numbers in a clinical setting. *Clinical Neurophysiology, 114*(12), 2294–2306.

Crane, P. D., Pardridge, W. M., Braun, L. D., Nyerges, A. M., & Oldendorf, W. H. (1981). The interaction of transport and metabolism on brain glucose utilization: a reevaluation of the lumped constant. *Journal of Neurochemistry, 36*(4), 1601–1604.

Cubon, V. A., Putukian, M., Boyer, C., & Dettwiler, A. (2011). A diffusion tensor imaging study on the white matter skeleton in individuals with sports-related concussion. *Journal of Neurotrauma, 28*(2), 189–201.

Davenport, N. D., Lamberty, G. J., Nelson, N. W., Lim, K. O., Armstrong, M. T., & Sponheim, S. R. (2016). PTSD confounds detection of compromised cerebral white matter integrity in military veterans reporting a history of mild traumatic brain injury. *Brain Injury, 30*(12), 1491–1500.

Delouche, A., Attye, A., Heck, O., Grand, S., Kastler, A., Lamalle, L., et al. (2016). Diffusion MRI: pitfalls, literature review and future directions of research in mild traumatic brain injury. *European Journal of Radiology, 85*(1), 25–30.

Dusick, J. R., Glenn, T. C., Lee, W. N., Vespa, P. M., Kelly, D. F., Lee, S. M., et al. (2007). Increased pentose phosphate pathway flux after clinical traumatic brain injury: a [1,2-13C2]glucose labeling study in humans. *Journal of Cerebral Blood Flow and Metabolism, 27*(9), 1593–1602.

Fenton, G. W. (1996). The postconcussional syndrome reappraised. *Clinical Electroencephalography, 27*(4), 174–182.

Fishman, I., Datko, M., Cabrera, Y., Carper, R. A., & Muller, R. A. (2015). Reduced integration and differentiation of the imitation network in autism: a combined functional connectivity magnetic resonance imaging and diffusion-weighted imaging study. *Annals of Neurology, 78*(6), 958–969.

Folkersma, H., Boellaard, R., Yaqub, M., Kloet, R. W., Windhorst, A. D., Lammertsma, A. A., et al. (2011). Widespread and prolonged increase in (R)-(11)C-PK11195 binding after traumatic brain injury. *Journal of Nuclear Medicine, 52*(8), 1235–1239.

Fontaine, A., Azouvi, P., Remy, P., Bussel, B., & Samson, Y. (1999). Functional anatomy of neuropsychological deficits after severe traumatic brain injury. *Neurology, 53*(9), 1963–1968.

Galea, L. A., Wainwright, S. R., Roes, M. M., Duarte-Guterman, P., Chow, C., & Hamson, D. K. (2013). Sex, hormones and neurogenesis in the hippocampus: hormonal modulation of neurogenesis and potential functional implications. *Journal of Neuroendocrinology, 25*(11), 1039–1061.

Gatson, J. W., Stebbins, C., Mathews, D., Harris, T. S., Madden, C., Batjer, H., et al. (2016). Evidence of increased brain amyloid in severe TBI survivors at 1, 12, and 24 months after injury: report of 2 cases. *Journal of Neurosurgery, 124*(6), 1646–1653.

Gentry, L. R., Godersky, J. C., & Thompson, B. (1988). MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. *AJR. American Journal of Roentgenology, 150*(3), 663–672.

Giza, C. C., & Hovda, D. A. (2001). The Neurometabolic Cascade of concussion. *Journal of Athletic Training, 36*(3), 228–235.

Gjedde, A., Wienhard, K., Heiss, W. D., Kloster, G., Diemer, N. H., Herholz, K., et al. (1985). Comparative regional analysis of 2-fluorodeoxyglucose and methylglucose uptake in brain of four stroke patients. With special reference to the regional estimation of the lumped constant. *Journal of Cerebral Blood Flow and Metabolism, 5*(2), 163–178.

Glenn, T. C., Kelly, D. F., Boscardin, W. J., McArthur, D. L., Vespa, P., Oertel, M., et al. (2003). Energy dysfunction as a predictor of outcome after moderate or severe head injury: indices of oxygen, glucose, and lactate metabolism. *Journal of Cerebral Blood Flow and Metabolism, 23*(10), 1239–1250.

Gowda, N. K., Agrawal, D., Bal, C., Chandrashekar, N., Tripati, M., Bandopadhyaya, G. P., et al. (2006). Technetium Tc-99 m ethyl cysteinate dimer brain single-photon emission CT in mild traumatic brain injury: a prospective study. *AJNR. American Journal of Neuroradiology, 27*(2), 447–451.

Grady, M. S., McLaughlin, M. R., Christman, C. W., Valadka, A. B., Fligner, C. L., & Povlishock, J. T. (1993). The use of antibodies targeted against the neurofilament subunits for the detection of diffuse axonal injury in humans. *Journal of Neuropathology and Experimental Neurology, 52*(2), 143–152.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America, 100*(1), 253–258.

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex, 19*(1), 72–78.

Gross, H., Kling, A., Henry, G., Herndon, C., & Lavretsky, H. (1996). Local cerebral glucose metabolism in patients with long-term behavioral and cognitive deficits following mild traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences, 8*(3), 324–334.

Haglund, Y., & Eriksson, E. (1993). Does amateur boxing lead to chronic brain damage? A review of some recent investigations. *The American Journal of Sports Medicine, 21*(1), 97–109.

Haglund, Y., & Persson, H. E. (1990). Does Swedish amateur boxing lead to chronic brain damage? 3. A retrospective clinical neurophysiological study. *Acta Neurologica Scandinavica, 82*(6), 353–360.

Hagmann, P., Jonasson, L., Maeder, P., Thiran, J. P., Wedeen, V. J., & Meuli, R. (2006). Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. *Radiographics, 26*(Suppl 1), S205–S223.

Han, K., Mac Donald, C. L., Johnson, A. M., Barnes, Y., Wierzechowski, L., Zonies, D., et al. (2014). Disrupted modular organization of resting-state cortical functional connectivity in U.S. military personnel following concussive 'mild' blast-related traumatic brain injury. *NeuroImage, 84*, 76–96.

Hattori, N., Huang, S. C., Wu, H. M., Liao, W., Glenn, T. C., Vespa, P. M., et al. (2003). PET investigation of post-traumatic cerebral blood volume and blood flow. *Acta Neurochirurgica. Supplement, 86*, 49–52.

Hattori, N., Swan, M., Stobbe, G. A., Uomoto, J. M., Minoshima, S., Djang, D., et al. (2009). Differential SPECT activation patterns associated with PASAT performance may indicate frontocerebellar functional dissociation in chronic mild traumatic brain injury. *Journal of Nuclear Medicine, 50*(7), 1054–1061.

Hessen, E., & Nestvold, K. (2009). Indicators of complicated mild TBI predict MMPI-2 scores after 23 years. *Brain Injury, 23*(3), 234–242.

Honce, J. M., Nyberg, E., Jones, I., & Nagae, L. (2016). Neuroimaging of concussion. *Physical Medicine and Rehabilitation Clinics of North America, 27*(2), 411–428.

Hong, Y. T., Veenith, T., Dewar, D., Outtrim, J. G., Mani, V., Williams, C., et al. (2014). Amyloid imaging with carbon 11-labeled Pittsburgh compound B for traumatic brain injury. *JAMA Neurology, 71*(1), 23–31.

Huang, M. X., Nichols, S., Robb, A., Angeles, A., Drake, A., Holland, M., et al. (2012). An automatic MEG low-frequency source imaging approach for detecting injuries in mild and moderate TBI patients with blast and non-blast causes. *NeuroImage, 61*(4), 1067–1082.

Huang, M. X., Nichols, S., Baker, D. G., Robb, A., Angeles, A., Yurgil, K. A., et al. (2014). Single-subject-based whole-brain MEG slow-wave imaging approach for detecting abnormality in patients with mild traumatic brain injury. *Neuroimage Clin, 5*, 109–119.

Humayun, M. S., Presty, S. K., Lafrance, N. D., Holcomb, H. H., Loats, H., Long, D. M., et al. (1989). Local cerebral glucose abnormalities in mild closed head injured patients with cognitive impairments. *Nuclear Medicine Communications, 10*(5), 335–344.

Hunter, J. V., Wilde, E. A., Tong, K. A., & Holshouser, B. A. (2012). Emerging imaging tools for use with traumatic brain injury research. *Journal of Neurotrauma, 29*(4), 654–671.

Hutton, B. F. (2014). The origins of SPECT and SPECT/CT. *European Journal of Nuclear Medicine and Molecular Imaging, 41*(Suppl 1), S3–16.

Inglese, M., Makani, S., Johnson, G., Cohen, B. A., Silver, J. A., Gonen, O., et al. (2005). Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *Journal of Neurosurgery, 103*(2), 298–303.

Iraji, A., Benson, R. R., Welch, R. D., O'Neil, B. J., Woodard, J. L., Ayaz, S. I., et al. (2015). Resting state functional connectivity in mild traumatic brain injury at the acute stage: independent component and seed-based analyses. *Journal of Neurotrauma, 32*(14), 1031–1045.

Israel, I., Ohsiek, A., Al-Momani, E., Albert-Weissenberger, C., Stetter, C., Mencl, S., et al. (2016). Combined [(18)F]DPA-714 micropositron emission tomography and autoradiography imaging of microglia activation after closed head injury in mice. *Journal of Neuroinflammation, 13*(1), 140.

Jacobs, A., Put, E., Ingels, M., Put, T., & Bossuyt, A. (1996). One-year follow-up of technetium-99 m-HMPAO SPECT in mild head injury. *Journal of Nuclear Medicine, 37*(10), 1605–1609.

Jantzen, K. J., Anderson, B., Steinberg, F. L., & Kelso, J. A. (2004). A prospective functional MR imaging study of mild traumatic brain injury in college football players. *AJNR. American Journal of Neuroradiology, 25*(5), 738–745.

Jarbo, K., & Verstynen, T. D. (2015). Converging structural and functional connectivity of orbitofrontal, dorsolateral prefrontal, and posterior parietal cortex in the human striatum. *The Journal of Neuroscience, 35*(9), 3865–3878.

Jbabdi, S., & Johansen-Berg, H. (2011). Tractography: where do we go from here? *Brain Connectivity, 1*(3), 169–183.

Johnson, V. E., Stewart, W., & Smith, D. H. (2013). Axonal pathology in traumatic brain injury. *Experimental Neurology, 246*, 35–43.

Johnstone, J., & Thatcher, R. W. (1991). Quantitative EEG analysis and rehabilitation issues in mild traumatic brain injury. *Journal of Insurance Medicine, 23*(4), 228–232.

Jorge, R. E., Acion, L., White, T., Tordesillas-Gutierrez, D., Pierson, R., Crespo-Facorro, B., et al. (2012). White matter abnormalities in veterans with mild traumatic brain injury. *The American Journal of Psychiatry, 169*(12), 1284–1291.

Kant, R., Smith-Seemiller, L., Isaac, G., & Duffy, J. (1997). Tc-HMPAO SPECT in persistent post-concussion syndrome after mild head injury: comparison with MRI/CT. *Brain Injury, 11*(2), 115–124.

Kennedy, M. R., Wozniak, J. R., Muetzel, R. L., Mueller, B. A., Chiou, H. H., Pantekoek, K., et al. (2009). White matter and neurocognitive changes in adults with chronic traumatic brain injury. *Journal of the International Neuropsychological Society, 15*(1), 130–136.

Koerte, I. K., Hufschmidt, J., Muehlmann, M., Lin, A. P., & Shenton, M. E. (2016). Advanced Neuroimaging of Mild Traumatic Brain Injury. In D. Laskowitz, & G. Grant (Eds.), *Translational Research in Traumatic Brain Injury* (Frontiers in Neuroscience). Boca Raton (FL).

Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain, 130*(Pt 10), 2508–2519.

Krishnamurthy, K., & Laskowitz, D. T. (2016). Cellular and Molecular Mechanisms of Secondary Neuronal Injury following Traumatic Brain Injury. In D. Laskowitz, & G. Grant (Eds.), *Translational Research in Traumatic Brain Injury* (Frontiers in Neuroscience). Boca Raton (FL).

Laskowski, R. A., Creed, J. A., & Raghupathi, R. (2015). Pathophysiology of Mild TBI: Implications for Altered Signaling Pathways. In F. H. Kobeissy (Ed.), *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects* (Frontiers in Neuroengineering). Boca Raton (FL).

Lee, R. R., & Huang, M. (2014). Magnetoencephalography in the diagnosis of concussion. *Progress in Neurological Surgery, 28*, 94–111.

Len, T. K., & Neary, J. P. (2011). Cerebrovascular pathophysiology following mild traumatic brain injury. *Clinical Physiology and Functional Imaging, 31*(2), 85–93.

Leon-Carrion, J., Martin-Rodriguez, J. F., Damas-Lopez, J., Barroso y Martin, J. M., & Dominguez-Morales, M. R. (2008a). Brain function in the minimally conscious state: a quantitative neurophysiological study. *Clinical Neurophysiology, 119*(7), 1506–1514.

Leon-Carrion, J., Martin-Rodriguez, J. F., Damas-Lopez, J., Martin, J. M., & Dominguez-Morales Mdel, R. (2008b). A QEEG index of level of functional dependence for people sustaining acquired brain injury: the Seville independence index (SINDI). *Brain Injury, 22*(1), 61–74.

Leveille, J., Demonceau, G., & Walovitch, R. C. (1992). Intrasubject comparison between technetium-99 m-ECD and technetium-99 m-HMPAO in healthy human subjects. *Journal of Nuclear Medicine, 33*(4), 480–484.

Levin, H. S., Wilde, E., Troyanskaya, M., Petersen, N. J., Scheibel, R., Newsome, M., et al. (2010). Diffusion tensor imaging of mild to moderate blast-related traumatic brain injury and its sequelae. *Journal of Neurotrauma, 27*(4), 683–694.

Lewine, J. D., Davis, J. T., Sloan, J. H., Kodituwakku, P. W., & Orrison Jr., W. W. (1999). Neuromagnetic assessment of pathophysiologic brain activity induced by minor head trauma. *AJNR. American Journal of Neuroradiology, 20*(5), 857–866.

Lipton, M. L., Gulko, E., Zimmerman, M. E., Friedman, B. W., Kim, M., Gellella, E., et al. (2009). Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology, 252*(3), 816–824.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*(6843), 150–157.

Loosemore, M., Knowles, C. H., & Whyte, G. P. (2007). Amateur boxing and risk of chronic traumatic brain injury: systematic review of observational studies. *BMJ, 335*(7624), 809.

MacFarlane, M. P., & Glenn, T. C. (2015). Neurochemical cascade of concussion. *Brain Injury, 29*(2), 139–153.

Magistretti, P. J., & Pellerin, L. (1996). The contribution of astrocytes to the 18F-2-deoxyglucose signal in PET activation studies. *Molecular Psychiatry, 1*(6), 445–452.

Magistretti, P. J., Pellerin, L., Rothman, D. L., & Shulman, R. G. (1999). Energy on demand. *Science, 283*(5401), 496–497.

Marks, W., Lasek, J., Witkowski, Z., Lass, P., Deja, W., Bialko, M., et al. (2006). Early brain spect in patients after minor craniocerebral trauma. *The Neuroradiology Journal, 19*(5), 569–576.

Marquez de la Plata, C. D., Garces, J., Shokri Kojori, E., Grinnan, J., Krishnan, K., Pidikiti, R., et al. (2011). Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. *Archives of Neurology, 68*(1), 74–84.

Mattioli, F., Grassi, F., Perani, D., Cappa, S. F., Miozzo, A., & Fazio, F. (1996). Persistent post-traumatic retrograde amnesia: a neuropsychological and (18F)FDG PET study. *Cortex, 32*(1), 121–129.

Mayer, A. R., Mannell, M. V., Ling, J., Gasparovic, C., & Yeo, R. A. (2011). Functional connectivity in mild traumatic brain injury. *Human Brain Mapping, 32*(11), 1825–1835.

McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., et al. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study. *Neurology, 53*(6), 1300–1308.

McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. *NeuroImage, 14*(5), 1004–1012.

McCrea, M., Prichep, L., Powell, M. R., Chabot, R., & Barr, W. B. (2010). Acute effects and recovery after sport-related concussion: a neurocognitive and quantitative brain electrical activity study. *The Journal of Head Trauma Rehabilitation, 25*(4), 283–292.

McCrory, P., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M., et al. (2009). Consensus statement on concussion in sport: the 3rd international conference on concussion in sport held in Zurich, November 2008. *Journal of Athletic Training, 44*(4), 434–448.

McLatchie, G., Brooks, N., Galbraith, S., Hutchison, J. S., Wilson, L., Melville, I., et al. (1987). Clinical neurological examination, neuropsychology, electroencephalography and computed tomographic head scanning in active amateur boxers. *Journal of Neurology, Neurosurgery, and Psychiatry, 50*(1), 96–99.

Mendez, M. F., Owens, E. M., Reza Berenji, G., Peppers, D. C., Liang, L. J., & Licht, E. A. (2013). Mild traumatic brain injury from primary blast vs. blunt forces: post-concussion consequences and functional neuroimaging. *Neuro Rehabilitation, 32*(2), 397–407.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function, 214*(5–6), 655–667.

Messe, A., Caplain, S., Paradot, G., Garrigue, D., Mineo, J. F., Soto Ares, G., et al. (2011). Diffusion tensor imaging and white matter lesions at the subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment. *Human Brain Mapping, 32*(6), 999–1011.

Mitsis, E. M., Riggio, S., Kostakoglu, L., Dickstein, D. L., Machac, J., Delman, B., et al. (2014). Tauopathy PET and amyloid PET in the diagnosis of chronic traumatic encephalopathies: studies of a retired NFL player and of a man with FTD and a severe head injury. *Translational Psychiatry, 4*, e441.

Mouzon, B. C., Bachmeier, C., Ferro, A., Ojo, J. O., Crynen, G., Acker, C. M., et al. (2014). Chronic neuropathological and neurobehavioral changes in a repetitive mild traumatic brain injury model. *Annals of Neurology, 75*(2), 241–254.

Nakayama, N., Okumura, A., Shinoda, J., Nakashima, T., & Iwama, T. (2006). Relationship between regional cerebral metabolism and consciousness disturbance in traumatic diffuse brain injury without large focal lesions: an FDG-PET study with statistical parametric mapping analysis. *Journal of Neurology, Neurosurgery, and Psychiatry, 77*(7), 856–862.

Newton, M. R., Greenwood, R. J., Britton, K. E., Charlesworth, M., Nimmon, C. C., Carroll, M. J., et al. (1992). A study comparing SPECT with CT and MRI after closed head injury. *Journal of Neurology, Neurosurgery, and Psychiatry, 55*(2), 92–94.

Niogi, S. N., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R. A., Sarkar, R., et al. (2008). Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3 T diffusion tensor imaging study of mild traumatic brain injury. *AJNR. American Journal of Neuroradiology, 29*(5), 967–973.

Niskanen, J. P., Airaksinen, A. M., Sierra, A., Huttunen, J. K., Nissinen, J., Karjalainen, P. A., et al. (2013). Monitoring functional impairment and recovery after traumatic brain injury in rats by FMRI. *Journal of Neurotrauma, 30*(7), 546–556.

Nuwer, M. (1997). Assessment of digital EEG, quantitative EEG, and EEG brain mapping: report of the American Academy of Neurology and the American clinical neurophysiology society. *Neurology, 49*(1), 277–292.

O'Donnell, L. J., & Pasternak, O. (2015). Does diffusion MRI tell us anything about the white matter? An overview of methods and pitfalls. *Schizophrenia Research, 161*(1), 133–141.

Paans, A. M. (1997). Positron emission tomography: background, possibilities and perspectives in neuroscience. *Acta Neurologica Belgica, 97*(3), 150–153.

Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends in Cognitive Sciences, 9*(2), 60–68.

Peerless, S. J., & Rewcastle, N. B. (1967). Shear injuries of the brain. *Canadian Medical Association Journal, 96*(10), 577–582.

Peskind, E. R., Petrie, E. C., Cross, D. J., Pagulayan, K., McCraw, K., Hoff, D., et al. (2011). Cerebrocerebellar hypometabolism associated with repetitive blast exposure mild traumatic brain injury in 12 Iraq war veterans with persistent post-concussive symptoms. *NeuroImage, 54*(Suppl 1), S76–S82.

Petrie, E. C., Cross, D. J., Yarnykh, V. L., Richards, T., Martin, N. M., Pagulayan, K., et al. (2014). Neuroimaging, behavioral, and psychological sequelae of repetitive combined blast/impact mild traumatic brain injury in Iraq and Afghanistan war veterans. *Journal of Neurotrauma, 31*(5), 425–436.

Povlishock, J. T. (1993). Pathobiology of traumatically induced axonal injury in animals and man. *Annals of Emergency Medicine, 22*(6), 980–986.

Povlishock, J. T., Marmarou, A., McIntosh, T., Trojanowski, J. Q., & Moroi, J. (1997). Impact acceleration injury in the rat: evidence for

focal axolemmal change and related neurofilament sidearm alteration. *Journal of Neuropathology and Experimental Neurology, 56*(4), 347–359.

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. *Nuclear Medicine Communications, 31*(11), 952–957.

Ramlackhansingh, A. F., Brooks, D. J., Greenwood, R. J., Bose, S. K., Turkheimer, F. E., Kinnunen, K. M., et al. (2011). Inflammation after trauma: microglial activation and traumatic brain injury. *Annals of Neurology, 70*(3), 374–383.

Randolph, C., & Miller, M. H. (1988). EEG and cognitive performance following closed head injury. *Neuropsychobiology, 20*(1), 43–50.

Robinson, M. E., Lindemer, E. R., Fonda, J. R., Milberg, W. P., McGlinchey, R. E., & Salat, D. H. (2015). Close-range blast exposure is associated with altered functional connectivity in veterans independent of concussion symptoms at time of exposure. *Human Brain Mapping, 36*(3), 911–922.

Romero, K., Lobaugh, N. J., Black, S. E., Ehrlich, L., & Feinstein, A. (2015). Old wine in new bottles: validating the clinical utility of SPECT in predicting cognitive performance in mild traumatic brain injury. *Psychiatry Research, 231*(1), 15–24.

Roy, D., McCann, U., Han, D., & Rao, V. (2015). Pathological laughter and crying and psychiatric comorbidity after traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences, 27*(4), 299–303.

Rutgers, D. R., Fillard, P., Paradot, G., Tadie, M., Lasjaunias, P., & Ducreux, D. (2008). Diffusion tensor imaging characteristics of the corpus callosum in mild, moderate, and severe traumatic brain injury. *AJNR. American Journal of Neuroradiology, 29*(9), 1730–1735.

Saatman, K. E., Duhaime, A. C., Bullock, R., Maas, A. I., Valadka, A., Manley, G. T., et al. (2008). Classification of traumatic brain injury for targeted therapies. *Journal of Neurotrauma, 25*(7), 719–738.

Scheibel, R. S., Newsome, M. R., Troyanskaya, M., Lin, X., Steinberg, J. L., Radaideh, M., et al. (2012). Altered brain activation in military personnel with one or more traumatic brain injuries following blast. *Journal of the International Neuropsychological Society, 18*(1), 89–100.

Scott, G., Ramlackhansingh, A. F., Edison, P., Hellyer, P., Cole, J., Veronese, M., et al. (2016). Amyloid pathology and axonal injury after brain trauma. *Neurology, 86*(9), 821–828.

Shin, Y. B., Kim, S. J., Kim, I. J., Kim, Y. K., Kim, D. S., Park, J. H., et al. (2006). Voxel-based statistical analysis of cerebral blood flow using Tc-99 m ECD brain SPECT in patients with traumatic brain injury: group and individual analyses. *Brain Injury, 20*(6), 661–667.

Shin, S. S., Verstynen, T., Pathak, S., Jarbo, K., Hricik, A. J., Maserati, M., et al. (2012). High-definition fiber tracking for assessment of neurological deficit in a case of traumatic brain injury: finding, visualizing, and interpreting small sites of damage. *Journal of Neurosurgery, 116*(5), 1062–1069.

Shin, S. S., Pathak, S., Presson, N., Bird, W., Wagener, L., Schneider, W., et al. (2014). Detection of white matter injury in concussion using high-definition fiber tractography. *Progress in Neurological Surgery, 28*, 86–93.

Sjaardema, H., & Glaser, M. A. (1942). The electro-encephalographic diagnosis of subdural hemorrhage. *Annals of Surgery, 116*(3), 452–460.

Skudlarski, P., Jagannathan, K., Calhoun, V. D., Hampson, M., Skudlarska, B. A., & Pearlson, G. (2008). Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. *NeuroImage, 43*(3), 554–561.

Slobounov, S. M., Gay, M., Zhang, K., Johnson, B., Pennell, D., Sebastianelli, W., et al. (2011). Alteration of brain functional network at rest and in response to YMCA physical stress test in concussed athletes: RsFMRI study. *NeuroImage, 55*(4), 1716–1727.

Smits, M., Houston, G. C., Dippel, D. W., Wielopolski, P. A., Vernooij, M. W., Koudstaal, P. J., et al. (2011). Microstructural brain injury in post-concussion syndrome after minor head injury. *Neuroradiology, 53*(8), 553–563.

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage, 17*(3), 1429–1436.

Sours, C., Zhuo, J., Janowich, J., Aarabi, B., Shanmuganathan, K., & Gullapalli, R. P. (2013). Default mode network interference in mild traumatic brain injury - a pilot resting state study. *Brain Research, 1537*, 201–215.

Sours, C., Rosenberg, J., Kane, R., Roys, S., Zhuo, J., Shanmuganathan, K., et al. (2015). Associations between interhemispheric functional connectivity and the automated neuropsychological assessment metrics (ANAM) in civilian mild TBI. *Brain Imaging and Behavior, 9*(2), 190–203.

Spence, A. M., Muzi, M., Graham, M. M., O'Sullivan, F., Krohn, K. A., Link, J. M., et al. (1998). Glucose metabolism in human malignant gliomas measured quantitatively with PET, 1-[C-11]glucose and FDG: analysis of the FDG lumped constant. *Journal of Nuclear Medicine, 39*(3), 440–448.

Spritzer, M. D., & Galea, L. A. (2007). Testosterone and dihydrotestosterone, but not estradiol, enhance survival of new hippocampal neurons in adult male rats. *Developmental Neurobiology, 67*(10), 1321–1333.

Stocker, R. P., Cieply, M. A., Paul, B., Khan, H., Henry, L., Kontos, A. P., et al. (2014). Combat-related blast exposure and traumatic brain injury influence brain glucose metabolism during REM sleep in military veterans. *NeuroImage, 99*, 207–214.

Strich, S. J. (1956). Diffuse degeneration of the cerebral white matter in severe dementia following head injury. *Journal of Neurology, Neurosurgery, and Psychiatry, 19*(3), 163–185.

Stulemeijer, M., Vos, P. E., van der Werf, S., van Dijk, G., Rijpkema, M., & Fernandez, G. (2010). How mild traumatic brain injury may affect declarative memory performance in the post-acute stage. *Journal of Neurotrauma, 27*(9), 1585–1595.

Sunami, K., Nakamura, T., Ozawa, Y., Kubota, M., Namba, H., & Yamaura, A. (1989). Hypermetabolic state following experimental head injury. *Neurosurgical Review, 12*(Suppl 1), 400–411.

Tebano, M. T., Cameroni, M., Gallozzi, G., Loizzo, A., Palazzino, G., Pezzini, G., et al. (1988). EEG spectral analysis after minor head injury in man. *Electroencephalography and Clinical Neurophysiology, 70*(2), 185–189.

Terry, D. P., Adams, T. E., Ferrara, M. S., & Miller, L. S. (2015). FMRI hypoactivation during verbal learning and memory in former high school football players with multiple concussions. *Archives of Clinical Neuropsychology, 30*(4), 341–355.

Thatcher, R. W., Walker, R. A., Gerson, I., & Geisler, F. H. (1989). EEG discriminant analyses of mild head trauma. *Electroencephalography and Clinical Neurophysiology, 73*(2), 94–106.

Thatcher, R. W., North, D. M., Curtin, R. T., Walker, R. A., Biver, C. J., Gomez, J. F., et al. (2001). An EEG severity index of traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences, 13*(1), 77–87.

Thelin, E. P., Just, D., Frostell, A., Haggmark-Manberg, A., Risling, M., Svensson, M., et al. (2016). Protein profiling in serum after traumatic brain injury in rats reveals potential injury markers. *Behavioural Brain Research*. doi:10.1016/j.bbr.2016.08.058.

Thomassen, A., Juul-Jensen, P., de Fine Olivarius, B., Braemer, J., & Christensen, A. L. (1979). Neurological, electroencephalographic and neuropsychological examination of 53 former amateur boxers. *Acta Neurologica Scandinavica, 60*(6), 352–362.

Thornton, K. E. (1999). Exploratory investigation into mild brain injury and discriminant analysis with high frequency bands (32-64 Hz). *Brain Injury, 13*(7), 477–488.

Toth, P., Szarka, N., Farkas, E., Ezer, E., Czeiter, E., Amrein, K., et al. (2016). Traumatic brain injury-induced autoregulatory dysfunction and spreading depression-related neurovascular uncoupling: Pathomechanisms, perspectives, and therapeutic implications. *American Journal of Physiology. Heart and Circulatory Physiology, 311*(5), H1118–H1131.

Trudeau, D. L., Anderson, J., Hansen, L. M., Shagalov, D. N., Schmoller, J., Nugent, S., et al. (1998). Findings of mild traumatic brain injury in combat veterans with PTSD and a history of blast concussion. *The Journal of Neuropsychiatry and Clinical Neurosciences, 10*(3), 308–313.

Turner, G. R., McIntosh, A. R., & Levine, B. (2011). Prefrontal compensatory engagement in TBI is due to altered functional engagement of existing networks and not functional reorganization. *Frontiers in Systems Neuroscience, 5*, 9.

Uruma, G., Hashimoto, K., & Abo, M. (2013). A new method for evaluation of mild traumatic brain injury with neuropsychological impairment using statistical imaging analysis for Tc-ECD SPECT. *Annals of Nuclear Medicine, 27*(3), 187–202.

van den Heuvel, M., Mandl, R., Luigjes, J., & Hulshoff Pol, H. (2008). Microstructural organization of the cingulum tract and the level of default mode functional connectivity. *The Journal of Neuroscience, 28*(43), 10844–10851.

Van Horn, J. D., Bhattrai, A., & Irimia, A. (2016). Multimodal imaging of Neurometabolic pathology due to traumatic brain injury. *Trends in Neurosciences, 40*(1),39–59.

Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, L. J., Bruno, M. A., Boveroux, P., Schnakers, C., et al. (2010). Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain, 133*(Pt 1), 161–171.

Vecchio, F., Miraglia, F., Curcio, G., Altavilla, R., Scrascia, F., Giambattistelli, F., et al. (2015). Cortical brain connectivity evaluated by graph theory in dementia: a correlation study between functional and structural data. *Journal of Alzheimer's Disease, 45*(3), 745–756.

Vespa, P. M., Boscardin, W. J., Hovda, D. A., McArthur, D. L., Nuwer, M. R., Martin, N. A., et al. (2002). Early and persistent impaired percent alpha variability on continuous electroencephalography monitoring as predictive of poor outcome after traumatic brain injury. *Journal of Neurosurgery, 97*(1), 84–92.

Walker, R. C., Purnell, G. L., Jones-Jackson, L. B., Thomas, K. L., Brito, J. A., & Ferris, E. J. (2004). Introduction to PET imaging with emphasis on biomedical research. *Neurotoxicology, 25*(4), 533–542.

Wang, Y., Yue, X., Kiesewetter, D. O., Niu, G., Teng, G., & Chen, X. (2014). PET imaging of neuroinflammation in a rat traumatic brain injury model with radiolabeled TSPO ligand DPA-714. *European Journal of Nuclear Medicine and Molecular Imaging, 41*(7), 1440–1449.

Ware, J. B., Biester, R. C., Whipple, E., Robinson, K. M., Ross, R. J., & Nucifora, P. G. (2016). Combat-related mild traumatic brain injury: association between baseline diffusion-tensor imaging findings and long-term outcomes. *Radiology, 280*(1), 212–219.

Wheeler-Kingshott, C. A., & Cercignani, M. (2009). About "axial" and "radial" diffusivities. *Magnetic Resonance in Medicine, 61*(5), 1255–1260.

Wilde, E. A., McCauley, S. R., Hunter, J. V., Bigler, E. D., Chu, Z., Wang, Z. J., et al. (2008). Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology, 70*(12), 948–955.

Wilde, E. A., Bouix, S., Tate, D. F., Lin, A. P., Newsome, M. R., Taylor, B. A., et al. (2015). Advanced neuroimaging applied to veterans and service personnel with traumatic brain injury: state of the art and potential benefits. *Brain Imaging and Behavior, 9*(3), 367–402.

Wu, H. M., Huang, S. C., Vespa, P., Hovda, D. A., & Bergsneider, M. (2013). Redefining the pericontusional penumbra following traumatic brain injury: evidence of deteriorating metabolic derangements based on positron emission tomography. *Journal of Neurotrauma, 30*(5), 352–360.

Yamaki, T., Imahori, Y., Ohmori, Y., Yoshino, E., Hohri, T., Ebisu, T., et al. (1996). Cerebral hemodynamics and metabolism of severe diffuse brain injury measured by PET. *Journal of Nuclear Medicine, 37*(7), 1166–1170.

Yang, J., Wu, Z., Renier, N., Simon, D. J., Uryu, K., Park, D. S., et al. (2015). Pathological axonal death through a MAPK cascade that triggers a local energy deficit. *Cell, 160*(1–2), 161–176.

Yokoyama, K., Matsuki, M., Shimano, H., Sumioka, S., Ikenaga, T., Hanabusa, K., et al. (2008). Diffusion tensor imaging in chronic subdural hematoma: correlation between clinical signs and fractional anisotropy in the pyramidal tract. *AJNR. American Journal of Neuroradiology, 29*(6), 1159–1163.

Yuh, E. L., Cooper, S. R., Mukherjee, P., Yue, J. K., Lingsma, H. F., Gordon, W. A., et al. (2014). Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study. *Journal of Neurotrauma, 31*(17), 1457–1477.

Zhang, K., Johnson, B., Pennell, D., Ray, W., Sebastianelli, W., & Slobounov, S. (2010b). Are functional deficits in concussed individuals consistent with white matter structural alterations: combined FMRI & DTI study. *Experimental Brain Research, 204*(1), 57–70.

Zhang, J., Mitsis, E. M., Chu, K., Newmark, R. E., Hazlett, E. A., & Buchsbaum, M. S. (2010a). Statistical parametric mapping and cluster counting analysis of [18F] FDG-PET imaging in traumatic brain injury. *Journal of Neurotrauma, 27*(1), 35–49.

Zhou, Y., Milham, M. P., Lui, Y. W., Miles, L., Reaume, J., Sodickson, D. K., et al. (2012). Default-mode network disruption in mild traumatic brain injury. *Radiology, 265*(3), 882–892.

Zhu, D. C., Covassin, T., Nogle, S., Doyle, S., Russell, D., Pearson, R. L., et al. (2015). A potential biomarker in sports-related concussion: brain functional connectivity alteration of the default-mode network measured with longitudinal resting-state fMRI over thirty days. *Journal of Neurotrauma, 32*(5), 327–341.