Functional Neuroradiology of Traumatic Brain Injury

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Introduction

About 50–60 million people worldwide sustain traumatic brain injury (TBI) every year [1]. In the United States alone, 1.7 million people sustain a head trauma each year, and an estimated 275,000 Americans are admitted to hospital yearly following TBI. Of all head-injured patients, approximately 10% sustain fatal brain injury [2]. Lifelong disability is common in those who survive: in the USA, around 5.3 million people are estimated living with a TBI-related disability, and in the European Union, approximately 7.7 million people have residual disabilities after TBI [2]. The incidence of TBI worldwide is rising, mainly owing to injuries associated with the increased use of motor vehicles in the middle-income and low-income countries. In high-income countries, a shift in the population affected by TBI towards older age groups has been observed in recent decades, as a result of increased life expectancy and greater mobility in the elderly. The leading cause of TBI is therefore injury related to falls, followed by motor vehicle or traffic collisions, and external cause of being "struck by or against." The most widely used clinical classification of brain trauma is the Glasgow Coma Scale (GCS) [3], which allows the recording of the level of consciousness through the assessment of eye, motor, and verbal responses. According to GCS, TBI can be dived into: (1) mild (GCS score of 13–15); (2) moderate (GCS score of 12–9); severe (GCS scores of 8 or less. Most traumatic brain injuries are mild in severity: the annual incidence of mild TBI is 224 per 100,000 person–years, almost 10 times the incidence of moderate TBI and 17 times the incidence of severe TBI [4]. Despite the term "mild" TBI, there is increasing evidence that even minimal traumatic brain injuries may result in persistent and disabling physical (headache, dizziness, fatigue) and cognitive (attention, memory, executive function deficits) sequelae. This group of symptoms has been termed post-concussion symptoms and when these symptoms persist for months or longer they have been referred to as the post-concussion syndrome [5, 6]. Particularly at risk to mild TBI are males between 15 and 24 years old, and individuals in lower socioeconomic groups.

The TBI lesions can be divided into primary and secondary injuries, according to their relationship to the traumatic event. Primary lesions are those that arise as a direct result of the traumatic force and include skull fractures, extra-axial hemorrhages, and intra-axial lesions such as cortical contusion, subcortical gray matter injury, diffuse axonal injury (DAI), and intra-ventricular hemorrhage. Secondary lesions are complications of trauma and include cerebral herniation, diffuse cerebral edema, infarction, and secondary hemorrhage; secondary lesions are potentially preventable, provided that appropriate treatment is promptly started [7]. Among TBI injuries, cerebral contusions are the most common, accounting for approximately half of all traumatic parenchymal lesions. They tend to evolve over time and are more apparent on delayed scans than at the time of initial imaging. They occur in very characteristics locations: nearly half involve the temporal lobes, with the orbital surfaces of the frontal lobes frequently affected. Contusions that occur at 180° opposite to the site of direct impact are common and are called "*contre-coup*" lesions. Contusions commonly involve both the gray matter and the contiguous subcortical white matter and are characterized by perivascular microhemorrhages which tend to coalesce over time into more confluent hematomas [8]. DAI is the second most common parenchymal lesion seen in TBI. Most DAIs are caused by high velocity motor vehicle collisions and are dynamic, non-

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impact injuries resulting from the inertial forces of rotation generated by sudden changes in acceleration/deceleration. Indeed, the cortex moves at different speed relative to underlying deep brain structures, resulting in axonal stretching, especially at the gray-white matter interface. The rapid deformation of white matter at the instant of trauma can lead to mechanical failure: a cascade of adverse events occurs, including proteolysis of the axonal cytoskeleton and ion fluxes. Cellular swelling with cytotoxic edema ensues, altering brain anisotropy. The vast majority of DAIs are microscopic and non-hemorrhagic: tears of penetrating vessels may cause small ovoid hemorrhages that sometimes are the only gross evidence of underlying axonal injury. DAI typically occurs in the subcortical and deep white matter: the cortex is usually spared. DAI is present in almost ¾ of patients with moderate-to-severe TBI and typically evolves over time [7]. A radiological classification of DAI was proposed by Adams in 1989 and divides DAI into three grades [9]:

- Grade I: involves gray-white matter interfaces, parasagittal regions of frontal lobes, and periventricular temporal lobes. Parietal and occipital lobes, internal and external capsules, and cerebellum are often inapparent on conventional imaging.
- Grade II: involves corpus callosum (especially posterior body and splenium) in addition to grade I locations, observed in approximately 20% of patients.
- Grade III: involves brainstem in addition to grade I and II locations (midbrain, superior cerebellar peduncles, medial lemnisci and corticospinal tracts).

Recently, it has been suggested to extend this classification to include a grade IV, indicating the presence of lesions located specifically in the diencephalic structures (thalamus) and the mesencephalic tegmentum, which are associated with very poor long term outcomes [10, 11].

Imaging is absolutely critical to diagnosis and management of the patient with TBI. Computerized tomography (CT) is considered the best screening tool for acute brain trauma. CT is fast, effective, and inexpensive and depicts both bone and parenchymal injuries. Although magnetic resonance imaging (MRI) allows more precise identification and definition of DAI, small cortical contusions, and brainstem lesions, its use as a routine screening procedure in the setting of acute brain trauma is uncommon: MRI is most widely used in the subacute-chronic stage of TBI, monitoring edema, evolution of hemorrhage, and evaluation of lesions that may underlie post-traumatic epilepsy. Among conventional MRI sequences, diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), and gradient-recalled-echo (GRE) T2* sequences are particularly useful in imaging TBI. Susceptibility weighted and GRE-T2* sequences are sensitive to the presence of products of blood breakdown such as hemosiderin and ferritin. These sequences exploit the loss of signal intensity created by disturbance of a homogeneous magnetic field. These disturbances can be caused by various paramagnetic or diamagnetic substances such as iron-laden tissues, calcium, clots, partially deoxygenated venous blood, and air/tissue interfaces. As spins encounter heterogeneity in the local magnetic field, they precess at different rates and cause overall signal-intensity loss in T2*-weighted images. The phase image of SWI accentuates the paramagnetic properties of blood products such as deoxyhemoglobin, methemoglobin, and hemosiderin. Therefore, SWI is particularly useful for detecting intravascular venous deoxygenated blood as well as extravascular blood products. Furthermore, the phase and magnitude images of SWI sequence can be used to create projection images to show vessel contiguity. SWI is strongly sensitive to magnetic susceptibility effects and, for this purpose, is significantly more sensitive than GRE-T2* sequences (Fig. 14.1) [12, 13]. In a large study of individuals with TBI, SWI was found to quantify a greater lesion volume than did fluid attenuated inversion recovery (FLAIR). Moreover, SWI was able to identify TBI-related lesions in almost one-third of patients for whom FLAIR was unable to detect any lesions. Greater overall SWI volume, as well as frontal SWI volume, was found to relate to the severity of TBI. Conversely, no association was found between FLAIR lesion volume and injury severity [14]. Babikian et al. compared the efficacy of SWI versus proton MR spectroscopic (^{1}H-MRS) as a predictor of long-term neuropsychological functions after pediatric brain injury [15]. Lesion volume explained over 32% of the variance in cognitive performance, explaining an additional 19% beyond magnetic resonance spectroscopic metabolite variables. Significant correlation was found between total volume of lesions measured on SWI and neuropsychological scores. Notably, lesions in deeper brain regions were more strongly associated with poorer neuropsychological performance. Recently, a quantitative susceptibility mapping approach has been proposed, which could be used to differentiate hemorrhages from veins in TBI patients in a semi-automated manner with reasonable sensitivity and specificity [16].

Diffusion-weighted imaging (DWI) is a noninvasive functional MRI sequence that measures the random movement of water molecules in the brain. It allows differentiation between cytotoxic and vasogenic edema: cytotoxic edema is classically present in ischemia and is the consequence of shift of water from extra- to intracellular compartment; vasogenic edema is determined by the shift of water from the vessels toward the extracellular space. Since both cytotoxic and vasogenic edema occurs after TBI associated with DAI, DWI may help differentiate these two types of edema in patients with head trauma [17]. This has important clinical

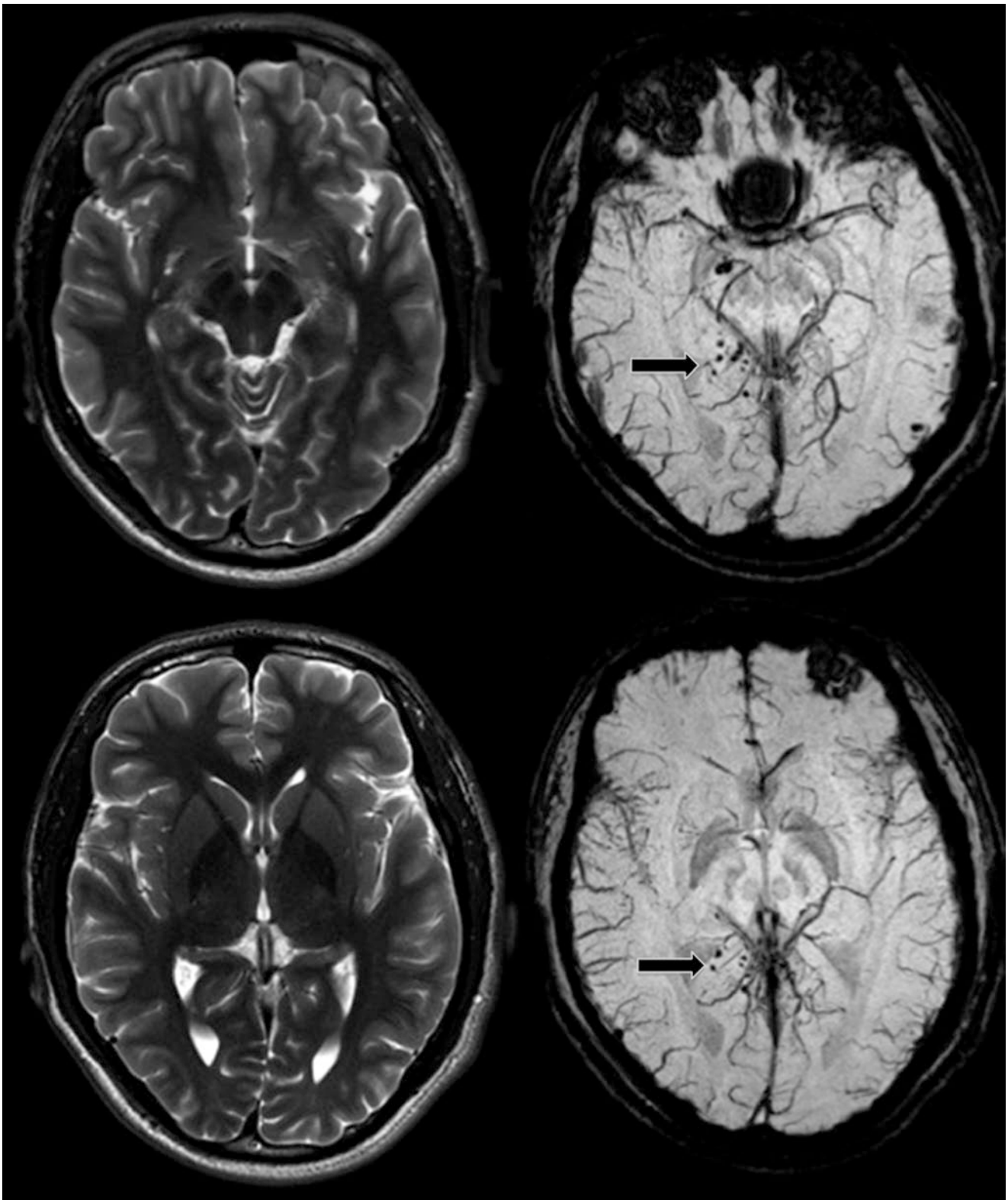

Fig. 14.1 Selected axial T2-weighted (T2W) and corresponding susceptibility weighted (SWI) images from a 40-year-old male who suffered a mild TBI. The patient had a GCS of 13 and a good outcome. Note that T2W images (left) do not demonstrate any parenchymal lesions, whereas minIP reconstructions from SWI (right) clearly show some foci of susceptibility in the medial part of the temporal lobe (arrows)

implications because, while cytotoxic edema is described as irreversible, vasogenic edema is typically considered a reversible damage. The restriction of water associated with TBI is thought to be related to [1] a failure of energy metabolism and the consequent membrane pump failure and [2] reduction in the extracellular space volume caused by cell swelling [18]. In addition to revealing the different nature of the lesion related injury, DWI detects more DAI lesions when compared to fast spin-echo T2-weighted or GRE T2* and susceptibility-weighted images in patients with head trauma. Due to the higher sensitivity to foci of acute shearing injury, DWI is particularly useful for the detection of DAI in the diagnostic setting [19]. In a recent study of moderate and severe TBI, DWI lesions in the corpus callosum were the most important predictive MRI variable of negative outcome [20].

Despite all these advantages, conventional MRI has the following limitations: (1) it underestimates the extent of the injury; (2) it lacks pathological specificity; (3) it yields a poor correlation with functional deficits; and (4) it does not provide quantitative pathophysiological markers to determine prognosis and to monitor treatment response. In addition, while severe trauma is usually evident on conventional MRI as hemorrhagic lesions or contusions or extensive DAI assessed by DWI, mild and moderate trauma is often associated with "microscopic" damage not visible on conventional MRIs. These limitations have prompted the development and implementation of new quantitative and functional MRI techniques that can help determine the severity and extent of brain injury, help elucidate the pathophysiology of TBI, prevent secondary damage, and provide useful prognostic information.

New advanced MRI techniques such as diffusion tensor imaging (DTI), proton MR spectroscopy (^{1}H-MRS), arterial spin labeling (ASL) perfusion MRI, and resting state (RS) functional MRI (fMRI) serve as the guidelines in this chapter for discussing the use and role of advanced functional imaging in TBI.

Diffusion Tensor Imaging (DTI)

The microstructural integrity of white matter tracts can be evaluated with diffusion tensor imaging (DTI) [21]. Physical principles and clinical applications of DTI are extensively reviewed in Chaps. 39, 40 and 41. DTI fiber-tracking has found clinical and scientific applications in both the localization and the quantitative assessment of white matter microstructural integrity in several fields such as basic neuroscience and diagnostic neuroradiology. Specifically, fiber tracking uses the diffusion tensor of each voxel to reconstruct an axonal tract from voxel to voxel in order to identify discontinuity on fibers. The implications of DTI in TBI are in studying the consequences of trauma on the integrity of white matter bundles within several neuronal systems, such as motor, sensory, emotional, and cognitive systems. Indeed, DTI-derived parameters, such as fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD), have been shown to be extremely useful for the study of white matter in TBI-associated DAI. In order to investigate their underlying pathological substrate, FA and MD were first applied to the study of an experimental animal model of traumatic axonal injury. Changes in FA and MD were validated by histological examination and showed that DTI was more sensitive to microscopic injury than conventional MRI sequences. Decreased FA, reflecting demyelination, and persistent axonal injury distinguished injured from control mice with no overlap between groups [22]. A recent study extended previous findings about the correlation of high-resolution DTI values and ex-vivo immunohistochemistry staining of neurons, astrocytes, and microglia in the ferret—a species that share with humans a gyrencephalic cortex and high white matter volume [23]. Moreover, Magnoni et al. demonstrated in humans that acute microdialysis measurements of axonal cytoskeletal protein tau in the extracellular space correlate well with DTI-derived measures of reduced brain white matter integrity [24].

Several DTI studies focused on the investigation of the mechanisms of DAI after acute TBI [25–28] (Table 14.1). Arfanakis et al. first tested the hypothesis that DAI is associated in the short term with decreased diffusion anisotropy. In this study, immediately after trauma, patients displayed significant reduction in FA in several regions compared with the homologous ones in the contralateral hemisphere [25]. By using both whole-brain DTI histogram-derived and region of interest approach, Inglese et al. studied 46 patients with mild TBI at different time intervals from injury and matched controls. While no abnormalities could be detected in the whole-brain analysis, a significant reduction in FA and increase in MD were found in regions of interest placed on the corpus callosum, internal capsule, and centrum semiovale (Fig. 14.2) [26]. Murugavel et al. found that, 2 days after trauma, concussed athletes exhibited higher RD and reduced FA in several white matter tracts, including the right posterior internal capsule, compared to controls, with a progressive recovery in the next 2 weeks [28]. Sidaros et al. performed a prospective longitudinal study of 30 adult patients admitted for subacute rehabilitation following severe TBI. At baseline, FA was reduced in all the investigated white matter regions in patients compared to controls. At follow-up, FA had increased in the internal capsule and in centrum semiovale primarily in patients with favorable outcome, whereas in patients with unfavorable outcome, FA remained decreased [29]. Besides its role as a prognostic marker of clinical outcome, DTI thus might also serve as a tool for revealing changes in the neural tissue during recovery.

Table 14.1 Summary of diffusion imaging studies in traumatic brain injury

Authors	Subjects	MR protocol	Results
Inglese et al. [26]	46 patients with mild TBI and 29 healthy controls	DTI with echo planar sequence using 6 diffusion-encoding directions. Whole-brain histograms and ROIs analysis	Reduction in FA and increase in MD in the corpus callosum, internal capsule, and centrum semiovale compared to healthy controls
Niogi et al. [42]	43 mild TBI patients and 23 normal controls	DTI with single-shot spin echo pulse sequence using 55 diffusion-encoding directions	Tract-specific variation in microstructural white matter integrity was the responsible for the variation in performance in specific cognitive domains
Ling et al. [30]	50 subjects with mild TBI and 50 healthy controls	DTI with twice-refocused spin echo pulse sequence using 30 diffusion-encoding directions. ROIs analysis and voxel-wise analysis	Increased FA and reduced RD in several white matter tracts in semi-acute injury, which appear to normalize with recovery
Murugaval et al. [28]	21 sport-related concussed subjects and 16 healthy controls	DTI with single-shot spin echo pulse sequence using 64 diffusion-encoding directions. Voxel-wise analysis	Higher RD and reduced FA in several white matter tracts, with a progressive recovery in the next 2 weeks
Meier et al. [32]	40 subjects with sport-related concussion and 46 healthy controls	DTI with single-shot spin echo pulse sequence using 30 diffusion-encoding directions. ROIs analysis	Concussed athletes exhibited increased FA in several white matter tracts at each visit post-concussion with no longitudinal evidence of recovery
Churchill et al. [50]	31 subjects with sport-related concussion and 37 healthy controls	Two-shell DTI protocol with both 30 and 64 diffusion-encoding directions. Voxel-wise analysis	Elevated FA and decreased MD for concussed athletes, along with increased V_{IC} and reduced ODI, indicating greater neurite density and coherence of neurite orientation within white matter
De Simoni et al. [37]	42 patients with mild TBI and 21 healthy controls	DTI with single-shot spin echo pulse sequence using 64 diffusion-encoding directions. ROIs analysis	TBI patients showed reduced FA in several white matters tracts connecting caudate to anterior cingulate cortex, which correlates with cognitive impairment
Lancaster et al. [55]	17 concussed subjects and 20 healthy controls	DTI with single-shot spin echo pulse sequence using 30 diffusion-encoding directions. Voxel-wise analysis	Widespread decreased mean and axial diffusivity compared to control subjects. Kurtosis metrics were significantly higher in concussed athletes in the acute phase, with subsequent normalization

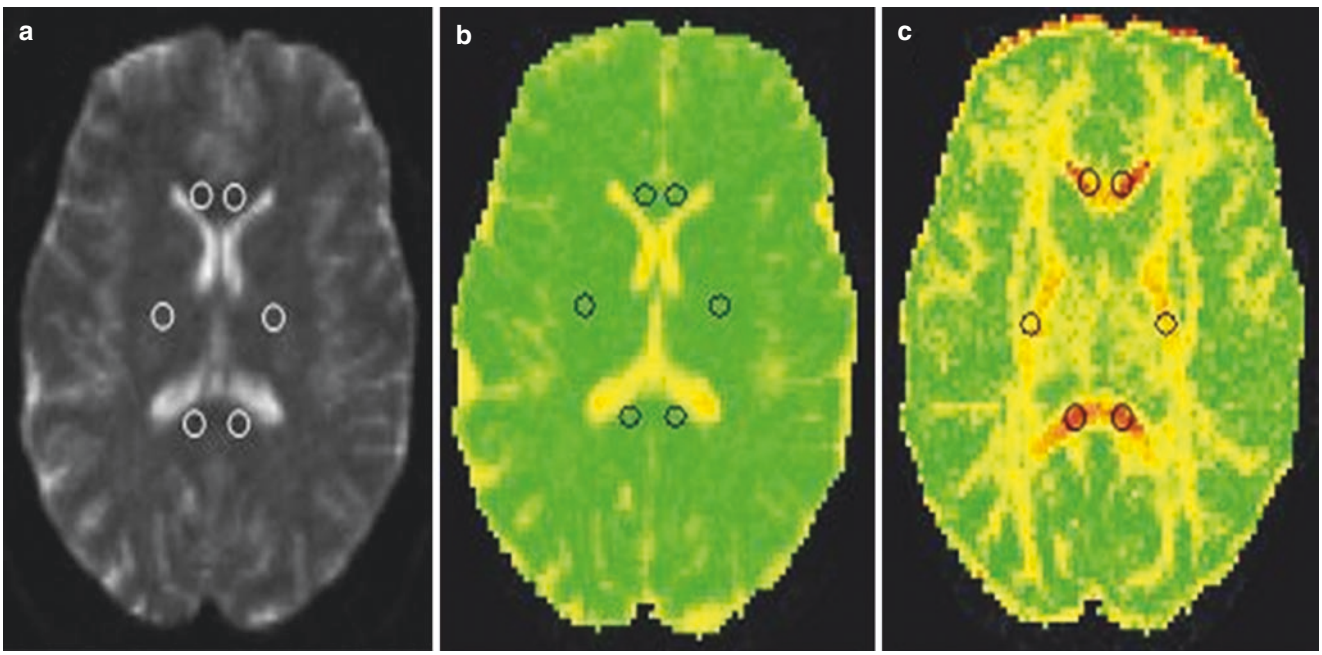

Fig. 14.2 Selected axial T2-weighted image (**a**), color-coded mean diffusivity (MD) map (**b**), and color-coded fractional anisotropy (FA) map (**c**) from a patient with mild TBI and no visible abnormalities on the conventional MR scan. Circular ROIs are placed in the white matter regions, which are site of predilection of DAI: Posterior limb of the internal capsule, genu, and splenium of corpus callosum bilaterally. In our study, the FA and MD in the genu of corpus callosum and the posterior limb of the internal capsule were significantly different in the group of TBI patients compared to sex- and aged-matched healthy controls. (Adapted from Inglese et al. [26])

However, the interpretation of DTI findings in the early phases after TBI is not straightforward due to the variability of DTI results among studies. Indeed, recent studies have shown opposite effects, with elevated FA and decreased MD reported early after TBI [30–32].

Ling et al. showed increased FA and reduced RD in several white matter tracts in semi-acute injury, which appear to normalize with recovery [30]. Similar findings were observed in 21 patients who demonstrated significantly greater FA as a result of reduced RD, in the corpus callosum and several white matter tracts in semi-acute TBI [31]. Meier et al. investigated FA longitudinally in concussed athletes and found higher FA in several WM tracts at each time point compared to healthy controls, with no evidence of recovery over time [32].

The discrepancy among these studies can be explained by several factors including methodological issues, different degree of severity of TBI in patients enrolled (with diverse contribution of vasogenic and cytotoxic edema), different intervals from the traumatic event at the time of MRI, and different follow-up periods. Mechanisms of cellular damage including metabolic disruption and cytotoxic edema have been proposed to explain acutely reduced diffusivity following stroke and injury, while vasogenic edema is generally considered to underlie increased diffusivity. While cellular disruption generally precedes vasogenic edema in stroke, this may not always be the case in brain injury. Indeed, acutely increased FA may indicate brain regions that undergo edema without cellular disruption, while regions with acutely decreased diffusivity are more likely to have metabolic or other cellular disruption that will result in degeneration [33]. Greater consistency of DTI findings is found in the chronic phase after TBI (especially in patients with post-concussive syndrome), where reduced FA and increased MD have been extensively reported, reflecting long-term loss of white matter integrity after TBI [34–37]. DTI is particularly useful in evaluating the long-term cognitive deficits which are frequently observed after TBI. The two most common neuropsychological dysfunctions associated with mild TBI are attentional control and memory [38]. A recent meta-analysis of studies that examined the specific relationship between DTI parameters and cognitive test performance provided strong evidence of an in vivo association between markers of underlying injury-related neuropathology and cognitive dysfunction. The associations were significant for the combined results across all cognitive domains (i.e., general cognition), and within the specific domains of attention, memory, and executive function [39]. FA resulted to be the most sensitive metric for detecting post-TBI cognitive decline. As highlighted in other studies [26, 40], representative white matter regions, such as the corpus callosum and internal capsule, perform better than whole-brain white matter for reflecting a wide range of cognitive domains, including memory, attention, and executive functions [41]. Niogi et al. found a highly specific brain-behavior relationship consisting in the correlation between attentional control and FA in left hemisphere anterior corona radiata, and the correlation between memory performance and FA in the uncinate fasciculus [42]. Xiong et al. confirmed a significant correlation between MD and FA of several white matter tracts and Mini Mental State Examination (MMSE) and measures of working memory and processing speed abilities [43]. Veeramuthu and coauthors demonstrated that chronic-phase FA and RD values in the corona radiata, anterior limb of internal capsule, cingulum, superior longitudinal fasciculus, optic radiation, and genu of corpus callosum showed significant associations with several neuropsychological outcome [44]. DTI measures of deep-gray matter structures were also investigated, and thalamus and caudate structural connectivity was found to be significantly associated with performance in different neuropsychological domains [37, 45].

DTI, however, has several inherent limitations [46]. Crossing fibers, present in the majority of human white matter voxels, are an issue that cannot be properly addressed by DTI, which would yield lower FA values in voxels with complex fiber configurations. High angular resolution diffusion imaging methods have recently been developed to overcome these shortcomings. Constrained spherical deconvolution (CSD) is one of these methods, and is shown to be a robust way to resolve the crossing fiber in white matter tracts [47]. CSD-based tractography has recently been used in TBI research, confirming significantly decreased FA and increased RD in patients with TBI compared with healthy controls [48]. Another promising advanced DTI technique is the neurite orientation dispersion and density imaging (NODDI) [49]. This method acquires imaging data at multiple different diffusion weightings, with each sampling many different spatial orientations at high angular resolution. These data, along with a three compartments geometric model of diffusion, are used to estimate fractional water contributions of different tissue types within each voxel. Moreover, this model computes the orientation dispersion index (ODI), which measures the amount of angular variation among neurites in a given voxel and the intracellular volume fraction (VIC). Churchill and colleagues found elevated FA and decreased MD, along with increased VIC and reduced ODI, for concussed athletes compared to healthy controls, indicating greater neurite density and coherence of neurite orientation within white matter [50]. Increased FA after brain injury has been previously interpreted as a marker of axonal regrowth, and the increased VIC and reduced ODI detected in this study supports this mechanism as a cause of the observed FA and MD differences among athletes with a history of concussion.

Finally, DTI can only model Gaussian diffusion while not all diffusion processes that occur in the brain are Gaussian. Diffusion kurtosis imaging (DKI) quantifies the departure of water diffusion from the Gaussian behavior typical of a simple solution and is a specific indicator of microstructural complexity [51]. It has been found to be particularly sensitive to the type of microstructural variations that occur in brain tissue. DK tensor imaging may be particularly relevant for measuring the effects of brain injury, since the complex cascade of neurochemical and neurophysiological changes that occur following brain injury may lead water molecules to diffuse in highly complex trajectories (Fig. 14.3) [52]. However, longitudinal studies have yielded inconsistent results, with some studies demonstrating decreased mean kurtosis and radial kurtosis in TBI patients 10 days, 1 month, 6 and 9 months postinjury [45, 53], while others showing increased axial kurtosis at 24 h and 8 days after concussion [54] with normalization over 6 months [55].

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)

Proton MR spectroscopy (^{1}H-MRS) is a noninvasive imaging technique that allows quantification of several brain neurochemicals such as *N*-acetylaspartate (NAA), a marker of neuronal integrity; creatinine (Cr), a marker of energy supply; choline (Cho), a marker of cell membrane turnover; lactate (Lac), a marker of anaerobic metabolism; myoinositol (mI), an osmolyte selectively present in astrocytes; and glutamate/glutamine (Glx) a marker of cytotoxicity [56]. ^{1}H-MRS has been particularly helpful in (1) detecting brain metabolic abnormalities in patients with TBI with conventional MRI normal scans but with persistent symptoms, (2) demonstrating persistent damage at a cellular level in both early and late stages of TBI, and (3) elucidating the mechanisms leading to tissue damage. Table 14.2 reports the most relevant ^{1}H-MRS studies on TBI.

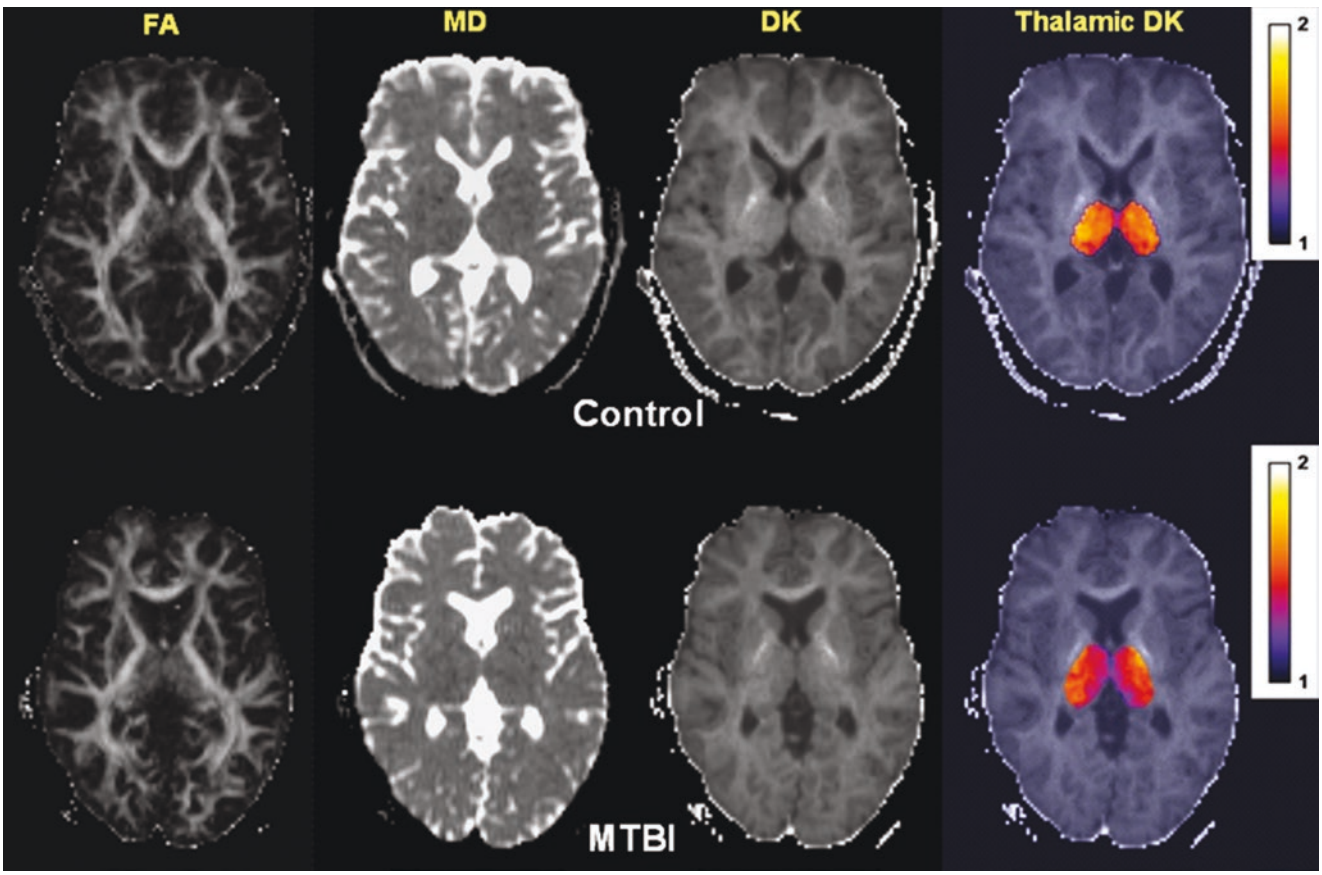

Fig. 14.3 Selected FA and MD (from DTI) and DK (from DKI) maps of a patient with mild TBI (MTBI, bottom row) and an age-matched normal control (top row). Note the obvious decrease in DK level on the thalamic color-graded DK map with optimum threshold in the patient as compared to the normal control. On FA maps, the values of gray matter (GM) are very low, indicating its isotropic nature, making FA an insensitive measure for GM. (Figure courtesy of Jens Jensen, Ph.D. and Robert I. Grossman M.D., New York University, NY)

Table 14.2 Summary of MRS studies in traumatic brain injury

Authors	Subjects	Brain region	Results
Holshouser et al. [57]	40 children with mild to severe TBI	Two-dimensional ^{1}H-MRS through the corpus callosum	Decrease in NAA/Cr and increase in Cho/Cr was observed in both visibly injured and normal appearing brain. NAA/Cr decreased more in patients with poor outcomes than in those with good outcomes
Babikian et al. [68]	40 children and adolescents with mild to severe TBI	Single voxel ^{1}H-MRS from normal appearing and visibly injured corpus callosum	Moderate correlation between the NAA level and the cognitive scores was found. Mild to moderate association was found between glutamate, glutamine and myoinositol and cognitive scores
Cohen et al. [64]	20 patients with mild TBI and 19 healthy controls	Whole brain NAA concentration with nonlocalizing MRS	Patients with mild TBI showed a 12% decrease in whole brain NAA relative to healthy controls
Tollard et al. [61]	43 patients with severe TBI and 15 healthy controls	NAA/Cr ratio and FA were extracted in several ROIs	Analysis of combined FA and ^{1}H-MRS data separated the groups of patients with unfavorable and favorable outcome without overlap
George et al. [67]	43 patients with mild TBI and 21 healthy controls	ROI-based metabolic measurements	Reduced Cho/Cre ratio in the thalamus and centrum semiovale compared to healthy controls. Creatine was correlated with cognitive performance
Friedman et al. [72]	11 adolescents with mild TBI and 11 healthy controls	GABA/creatine was measured in left-sided frontal lobe and central posterior cingulate regions. The frontal voxel was positioned to overlap with patient-specific activation on a 1-back working memory task	Increased GABA/Cre ratio in frontal regions colocalized with working memory task activation after sport concussion
Dennis et al. [69]	29 children with moderate-to-severe TBI and 23 healthy controls	DTI-derived parameters and NAA and Cho measures ROIs analysis	Tracts with poorer WM organization also showed lower NAA. No NAA alterations in tracts with normal DTI metrics

The initial ^{1}H-MRS investigations in adult patients with moderate-to-severe head trauma showed elevated Cho, as a result of myelin and cellular membranes shearing and astrogliosis, and reduced NAA due to the neuronal and axonal injury [57]. A decrease of NAA was detected, although to a lesser extent, also in regions appearing normal on conventional MRIs: while in visibly injured brain, NAA decrease is more likely to be determined by primary injury, in normal appearing brain tissue, it is likely to reflect diffuse axonal injury or Wallerian degeneration secondary to the primary injury [58]. To investigate its prognostic value, single voxel ^{1}H-MRS was employed to study prospectively the brainstem of 40 consecutive patients with severe TBI. While MRI and ^{1}H-MRS taken separately could not distinguish patients with different range of Glasgow Outcome Scale (GOS) scores (a scale which assess the degree of recovery after TBI), a combined analysis of combined ^{1}H-MRS and MRI data enabled the separation among patients with GOS 1–2, GOS 3, and GOS 4–5 with no overlap between groups. Thus, suggesting that ^{1}H-MRS can predict the long-term neurological outcome in severe TBI, especially the persistent vegetative state [59]. A recent study revealed areas of significantly reduced NAA and increased Cho, predominately located in frontal and parietal white matter, which evolved over 28 months. A map of the ratio of Cho/NAA showed the greatest sensitivity to change, which indicated additional metabolic changes throughout white matter. The metabolic changes reduced over time following injury, though with abnormal values remaining in periventricular regions [60].

In a more recent study, DTI and ^{1}H-MRS were combined to investigate their ability to predict 1-year outcome in 43 patients with severe TBI [61]. After 1 year, 44% of patients had unfavorable outcomes (death, persistent vegetative state, or minimally conscious state) and 56% favorable outcomes (normal consciousness with or without functional impairments). FA and ^{1}H-MRS findings were different between the outcome groups with supratentorial and infratentorial FA, NAA/Cre in the pons, in the thalamus, and in the insula being the significant variables. Combined FA and ^{1}H-MRS data were able to separate the unfavorable outcome, favorable outcome, and control groups without overlaps, suggesting that these techniques, used in combination, can allow a much better prognostic evaluation in the acute post-traumatic stage. As mentioned earlier, the capacity of severe, moderate, and even mild TBI to cause cognitive impairment has been increasingly recognized. Ariza et al. investigated the correlations between cognitive performance and NAA concentrations in twenty patients with moderate and severe TBI in comparison to matched healthy controls [62]. The decrease of NAA in the basal ganglia was correlated with measures of speed, motor scanning, and attention suggesting the involvement of the frontostriatal networks.

Unlike in moderate-to-severe TBI, ^{1}H-MRS studies focusing on patients with mild TBI have produced controversial results [63–65]. Using whole brain NAA, Cohen et al. reported a 12% decrease of NAA in patients with mild TBI compared to healthy controls (Fig. 14.4) [64]. However, the same authors did not find a significant decrease of NAA in the thalamus of mild TBI patients when using multi-voxel ^{1}H-MRS [66]. This, however, might be explained by a "milder" involvement of thalami in the pathological process

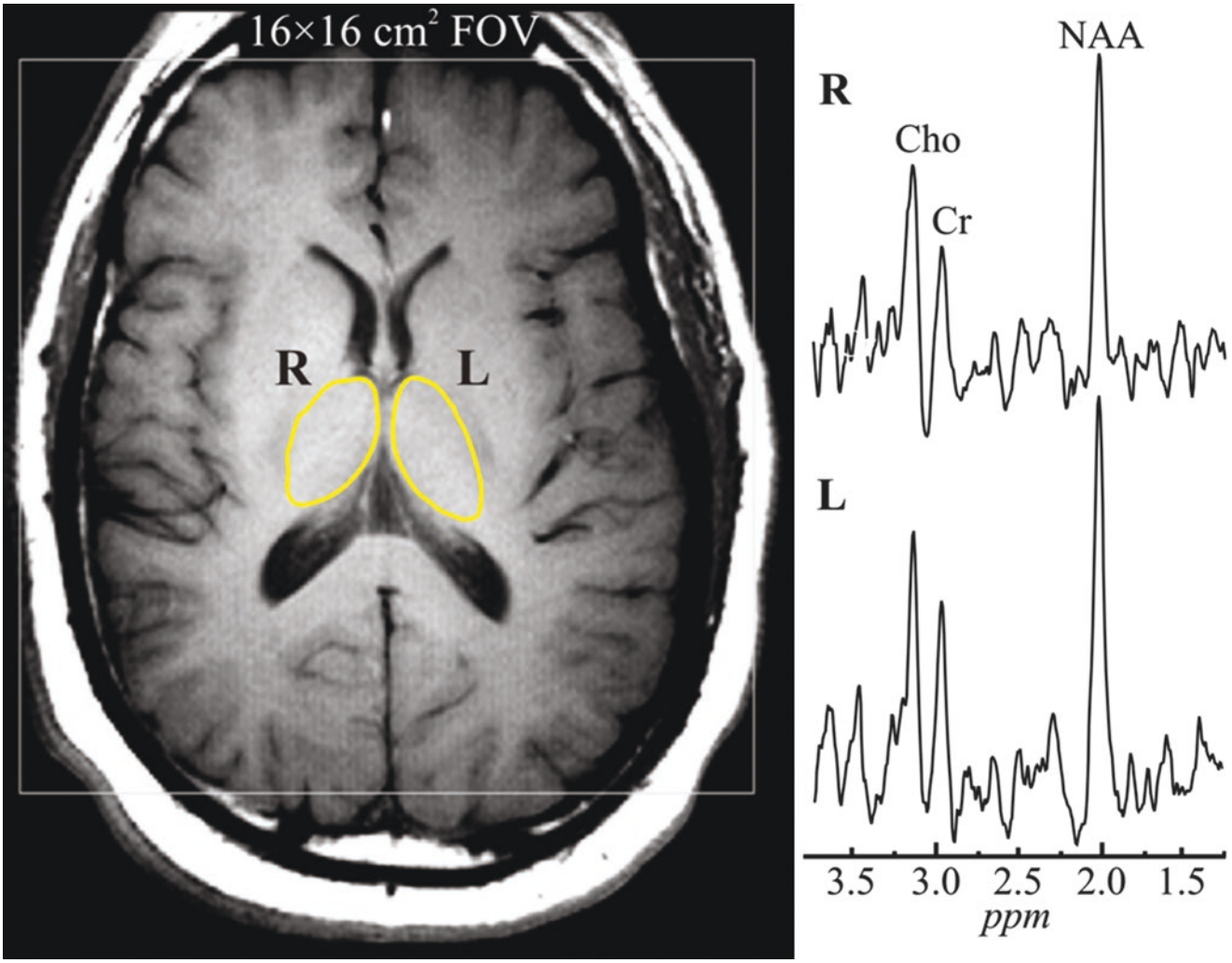

Fig. 14.4 Selected axial T1-weighted superimposed with the 16 × 16 cm² MRS FOV in a patient with mild TBI. Average spectra from the left and right thalamic regions are shown. Note the similarity of the bilateral spectra. (Figure courtesy of Ivan Kirov, Ph.D. and Oded Gonen, Ph.D., New York University, NY)

that characterizes the white matter to a greater extent. George et al. found decrease Cho/Cre ratio measured in the thalamus and centrum semiovale, which was associated with cognitive impairment [67], while Narayana and coworkers could not found any changes in brain metabolites in mild TBI [65].

Likewise in adults, significant decrease of NAA:Cre and NAA:Cho ratios were detected in the occipital gray matter of children with acute TBI relative to healthy control subjects [68]. Importantly, in this study the ^{1}H-MRS findings correlated with the severity of injury, duration of coma and poor neurological outcome, as measured by the Pediatric Cerebral Performance Category Scale score (PCPCS). A recent work combined DTI analyses with MRS to better understand white matter disruptions in children with moderate-to-severe traumatic brain injury. Tracts with poorer white matter organization, as shown by lower FA and higher MD and RD, also showed lower NAA, a marker of neuronal and axonal health and myelination [69]. Choline, a marker of inflammation, membrane turnover, or gliosis, did not show such associations. Longitudinal ^{1}H-MRS studies showed a temporal change of brain metabolites after trauma. While NAA/Cre was reduced and Cho/Cre increased in children with TBI as compared to controls at baseline, an increase in NAA/Cho and decrease in Cho/Cre ratios were detected 21 weeks after trauma, suggesting improvement in brain metabolism [70]. Ashwal and coauthors used ^{1}H-MRS to measure mI and Glx in addition to NAA, Cho, Cr and Lac: while patients with poor outcome had higher levels of mI in the occipital gray matter, the levels of Glx, although significantly higher, did not correlate with the clinical outcome [71]. Frontal-lobe MRS of γ-aminobutyric acid (GABA) was recently performed in eleven adolescents (age 14–17 years) who had sustained a first-time sport concussion and showed increased GABA/Cre level in a region colocalized with activation during a working memory task [72], suggesting that GABA measures could be of great interest in exploring cognitive impairment after TBI.

Brain Perfusion

There has been general interest in studying disturbances of cerebral blood flow (CBF) after traumatic brain injury. Increasing evidence indicates that regional ischemia plays a role in secondary brain injury in patients with brain trauma. A study on rodent models of brain trauma, such as the control cortical impact (CCI) model in rats, reported blood perfusion impairment with delayed cognitive deficits at 1 year of trauma, suggesting a long-term effect of TBI on CBF [73]. Moreover, a detailed neuropathological examination of the brains at autopsy performed in a series of 263 consecutive head injuries reported ischemic damage in 88–92% of these brains, suggesting that ischemic damage, a common observation after severe head injury, may be an important cause of mortality and morbidity [74]. In addition, in vivo studies using single photon emission computed tomography (SPECT), positron emission tomography (PET) [75], and xenon-enhanced computerized tomography (Xe-CT) [76], demonstrated regional perfusion abnormalities and decreased glucose metabolism. Although the results are not completely consistent in terms of global or regional perfusion abnormalities, these studies suggest that evaluation of ischemic and metabolic abnormalities may complement the clinical evaluation in the assessment of outcome after head injury. Perfusion changes may result from vasospasm, direct vascular injury, and/or a failure of cerebral autoregulation; in addition, the brain is more vulnerable to ischemic injury after TBI [77]. It has been demonstrated that there are distinct cerebral hemodynamic phases (hypoperfusion, hyperemia, and vasospasm) following severe head trauma. The majority of the initial imaging studies have focused on the acute stage of moderate-to-severe brain injury. Jacobs et al., however, reported a high prevalence of SPECT abnormalities in subjects even with mild TBI [78]. They also showed that SPECT abnormalities correlate well with the severity of the trauma, indicating that perfusion deficits might be a reliable predictor of a favorable clinical outcome in these patients [79]. However, nuclear medicine techniques for measuring brain perfusion are limited by their low spatial resolution, the use of a radioactive agent, and a relatively high cost.

CBF may be assessed non-invasively with arterial spin labeling (ASL) using MRI. The ASL sequence relies upon unique radiofrequency (RF) pulses that excite (or "label") water protons in the blood while passing through the neck arteries. The magnetization is followed for a period of time (limited by the T1-decay of blood) as the blood travels to the brain, wherein the label is transferred to the brain parenchyma via capillary exchange at a rate that is dependent on tissue perfusion, and ultimately detected by the MR system [80]. Using ASL, it has been demonstrated that CBF is reduced following moderate-to-severe TBI concussion and mild TBI [45, 81–84] (Fig. 14.5) with more prominent regional hypoperfusion in the posterior cingulate cortices,

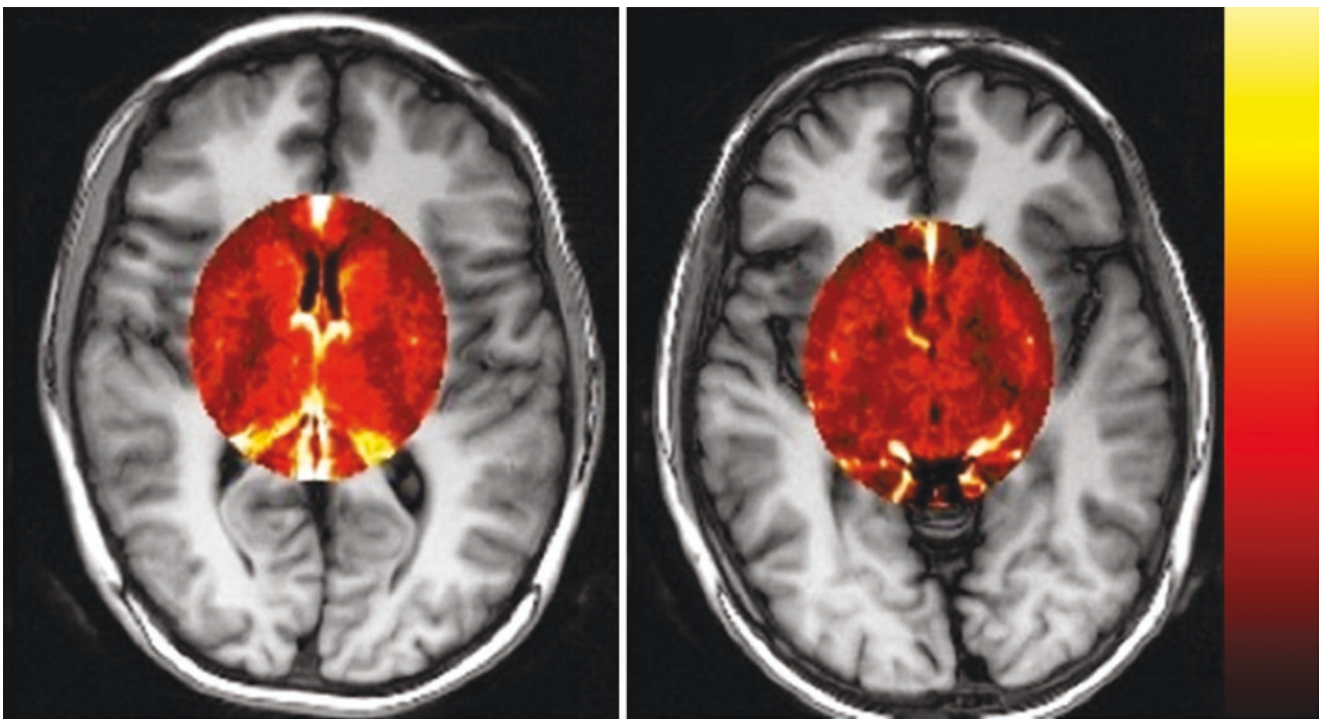

Fig. 14.5 Regional cerebral blood flow (CBF maps) obtained with True FISP ASL in an age-matched normal control (top) and in a patient (bottom) with TBI. Note the decreased level of CBF within the thalamic region in the patient as compared to the normal control. (Figure courtesy of Qun Chen, Ph.D., and Yulin Ge, M.D., New York University, NY)

Table 14.3 Summary of arterial-spin-labelling MRI studies in traumatic brain injury

Authors	Subjects	Results
Kim et al. [81]	27 subjects with moderate-to-severe TBI and 22 healthy controls	Prominent regional hypoperfusion was found in the posterior cingulate cortices, the thalami, and multiple locations in the frontal cortices
Meier et al. [82]	44 concussed subjects	Post-concussion, reduced CBF was found, with progressive longitudinal recovery. CBF in the dorsal mid-insular cortex was decreased at 1 month in slower-to-recover athletes and was inversely related to the magnitude of initial psychiatric symptoms
Churchill et al. [85]	35 subjects with mild TBI and 35 healthy controls	Mean CBF was not significantly different from healthy controls. Greater total symptom severity was associated with elevated posterior cortical CBF

the thalami, and multiple locations in the frontal cortices. However, results are heterogenous, with some studies reporting unaltered or even elevated perfusion at early injury [85] (Table 14.3). A longitudinal evaluation of concussed football players who underwent ASL 1 day, 1 week, and 1 month after injury found an early reduction in right insular and superior temporal sulcus perfusion that normalized at 1 month, although dorsal insular perfusion remained lower in subjects with persisting post-concussion symptoms [82]. However, perfusion abnormalities may persist even after the recovery of clinical symptoms: lower CBF in bilateral frontotemporal regions in chronic pediatric concussion patients was found despite normal results in detailed neuropsychological testing [83].

Resting-State Functional MRI

As discussed in Chap. 19 functional MRI (fMRI) measures neural activity-related changes in cerebral blood flow. As brain activity increases in a specific region, blood flow increases to meet the metabolic demand. The resulting local reduction in deoxyhemoglobin, measurable as T2* signal, causes an increase in MRI signal intensity that is measured by fMRI. Thus fMRI strictly relies on coupling of cerebral blood flow with neuronal activity (the so-called hemodynamic response) [86]. fMRI can be acquired while the subject is performing a task (task-fMRI), such as a cognitive or motor task, or while the subject is at rest (resting state fMRI, RS-fMRI). While task-fMRI detect higher signal areas reflecting increased activation of brain areas related to the specific task utilized, RS-fMRI measures spontaneous fluctuations of the BOLD signal within intrinsic connected networks at rest. Resting-state networks are composed of brain regions that show temporally correlated neural activity. The functional architecture of these networks in part reflects underlying structural connectivity: regions that are strongly connected by white matter tracts are likely to show similar functional properties. This phenomenon makes the function of resting-state networks vulnerable to the effects of TBI, because DAI commonly damages long-distance white matter tracts that connect nodes in these networks [87]. As a result, TBI can be viewed as a classic example of a disorder in which network disruption produces clinically important impairments. TBI patients often display significantly different activation patterns when compared to uninjured control subjects during the performance of motor and cognitive task and exhibit different resting-state functional connectivity within several brain areas [88]. In addition, both task-related and resting state fMRI are promising techniques for evaluating vegetative state, minimally conscious state, and brain death after trauma, a topic which is beyond the aims of this chapter.

Since deficits in working memory are commonly observed after TBI, the early fMRI investigations in patients with TBI focused on performance during memory tasks (Table 14.4). Indeed, although DTI and tractography can help by providing tools to detect fibers and white matter tracts disruption, the true functional significance of white matter microstructural damage in determining cognitive impairment is still unknown. It is conceivable that TBI patients try to overcome the consequences of interrupted fiber connections due to DAI by increasing the recruitment of brain regions subserving the neuronal circuits involved in cognitive, motor, visual, and sensory tasks. As a consequence, TBI patients display a more extensive brain activation pattern than that observed in healthy controls when performing these tasks. Augmented functional recruitment associated with normal performance is, therefore, a marker of reserve limit that may help predict the clinical outcome [38, 87].

McAllister et al. assessed patterns of regional brain activation during a working memory processing task in 12 patients within 1 month of mild TBI and in matched healthy controls. Although there was no difference in task performance between patients and non-injured controls, TBI patients showed significant increased activation especially in the right parietal and dorsolateral frontal regions. Thus, suggesting that injury-related changes in activation and modulation of working memory processing can underlie the memory complaints after TBI [89]. The same investigators found that mild TBI patients imaged few weeks after injury showed increased activation relative to non-injured control subjects during a working memory processing of increasing difficulty. As the difficulty of the task increased, despite a similar performance, patients with TBI showed no concurrent increase in the brain activation [90]. A possible explanation proposed by the authors is that TBI patients have already

Table 14.4 Summary of fMRI studies in traumatic brain injury

Authors	Subjects	fMRI paradigm	Results
Sanchez-Carrion et al. [92]	12 severe TBI and 10 healthy controls	Working memory task	Patients showed significant changes in brain activation over time; at the baseline observation there was a low activation in the right superior frontal gyrus. The difference decreased 6 months after trauma, leading to normalization
Turner et al. [91]	8 patients with moderate/severe TBI and 12 healthy subjects	Working memory task	Patients showed greater recruitment of interhemispheric and intrahemispheric regions of prefrontal cortex and posterior cortices despite equivalent task performance
Scheibel et al. [93]	30 moderate/severe TBI patients and 10 controls	Stimulus response compatibility task	In patients, lower GCS scores were associated with higher brain activation. The cingulated gyrus and thalamus were among the areas showing greatest increases of brain activation, owing to the greater vulnerability of midline structures in TBI
Stevens et al. [94]	30 subjects with mild TBI and 30 healthy controls	Functional connectivity (FC) analysis with independent component analysis (ICA)	Disordered functional connectivity was found for every neural circuit (increased or decreased FC), correlating with post-concussive symptoms
Hillary et al. [107]	21 subjects with moderate/severe TBI and 15 healthy controls	Functional connectivity (FC) analysis with independent component analysis (ICA). Graph theory analysis	Neural networks showed increased FC, and this change was disproportionately represented in brain regions belonging to the brain's core subnetworks
Shumskaya et al. [106]	43 subjects with moderate/severe TBI and 34 healthy controls	Functional connectivity (FC) analysis with independent component analysis (ICA)	Increased connectivity in sensorimotor, visual, default mode, executive, and cerebellar networks. Attention impairments were associated with increased connectivity in the sensorimotor network
Rangaprakash et al. [104]	87 subjects with mild TBI and post-traumatic stress disorder	Whole brain functional connectivity. ROIs based DTI analysis	Post-traumatic stress disorder and post-concussive syndrome are associated with hippocampal-striatal hyperconnectivity

recruited all cognitive reserves at lower levels of task difficulty. A pattern of greater recruitment of interhemispheric and intrahemispheric regions of prefrontal cortex and posterior cortices was observed in a homogeneous group of patients with moderate-to-severe TBI during a task of executive control processing in working memory, despite an equivalent task performance in patients and controls. Thus, providing evidence that increased functional recruitment can affect functional outcome after traumatic brain injury [91]. To investigate the evolution of impairment, Sanchez-Carrion et al. studied longitudinal changes in brain activation during a working memory task in patients with severe and diffuse TBI and in matched healthy controls [92]. Patients, but not controls, showed significant changes in brain activation over time. In particular, at the baseline observation there was a significant difference in the activation pattern with the TBI patients showing a low activation in the right superior frontal gyrus; the difference between patients and controls, however, decreased 6 months after trauma, leading to normalization of the brain activation pattern. This study suggests that a progressive normalization of the working memory activation pattern in severe TBI concurs with an improvement in cognitive performance. Scheibel et al. investigated the correlation of fMRI patterns of activation with the severity of the post-trauma status as assessed by GCS in patients with moderate-to-severe TBI. Cingulate gyrus and the thalamus were among the areas showing greatest increases of brain activation [93]. Importantly, the over-activation pattern varied with TBI severity with greater involvement of left-lateralized brain structures in patients with the most impaired GSC. Thus, supporting the concept that over-activation may be compensatory and improve, at least partially, the clinical performance.

Contrary to task-fMRI, mixed results from RS-fMRI following TBI are reported. Multiple studies have shown evidence of reduced functional connectivity of resting-state networks following TBI. Stevens et al. used independent component analysis to extract 12 distinct resting state networks from thirty mild TBI patients. Altered patterns of connectivity strength were found among all networks tested. Abnormal connectivity was noted between frontoparietal, frontotemporal, and interhemispheric sites [94]. Decreased functional connectivity was also found in separate investigations [95, 96] in the thalamus, caudate nucleus, hippocampus, posterior cingulate, lateral parietal cortices. TBI patients exhibit significantly decreased connectivity in the frontal brain areas even when the conventional structural imaging is negative [97]. In a longitudinal study assessing thalamic functional connectivity in mild TBI, increased functional connectivity over time was identified between the thalamus and the dorsal attention network that was associated with decreased pain and post-concussive symptoms,

suggesting that thalamic connectivity may serve as a quantitative measure of recovery extent following TBI [98]. The default mode network (DMN), which is believed to be important for self-reflection, is one of the most commonly interrogated RS networks in TBI. The DMN shows increased activity in healthy controls during rest and deactivation during attention-demanding tasks. Key regions of the default mode network include the medial prefrontal cortex, anterior and posterior cingulate, and posterior parietal lobule. Reduced network connectivity among key regions of the DMN in concussed patients during the first weeks following concussion, with recovery of DMN connectivity several months following concussion [99–101], has been identified. Furthermore, one study found a negative relationship between reduced posterior cingulate connectivity of the DMN and neurocognitive dysfunction in patients following concussion [102]. On the other hand, there is growing evidence for hyper-connectivity in TBI [103–105]. Shumskaya et al. found that attention abnormalities in TBI were associated with increased connectivity in the sensorimotor networks [106]. In addition, longitudinal studies have shown that despite decreasing functional connectivity during recovery, connectivity remained higher in moderate-to-severe TBI relative to healthy controls [107, 108]. Thus, hyper-connectivity in moderate and severe TBI patients may be present regardless of recovery phase (acute, subacute, or chronic phase) and does not represent a transient process. Differences in the results between studies may be attributed to differences in severity of TBI of the studied cohorts, region selection methods, time from injury, graph metrics utilized, the nature of connectivity studied, and extent of gray and white matter damage. However, it's important to notice that, in the acute setting, TBI patients have been demonstrated to have alterations in hemodynamic response which may confound RS-fMRI analysis and interpretation, if not properly accounted for in the analysis. Moreover, hemorrhage and contusions may alter the BOLD signal or produce artifact that limits evaluation [109].

In recent years, functional connectivity alterations associated with TBI have been studied using the so-called graph theory. This model-free approach examines different properties of the brain network such as integration (length of communication pathways, global efficiency), segregation (clustering behavior, hub formation, modularity), centrality (degree, betweenness centrality), and small-worldness [110]. Recent work has shown graph theory to be a promising method to model brain networks organization and to quantify their pathological deviations. A reduction in network efficiency together with an increased path length was observed in TBI [107, 111], implying a reduction in global integration. TBI patients exhibited many low-degree nodes, and less highly connected hubs [107], resulting in increased total strength of connections and clustering coefficient.

Conclusion

While SWI, DWI, and ASL are sensitive methods for detecting DAI and perfusion deficits even in mild TBI with conventional imaging, and are therefore widely used in the diagnostic setting. Conversely, the clinical diagnostic use of ^{1}H-MRS, DTI, and fMRI has not been fully demonstrated at this time. There is an urgent need for more controlled studies using standardized methods to evaluate imaging data and, equally important, there is a need for controlled longitudinal studies to determine the long-term evolution of imaging abnormalities in patients with TBI and their relationship with the clinical and behavioral outcomes. Finally, since each neuroimaging modality offers specific advantages to evaluate TBI and determine the appropriate treatment, comparison of modalities in a single study is also important to help establish how the modalities can be complementary and individualize treatment using these data. All the MRI modalities described in this chapter, and many new ones still in development, may allow earlier identification of possible chronic sequelae of tissue injury and better understanding of the pathophysiology of cell injury in TBI and, eventually, lead to the development of new neuroprotective treatments and effective rehabilitative strategies.

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