Chapter 24  Magnetic Resonance Imaging Application in the Area of Mild and Acute Traumatic Brain Injury
Implications for Diagnostic Markers?
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24.1. INTRODUCTION

Mild traumatic brain injury (mTBI) causes brain damage generally invisible for conventional imaging methods. Its diagnosis mostly relies on the patient’s history, subjective complaints and neuropsychological status. Long-term complication development is just scarcely linked to these clinical factors. Imaging markers would contribute not only to the diagnosis and prognosis of mTBI, but to the understanding of its pathomechanisms as well. Advanced Magnetic Resonance Imaging (MRI) methods offer new insights to the background of mTBI. The microscopic scale white matter disease following mTBI can be evaluated by Diffusion Tensor Imaging (DTI) and Susceptibility Weighted Imaging (SWI). It’s possible to detect subtle atrophy using advanced volumetric analyses of submillimeter resolution images, while biochemical aspects can be assessed by MR spectroscopy. Functional MRI (fMRI) provides information of altered and compensational brain activity due to injury. Further advanced MRI techniques and perspectives are discussed as well in the chapter.

Mild traumatic brain injury is a special field calling for advanced imaging methods, first of all magnetic resonance imaging (MRI) methods. The numerous definitions for mTBI and inconsistent nomenclature (e.g., concussion, minor head injury, minor brain injury, minor head trauma) show that the confinement of this clinical category is challenging. Diagnoses are mostly based on symptoms and self-reported history, yet no generally deployable objective marker exists; however, recent attempts for both imaging and biomarkers are promising. The most widely accepted criteria for mTBI are blunt trauma, Glasgow Coma Scale of 13–15, brief period (<30 minutes) of loss of consciousness, and brief period (<24 hours) of posttraumatic amnesia (Carroll et al., 2004; Mild Traumatic Brain Injury Committee, 1993). Inclusion of cases in which computed tomography (CT) scans show trauma-related pathology is debated; mostly these cases are excluded (i.e., mTBI is considered to be CT scan–negative). Indeed, CT scans are normal in about 90% of the cases fulfilling the aforementioned criteria; this fact is somewhat paradoxical considering the sometimes alarming neuropsychological signs and symptoms of these patients. The categorization of CT-positive mTBI cases as “complicated mTBI” (e.g., finding of focal contusion) seems to be useful because these cases generally deserve extra attention acutely; however, focal lesions may not predict the outcome 3 months after injury (Lannsjo et al., 2013). Clinical variables together with age may be stronger predictors for outcome (Jacobs et al., 2010).

Beyond the issues with definitions and diagnostic criteria, the greater problem from a clinical point of view is that the severity of the complaints or neuropsychological deficits at admission are only very scarcely linked to the prognosis and true severity of the injury. This means that, for example, loss of consciousness or the length of posttraumatic amnesia is not necessarily associated with the actual mechanical force suffered or the chance of developing persistent posttraumatic complaints. It is important to keep in mind that mTBI can be interpreted as “mild” only when compared with moderate or severe TBI, which is known to be life-threatening. In itself, mTBI is also potentially dangerous because in 10%–30% of cases it may lead to serious long-term complications significantly worsening life quality and disabling work or social interactions (see the following section). Additionally, considering its extremely high incidence (up to 500/100,000), mTBI deserves to be called a public health problem. Long-term complications may include such persisting acute symptoms as headache, dizziness, nausea, or concentration/memory problems, although new complaints may also develop in time such as depression, sleeping disorders, or anxiety. Patients suffering from repetitive mTBIs are especially exposed to long-term complications. This makes the decision of letting one return to work or return to play (in case of sports concussion) really serious. Still, without enough objective information of mTBI-related mechanisms, the background of long-term complications is not fully understood. It is debated whether
Because mTBI-related pathomechanisms remain elusive, therapeutic possibilities are also going to be limited. Presently, the only widely accepted treatment is rest, both physical and cognitive. Medications used merely serve as symptomatic treatment and their use is generally based on local anecdotal evidence (Meehan, 2011).

One reason why identification of the details of related mechanisms has been held up is that, generally, histopathological examination is not possible. Human histopathological observations are very scarce and are from the rare cases of mTBI accompanying fatal conditions. The vast majority of histological information and data about pathomechanism have been obtained from animal (mostly rodent) mTBI models (for an overview on neuropathology in mTBI, see Bigler and Maxwell, 2012). These models allow an infinite range of controlled observations on different elements of brain injury and have provided irreplaceable findings. However, all mTBI animal models suffer from the problem that mTBI can only be interpreted truthfully at the level of the human brain’s complexity. Most of the neuropsychological deficits characterizing this condition are hardly transposable to animals. For example, a mainstay element of the mTBI definition is posttraumatic amnesia. To be simplistic, mTBI, grossly, is the damage of a theoretical fraction of the human brain that an animal does not even have.

These concerns regarding mTBI diagnosis, prognosis evaluation, and pathomechanism have together called for noninvasive, highly sensitive contemporary imaging tools. Among these are single photon emission computed tomography, positron emission tomography, and MRI, the latter of which has become the most widely applied in mTBI studies because it is the most accessible, multimodal, and the least harmful because no ionizing radiation is used and, generally, no contrast agent has to be administered. Multimodality in MRI means that this method, depending on actual acquisition parameters, can provide different insights to the complex pathology of the damaged brain, from detailed microstructural to functional components. Unlike classic neuroradiological scan evaluation, assessment of advanced MRI data is based often on quantitative and statistical methods. This means that although visible images are created, the true information is held in the underlying numbers that allow objective, often group-wise analytical processes.

One of the most promising methods of the field is diffusion tensor imaging (DTI) that is able to detect change in water microcompartments due to microstructural pathology as axonal deformation and swelling. Focal microscopic bleeds developing as part of diffusion axonal imaging are most successfully detectable by susceptibility-weighted imaging (SWI), a method exploiting the magnetic property of iron. Recent efforts seem to validate the clinical importance of these methods (see the following section). High-resolution, three-dimensional, T1-weighted images allow precise volumetric analyses to be performed shedding light on subtle changes in the brain macrostructure because of, for example, edematous and atrophic mechanisms after injury. Beyond the advanced investigation of brain structure, magnetic resonance spectroscopy (MRS) offers information of the metabolic state of the brain by measuring specific magnetic signals from mainly the 1H nuclei in different metabolites. Getting to the functional level, the effect of injury on brain functions such as perception or cognitive tasks (memory and concentration functions are typically affected) can be investigated by functional MRI (fMRI). The following sections provide a brief overview of the benefits and also challenges of using these methods in the mTBI field.

24.2. ROUTINE MRI METHODS IN mTBI

Here, routine MRI refers to magnetic resonance techniques such as T1-, T2-, and spin density–weighted imaging and also fluid-attenuated inversion recovery assessed conventionally by a neuroradiologist. These modalities hold similar information on the injured brain as CT scans, so traumatic pathology such as epidural or subdural bleeding, contusion, or skull fracture can be identified. Nevertheless, CT is more appropriate for this purpose because it is more widely accessible, faster, and less expensive; furthermore, acute bleeding and skull fractures are better outlined. Hence it can be stated that CT is still the imaging method to be chosen to disclose traumatic conditions requiring neurosurgical intervention. The only exceptions may be cases of children or young women where ionizing irradiation has to be avoided. Then MRI may be considered as the first-line imaging tool. However, if the question is the presence of more subtle injuries such as small contusions or microscopic bleeding (hemorrhagic axonal injury), routine MRI is the preferable tool because it is far more sensitive to such lesions (Yuh et al., 2013). Unfortunately, to date, the clinical
value of these focal lesions is debated; no general conclusions can be drawn on how these lesions can be attributed to injury severity within the spectrum of mTBI or the outcome (Hughes et al., 2004). However, a recent study drew attention to the significance of routine MRI features by showing that lesion number accompanied by proper controlling for demographic, socioeconomic, and clinical features improved outcome predictions (Yuh et al., 2013). Although MRI is not yet considered cost beneficial for mTBI, it may become so in the future by developing cheaper magnetic resonance instruments (e.g., head-only MRI).

24.3. ADVANCED MRI METHODS IN mTBI

24.3.1. OVERVIEW

Thanks to the nonstop technical development of MRI, newer and newer methods are becoming available every year. Some of these are decades old but are often called advanced because their capabilities are still not fully discovered and generally need special operation and evaluation. Each can reveal certain special features of brain structure, function, and pathology, for example MRS shows metabolic profile, or DTI reveals microstructural condition. The object for research groups is to explore the clinical effectiveness of these modalities or to find new components of pathomechanism and their correlations in the field of mTBI. This section of the chapter discuss the most important advanced methods for mTBI such as DTI, SWI, fMRI, volumetric analysis, and MRS.

24.3.2. DTI: THE “FINGERPRINT” OF WHITE MATTER

DTI measures Brownian movement of water molecules and applies at least six diffusion gradient directions and thus is able to provide information of both extent and directionality of diffusion (Pierpaoli et al., 1996). Fractional anisotropy (FA) refers to the degree of directionality, calculated from the ratio of eigenvalues of the diffusion tensor, while mean diffusivity (MD) or the synonym apparent diffusion coefficient refers to the overall, directionally indifferent mobility of water molecules. The character of diffusivity in brain is widely accepted to be associated with fiber tracts (i.e., axons and myelin sheath) (Beaulieu, 2002). In the classic theory, in a direction parallel to axons, diffusion is greater than in the direction perpendicular to them, because cell membranes and other structures restrict diffusion. This is why white matter tracts can be visualized by DTI tractography. Though this concept has never been exactly confirmed, tremendous empirical data show that it works quite well. FA and MD are very sensitive parameters indicating subtle alterations of white matter because they are likely to be influenced by axon density, diameter, and continuity; myelin content; myelin sheath thickness; and interstitial water content. This way, DTI can reveal differences among healthy subjects as well (i.e., gender, aging, or education are known to have an effect on DTI parameters).

It is not surprising therefore that DTI is able to detect axonal pathology in severe TBI; however, it might be surprising that to date it has been accepted as fact that DTI finds white matter abnormalities in mTBI as well. This pathology includes axonal disintegration related to shear-strain deformation of the fiber structure as a mild version of diffuse axonal injury. Changes in water microcompartments because of vasogen or cytotoxic edema may also be present and are visible for DTI (Peled, 2007).

A large cohort of studies investigated diffusion in mTBI focusing on several different relationships (i.e., age, acute or chronic phase, clinical symptoms or neuropsychological tests, recovery, or sport- and combat-related injuries).

Many investigations on mTBI found reduced FA or elevated MD (apparent diffusion coefficient) in mildly injured patients (Figure 24.1) and often interpreted the findings as reduced integrity and misalignment of axonal and myelin structures because of shear-strain forces, including local expansion of axonal cylinder or axonal disconnection (Arfanakis et al., 2002; Inglese et al., 2005; Lipton et al., 2008; Miles et al., 2008; Nakayama et al., 2006). Later studies observed oppositely elevated FA or reduced MD acutely after mild injury over several white matter regions (Bazarian et al., 2007; Chu et al., 2010; Mayer et al., 2010). The suggested underlying mechanism was cytotoxic edema; in this condition, the injury altered function of gated ion channels, resulting in intracellular swelling and decreased extracellular water that may cause reduced radial diffusivity (Peled, 2007; Rosenblum, 2007; Wilde et al., 2008). The output yielded by DTI may show a summarized effect of the two basic mechanisms: microstructural disintegration and cytotoxic edema. A recent study also found bidirectional irregularities in DTI parameters after...
injury (Lipton et al., 2012). The actual dominance of these substantial mechanisms in the white matter may theoretically depend on temporal and spatial factors, attributes of the patient, and the circumstances of injury (Obenaus et al., 2007). Future research should shed light on the proper interpretation of the different diffusion indices possibly by focusing also on less robust parameters such as eigenvectors and eigenvalues and studying patient groups by well-homogenized study parameters.

Findings of follow-up studies are also various; some longitudinal studies revealed partial normalization of DTI indices after different periods (Arfanakis et al., 2002; Mayer et al., 2010; Rutgers et al., 2008), whereas other investigations indicated traumatic microstructural alteration to be more permanent (Bendlin et al., 2008) or even to evolve over time (MacDonald et al., 2011). It is likely that DTI parameters change quite dynamically after injury; this has been shown in a study comparing the acute and subacute phases that found dramatic differences in both FA and MD values (Toth et al., 2013). There are promising observations on the relationship of DTI findings with cognitive or psychological dysfunction (Milles et al., 2008; Niogi et al., 2008) and clinical outcome (Messe et al., 2011), especially in moderate to severe cases (Rutgers et al., 2008; Sidaros et al., 2008).

Besides temporal features of white matter changes, spatial characteristics also imply several questions. Though axonal pathology is regarded as mostly diffuse in mTBI, it is clear that some regions must be more vulnerable because of general mechanical and anatomical rules even if considering subject variability. For instance, posterior corpus callosum seems to be the most susceptible to mild injuries (Aoki et al., 2012). In some cases, injury of a certain white matter tract is obviously associated with accompanying complaints. In other situations, the complaint can be linked to the extent of overall injury. Based on clinical history, it is impossible to exactly draw the model of biomechanical forces and thus predict the predominant site (fascicle) of injury (this can be performed on sports concussion cases where video recordings are available and are analyzed by specialized computer algorithms). However, DTI offers retrospective assessment of the manifestation peak sites of axonal injury that can be correlated with occurring signs and symptoms. For example, in case of damaged tracts beginning from the hippocampal areas, impaired memory functions may be more easily understood. If imaging is performed in the chronic phase, it is challenging to decide if DTI abnormalities are a cause or a result of the clinical disorders because mTBI-independent disorders (e.g., depression) themselves may also be associated with DTI abnormalities (Maller et al., 2012). The specificity of posttraumatic neuropsychological testing for DTI resulting in mTBI is a topic of debate because non-TBI factors may affect both (Larrabee et al., 2013).

Although DTI brings up numerous issues to be solved—most importantly to be able to provide clinically useful information at subject level—it possibly could be the first advanced MRI method involved in the clinical arsenal for mTBI.

24.3.3. SWI Deployed to Find Microscopic Bleeding

SWI is particularly sensitive in detecting both intravascular venous deoxygenated blood and extravascular blood products (Haacke et al., 2009; Reichenbach et al., 1997). This method exploits the magnetic property of heme iron: iron causes local magnetic field distortion altering both T2 star relaxation times and phase data that are measurable and can be visualized by proper MRI sequencing. Anatomical structures do not appear well on these images, for example contrast is low between the cortex and white matter or cerebrospinal fluid. In turn, iron content, most importantly bleeding, is shown pronouncedly as hypodense (black) lesions (Figure 24.2).

SWI was shown to be the most sensitive modality for detecting microhemorrhage, primarily in pediatric TBI of mixed severity (Babikian et al., 2005; Tong et al., 2008). SWI does not only reveal more focal lesions in a certain patient than other MRI modalities such as T2-weighted imaging, fluid-attenuated inversion recovery, gradient-recalled echo, or CT does, but SWI hemorrhagic lesions are more unmistakable than lesions on other imaging modalities. This is supported by interrater-reliability data (Geurts et al., 2012).

It was possible to explore correlation of SWI lesion number, volume, and location with neuropsychological functioning (Babikian et al., 2005) or with outcome (Tong et al., 2008) in children. A pediatric patient can be reliably placed in the spectrum of mild-to-severe TBI based on SWI, with a better prediction of cognitive outcome (Beauchamp et al., 2013).
In contrast, adult data and especially studies focusing strictly on mTBI are limited. A study proved the superiority of SWI over CT and conventional MRI in sensitivity to microhemorrhage in a group of adults with dominantly severe TBI patients (Akiyama et al., 2009).

Microhemorrhages do not seem that frequent in mTBI. Based on a study of amateur and professional boxers (Hasiloglu et al., 2011) and on experiences of SWI using diagnostic centers, SWI lesions in mTBI occur in about 1 or 2 of 10 patients. Large amounts of observations were needed to draw correlations with clinical parameters, such as outcomes besides this lesion occurrence. An attempt to do was successfully done by Yuh et al., who found that four hemorrhagic lesions detected early after injury can be regarded as the threshold for predicting poorer 3-month outcomes (Yuh et al., 2013).

**24.3.4. Atrophy, Edema Revealed by Volumetric Analysis**

Brain volume changes such as edema and chronically developing atrophy are known mechanisms in severe TBI. These dramatic volume disorders can be evaluated well by classical neuroradiological methods such as manual morphometric measurements. Different manifestations of brain atrophy after injury were identified in a large number of morphometric studies conducted on mixed (mainly moderate to severe) TBI populations (Bigler et al., 1997; Fearing et al., 2008; Kim et al., 2008; Wilde et al., 2005). Injury severity or cognitive function was correlated with atrophy rate (Bigler et al., 2002; Levine et al., 2008); in one group, outcome was found to be independent from atrophy (Bendlin et al., 2008). The association of posttraumatic stress disorder with atrophy of whole brain (Woodward et al., 2007), corpus callosum (Villarreal et al., 2004), anterior cingulum (Kitayama et al., 2006), and hippocampus (Villarreal et al., 2002) was presented in some studies.

However, in mTBI, the volume changes are not that apparent (i.e., if present at all, they are too subtle for routine neuroradiology methods to detect them), hence far fewer data are available. Furthermore, an important point is that when comparing two healthy subjects’ brain volumes, even if they are normalized for total intracranial volumes, we can find great differences between structure volumes. For instance, if we compare the normalized ventricular volume of two healthy subjects of the same age, gender, or education, a two-fold or even larger difference can be found.

Hence, it is clear that detecting a volume change of a few percentages and regarding it as a trustworthy consequence of mTBI is quite problematic. For such investigations, structural images of the highest possible resolution are needed, in addition to proper quantitative-automatic volumetric analysis algorithms and a high-enough subject number (Figure 24.3). Follow-up arrangements are also advantageous (Ross, 2011). Among the few volumetric studies focusing on homogenous mTBI groups, MacKenzie et al. found global atrophy developed in 3 months in a group of mild and moderate injured patients that was correlated with length of consciousness (MacKenzie et al., 2002); the presence of atrophy in mTBI was supported by others as well (Zhou et al., 2013). Gray matter atrophy was detected years after injury by Cohen et al. in an mTBI group (Cohen et al., 2007). Messe et al. showed gray matter volume to be decreased, but not to be predictive for outcome (Messe et al., 2011). A study concentrating on the acute-subacute phase of mTBI detected cortical gray matter and ventricle volume changes over the first month after injury proposed to be due to recovery from an initial subtle edema (Toth et al., 2013).

Although group-wise studies providing valuable data of mTBI volumetric changes are gathering, the single time point volumetric assessment at the subject level is not informative enough in mTBI. However, follow-up volumetric analysis was shown to possibly be beneficial in single cases as well (Ross et al., 2013).

**24.3.5. Functional MRI: Closer to Understanding Cognitive Disorders**

fMRI detects local hemodynamic changes following increased metabolic rate in neural activity, by measuring the blood oxygen-level dependent (BOLD) contrast (Nair, 2005; Ogawa et al., 1992). Specific cognitive, motor, memory tasks, or sensory stimulation are repeated and the associated BOLD signals are compared (Moonen, 2000). Functional connectivity investigation reveals brain areas with correlated fluctuations (i.e., coupled functionality) during an experimental task or resting state (in the absence of any active task or external stimulus) (Rogers et al., 2007).

Cognitive disorders such as impaired processing speed, concentration, and memory problems are typical in mTBI.
fMRI is hence a plausible tool in mTBI to better understand underlying neural function abnormalities and plasticity or to detect specific mTBI-related functional patterns (McDonald et al., 2012). An outstanding advance of fMRI is the opportunity to measure actual task performance of a patient simultaneously with functional imaging. For example, during a memory task, the number of correct answers or reaction speed can be quantified. This helps the observer interpret the functional imaging findings (e.g., additional activations in an injured patient performing as well as a control subject is likely to mean a compensational neural recruitment).

Most studies concentrated on memory functions, especially working memory (Chen et al., 2004; McAllister et al., 1999; McAllister et al., 2001; Pardini et al., 2010; Perlstein et al., 2004; Smits et al., 2009). The altered activation of primarily the dorsolateral prefrontal cortex was suggested to underlie working memory dysfunctions. A few studies focused on spatial working memory or declarative/episodic memory (Figure 24.4) (Russell et al., 2011; Slobounov et al., 2010; Stulemeijer et al., 2010).

In these studies, various injury-related changes of BOLD signal levels and distribution were detected. Some investigators found attenuated activation in mTBI patients compared with healthy subjects that may be a result of an injured neural network (Chen et al., 2004; Gosselin et al., 2011; Lovell et al., 2007; Perlstein et al., 2004). Others reported increased or additional activation (i.e., involvement of new, normally silent areas) (McAllister et al., 1999; Slobounov et al., 2010; Smits et al., 2009). The latter findings are generally considered to be an effect of neural reorganization or functional accommodation. The discrepancy across these findings of hypo- and hyperactivation patterns in mTBI memory tasks was somewhat resolved by a recent study pointing out the significance of a working memory task being considered a continuous or a discrete task (Bryer et al., 2013).

Correlation between BOLD signal changes and neuropsychological findings or task performance was proposed by some studies (Lovell et al., 2007; Smits et al., 2009; Stulemeijer et al., 2010); however, the alteration of BOLD signal distribution was observed independently of clinical complaints or performance as well (McAllister et al., 1999; Slobounov et al., 2010). Because fMRI can reveal abnormal memory functional activity beside normal behavioral performance of the patients, it was suggested to be a more sensitive tool for neuropsychological evaluation than classical tests (Chen et al., 2012). A relatively low number of longitudinal studies showed the cessation of symptoms over time to be associated with the normalization of cortical patterns (Chen et al., 2008; Lovell et al., 2007).

The recent wave of resting state fMRI studies on mTBI patients provided further important insights into the functionality of the injured brain. In this method, the brain’s intrinsic connections (functional connectivity) are mapped by the analysis of low-frequency fluctuations. An important network of a resting (or deactivation) state of the brain is called the default mode network. The default mode network involves brain areas such as the medial prefrontal cortex and parietal and retrosplenial areas (Deco et al., 2011). The extent of these areas and their connectivity strength may be altered because of injury. Depending on explored areas, both decreased and increased connectivity were registered (Johnson et al., 2012b; Mayer et al., 2011; Slobounov et al., 2011; Tang et al., 2011). Alterations in the default mode network connectivity were suggested to be predictive for acute neuropsychological complaints (Johnson et al., 2012b; Mayer et al., 2011) and for later developing postconcussion syndrome as well (Messe et al., 2013).

Abnormal functional patterns in mTBI can be interpreted both as a cause or a consequence of neuropsychological malfunction that is a challenging theoretical, near-philosophical question. If certain cortical areas or linked axonal pathways are injured and cause complaints, those may appear as altered function. However, it is also possible that injury causes a more general and complex abnormality and a certain local BOLD signal alteration is its only mark. Integration of structural and functional connectivity data may be a subsequent step to elucidate these dilemmas (Sharp and Ham, 2011).

Because of the inherent heterogeneity of mTBI, future fMRI studies should strain after larger and more characterized cohorts by means of injury type, age, psychosocial factors, and image acquisition timing after injury to fully exploit the possibility of understanding cognitive sequelae of mTBI held by fMRI.

24.3.6. **Virtual Biopsy** of mTBI: MRS

By measuring chemical compound-specific magnetic signals from 1H nuclei, MRS offers metabolic information of
the brain tissue in vivo. This method can be used to detect and characterize altered metabolism in mTBI. Metabolic disorder is believed to start with the neural shear-strain deformation leading to abnormal ion flow through cell membranes triggering excitatory factors (e.g., glutamate) followed by compensatory mechanisms (increased glycolysis and ATP generation). Manifestation of cell death and inflammation may also interlard the metabolic picture.

The main peaks of a proton MRS spectrum refer to metabolites revealing important data about the brain’s injured state: N-acetylaspartate (NAA) is a marker of neuronal integrity and viability; choline is a membrane marker altered in membrane damage (e.g., from diffusion axonal imaging or inflammation and also during proliferation); myo-inositol is regarded a glial marker; lactate is attributed to ischemic /hypoxic conditions; creatine (Cr) and phosphocreatine are related to energy metabolism but are often assumed to be relatively constant so are widely used as an internal reference for other peaks; and glutamate and glutamine (glx when combined) are important neurotransmitters or metabolites (glutamine).

Decreased levels of NAA seem to be convincing in characterizing the acute phase of mTBI in adults, which is reasonable considering the lower NAA turnover capacity of the injured neurons (Cecil et al., 1998; Henry et al., 2011; Maugans et al., 2012; Vagnozzi et al., 2010; Yeo et al., 2011). NAA decrease may be postulated a marker for impact severity, when the spectrum is obtained soon after the trauma. However the later (subacute to chronic) fate of NAA levels is more contradictory. Some longitudinal studies have shown NAA levels return to normal over a few weeks (Henry et al., 2011; Vagnozzi et al., 2010). This implies NAA is also able to reflect recovery, at least of the neural tissue—this is not necessary linked to the patients’ neuropsychological status; nevertheless, a study elucidated significant associations between NAA levels and neuropsychological test results in the subacute phase (Govind et al., 2010). On the other hand, a considerable amount of studies have found abnormal NAA levels while still in the chronic phase (Cecil et al., 1998; Cohen et al., 2007; Garnett et al., 2000; Govindaraju et al., 2004; Kirov et al., 2007), indicating mTBI can potentially cause persistent alteration. Yet it is hard to evaluate the clinical significance of these definitive changes because many of these studies had no information concerning the patients’ neuropsychological state or the available clinical correlations were inconsistent. Some studies support that NAA levels are sensitive to postconcussive symptoms (Kirov et al., 2013; Sarmento et al., 2009), whereas others state that MRS may detect metabolic abnormalities even after the patient’s clinical recovery (Johnson et al., 2012a). Interestingly, premorbid intelligence may also affect the neurometabolite normalization rate (Yeo et al., 2011).

A factor definitely worsening both clinical outcome and neurometabolite abnormalities is if head injury is repetitive. The classical theory holding that recurrent brain injury has a cumulative effect has been supported by MRS studies, by means of extraneurometabolite alterations when compared with a single mTBI episode (Vagnozzi et al., 2008). These observations are promising in predicting or evaluating chronic traumatic encephalopathy.

Some studies indicated that the instability of Cr levels in mTBI has important connotations (Gasparovic et al., 2009; Yeo et al., 2011). First, this means that Cr may not work well as an internal reference for metabolite ratios in brain injuries, which, at least partially, explains inconsistencies among MRS studies on mTBI. Second, altered Cr levels as energy markers may be attributed to hypo- or hypermetabolic state (Castillo et al., 1996), as known from different diseases as well (Hattingen et al., 2008).

Although MRS is a relatively time-consuming magnetic resonance method because of its noninvasiveness, it is a unique tool for the longitudinal metabolic description of mTBI. Therefore it holds great promise in better characterizing the injured brain and also as a clinical tool. The provided data may be particularly important adjuncts when interpreting other MRI modality findings.

### 24.3.7. Further Evolving Advanced MRI Methods

An “upgraded” version of DTI, diffusion spectrum imaging, is believed to resolve crossing fibers (unlike conventional DTI). This method recently provided novel insights into the human white matter microstructure (Hagmann et al., 2008; Wedeen et al., 2008). This, together with novel connectomic techniques (Irimia et al., 2012) and functional connectivity data, may revolutionize understanding alterations in mTBI at the brain network level. Some preliminary data already indicate distinct structural connectivity alterations.
Iron deposition detection and quantification was proposed to be advantageous in mTBI based on previous animal study observations of nonfocal hemoglobin degradation products resulting from oxidative stress and blood–brain barrier dysfunction. For this, magnetic field correlation was used by a group that found abnormal iron accumulation in deep gray matter (Raz et al., 2011).

Beyond function-related neurovascular abnormalities presented by fMRI studies, general hemodynamic (i.e., perfusion disorders) are also likely to occur in mTBI. MRI offers different methods to assess perfusion, such as arterial spin labeling or dynamic contrast-enhanced perfusion imaging. A few studies on mTBI revealed quite specific regional cerebral blood flow deficits attributable for neuropsychological malfunctions (Ge et al., 2009; Liu et al., 2013).

24.4. CONCLUSION AND PERSPECTIVES

Over just more than a decade, advanced MRI studies provided results that brought reappraisal of mTBI. It turned out that the so-called mild injury is characterized by a rather complex pathophysiology that was previously not recognized, or was only hypothesized. Both structural and functional components have become objectively and noninvasively examinable. The multimodality of MRI offers different insights into mTBI sequelae within one patient at a certain time point, and divergent data may be integrated to better interpret results. Beyond the theoretical mapping of this pathological state, contemporary research is very close to yielding clinically useful MRI markers. This means that in cases where routine imaging such as CT does not indicate pathology calling for urgent care, more advanced methods may gain ground and become a useful adjunct in diagnosis, prognosis, and follow-up of mTBI.

Presently, the main limiting factors of such deployment are the heterogeneity of mTBI and the problematic standardization of these methods. Advanced MRI methods are generally quite sensitive but in turn not specific enough for different etiologies. Normal intersubject variability may be in some cases bigger than mTBI-related alteration of a MRI parameter. Similar alterations may be caused by numerous other pathologies, but for instance many parameters are altered due to normal aging or education as well. Yet, the main findings are drawn from group analyses. Future research should enable the clinically feasible application of advanced MRI methods at the subject level.

REFERENCES


neuroimaging study.
Voxel-wise statistical comparison of DTI parameters between an acute-phase mTBI group (n = 15) and an age-, sex-, and education-matched healthy control group. Red-yellow indicates voxels of significant (corrected p < 0.05) difference between the groups: FA refers to fractional anisotropy, which was decreased in the mTBI group compared with controls; MD refers to mean diffusivity, which was increased in the mTBI group compared with controls. Green voxels indicate white matter tract midlines where no significant difference was found. Background image is an average FA map of the two groups. To achieve these data and images, tract-based spatial statistics, which is part of the FSL software library, was used. (Courtesy of FMRIB Oxford).
FIGURE 24.2

SWI of an mTBI patient. Hypodense lesions (black dots) indicate microscopic bleeding (i.e., hemorrhagic axonal injury). This patient had a Glasgow Coma Scale score of 14 at admission, reported loss of consciousness, and also posttraumatic amnesia.
FIGURE 24.3

This figure demonstrates brain tissue edge displacement of an mTBI patient occurring between the acute (48 hours) and subacute phase (32 days) after injury. Blue indicates brain volume decrease, whereas red indicates brain volume increase along tissue borders. It can be seen that, around the ventricles, virtually only blue can be observed. This means that more than 1 month after injury, this patient's ventricles were expanding. This can be a result of recovering initial edema or developing atrophy as well. These images were generated using the “SIENA” two time point estimation tool, part of the FSL software library. These volume changes can be quantified when necessary (Courtesy of FMRIB Oxford).
fMRI group analysis reveals attenuated activation during a spatial retrieval memory task (Roland’s Hometown Walking task) in mTBI patients (n = 12) compared with age- and sex-matched healthy subjects. Red-yellow indicates significantly lower activations, which can be seen at the left parahippocampus and the temporal poles.

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