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Chapter 21

Neuroimaging of brain trauma in sports

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Abstract

Computed tomography (CT) and magnetic resonance imaging (MRI) have revolutionized the assessment of traumatic brain injury (TBI) by permitting rapid detection and localization of acute intracranial injuries. In concussion, the most common presentation of sports-related head trauma, CT and MRI are unrevealing. This normal appearance of the brain on standard neuroimaging, however, belies the structural and functional pathology that underpins concussion-related symptoms and dysfunction. Advances in neuroimaging have expanded our ability to gain insight into this microstructural and functional brain pathology. This chapter will present both conventional and more advanced imaging approaches (e.g., diffusion tensor imaging, magnetization transfer imaging, magnetic resonance spectroscopy, functional MRI, arterial spin labeling, magnetoencephalography) to the assessment of TBI in sports and discuss some of the current and potential future roles of brain imaging in the assessment of injured athletes.

INTRODUCTION

The advent of cross-sectional neuroimaging, first using computed tomography (CT) and later magnetic resonance imaging (MRI), revolutionized the assessment of traumatic brain injury (TBI) by permitting rapid noninvasive detection and localization of intracranial hemorrhage, contusion, and edema. Further refinements of imaging methods, such as susceptibility-weighted imaging, further improved the effectiveness of neuroradiologic assessments of TBI. It is, however, unusual for sport-related concussion and mild TBI (mTBI) to result in grossly visible injury of the type so exquisitely detected in moderate to severe TBI. Further advances in neuroimaging, both in terms of measurement and analysis approaches, have expanded our ability to see beyond macroscopic injury and elucidate the microstructural injury and associated functional consequences that underlie the pathophysiologic and functional effects of concussion. This overview will describe both conventional and more advanced imaging approaches to assessment of sports-related brain injuries, and discuss some of the current and potential future roles of neuroimaging in the assessment of injured athletes.

NEUROIMAGING OF MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

In players sustaining a more severe injury, such as those sustaining loss or alteration of consciousness, emergency neuroimaging may be warranted to rule out life-threatening injury that may require neurosurgical care. Nonenhanced CT of the head is the mainstay of imaging in this scenario, as it is widely available and can be performed very quickly to evaluate for the presence of primary injuries such as intracranial hemorrhage and skull fracture, edema, mass effect, or vascular injury. CT angiography is useful for rapid and high-resolution

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assessment of the integrity of the major arteries and veins of the head and neck, e.g., to identify laceration, thrombosis, or dissection. CT is widely employed for triage and to determine if neurosurgical intervention is needed. The increasing widespread use of CT has raised concerns of the risks associated with an increasing radiation exposure to both adult and pediatric populations (Brenner and Hall, 2007). Conventional MRI, including diffusion-weighted imaging, is useful in evaluating acute injury due to contusion, shear forces, or ischemia. MRI, particularly susceptibility-weighted imaging, is far superior to CT for the detection of microhemorrhage, and may be more sensitive than CT to detect subarachnoid blood, when T2-weighted fluid-attenuated inversion recovery imaging is employed.

PRIMARY INTRACRANIAL INJURY

Intracranial bleeding is a common finding in moderate to severe head injuries (Osborn, 2013). Since the skull serves as an unyielding enclosure to the brain, the volume added to the intracranial space by hemorrhage can ultimately result in mass effect and vasogenic edema, which compress the brain parenchyma, compromise vascular flow, and may ultimately lead to herniation and death if emergency surgery is not performed in a timely manner. Arterial bleeds are particularly worrisome due to their higher pressures, which can be compounded in the setting of arterial hypertension.

Extra-axial hemorrhage can involve bleeding into the epidural, subdural, and subarachnoid spaces. Epidural hematoma is limited by dural attachment at cranial sutures. On cross-sectional images, this results in a biconvex (lens-shaped) collection of blood within the epidural space that is classically associated with arterial laceration, most commonly the middle meningeal artery due to adjacent skull fracture (Fig. 21.1). Epidural hematoma may also occur due to venous injury, including injury of the dural venous sinuses. Although epidural hematoma is generally a surgical emergency with high risk of mortality and need for emergency surgical evacuation, some epidural hematomas resulting from venous bleeding, such as at the temporal pole, have a benign natural history and do not require evacuation (Kim and Gean, 2011).

Subdural hematomas typically manifest as crescent-shaped collections of blood on cross-sectional imaging. These expand the potential subdural space and are typically caused by injury of bridging cortical veins. Subdural hematomas are limited by the falx/tentorium and the arachnoid membrane.

Subarachnoid hemorrhage is also a common finding in moderate to severe TBI, with acute blood seen within the subarachnoid space, particularly within cerebral sulci. Subarachnoid hemorrhage results from injury of cortical arteries and veins, or parenchymal brain injury extending into the subarachnoid space. Because the subarachnoid space is contiguous with the ventricles of the brain, subarachnoid hemorrhage commonly redistributes blood though the ventricular system. Alternately, intraventricular hemorrhage due to extension from adjacent parenchymal injuries can extend into the subarachnoid space (Fujitsu et al., 1988).

Intracerebral (parenchymal) hemorrhage is characteristic of more severe TBIs and generally has two forms: hemorrhagic contusion/laceration of brain tissue, and microhemorrhage due to diffuse axonal injury. The latter typically occurs in the deep white matter (e.g., corpus callosum and brainstem) and at the cortical gray–white-matter interface (Fig. 21.2).

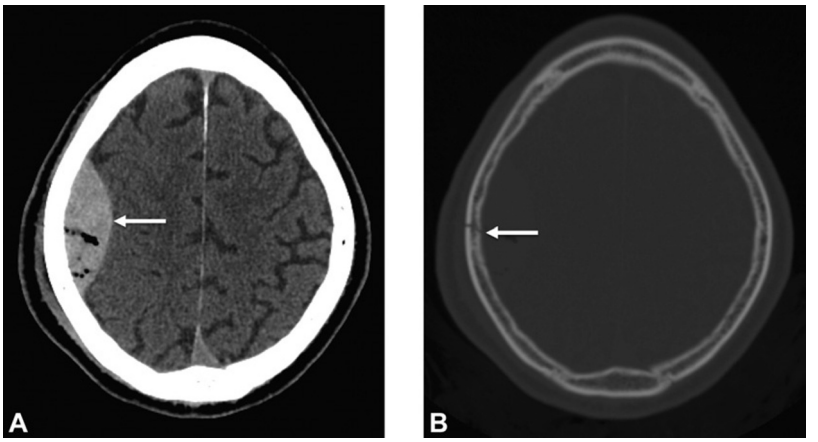

Fig. 21.1. (**A**) Epidural hematoma (*arrow*). This noncontrast computer tomography image of the head of a patient with traumatic brain injury demonstrates an acute right-sided epidural hematoma which is biconvex in shape and causing compression of the adjacent brain parenchyma (**A**). Epidural hematomas are often seen with a skull fracture (*arrow*), as in this case (**B**). This patient also had pneumocephalus due to communication outside the skull. Note the soft-tissue swelling adjacent to the injury site.

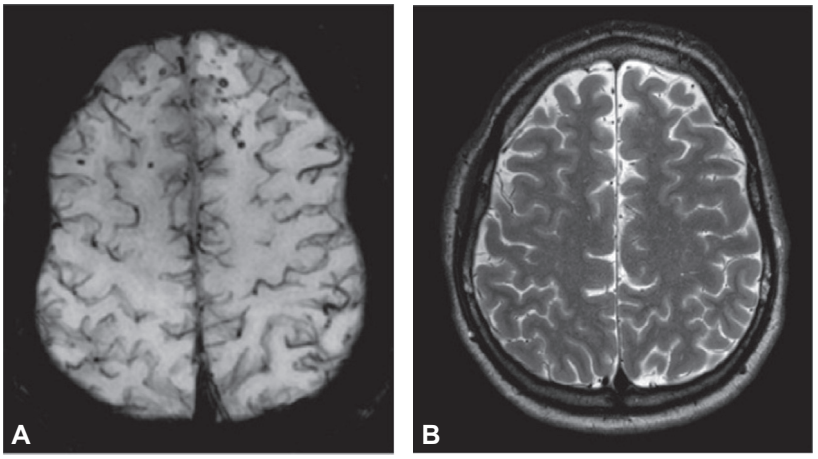

Fig. 21.2. (**A**) Diffuse axonal injury. Susceptibility-weighted imaging is highly sensitive to hemorrhage. In this patient with traumatic brain injury, foci of microhemorrhage are seen as a low signal within the anterior bilateral frontal lobes, and primarily located at the gray–white-matter junction, consistent with axonal shearing injuries seen in diffuse axonal injury. Conventional T2 imaging (**B**) underestimates such injuries.

SECONDARY INTRACRANIAL INJURY

Conventional imaging is also useful to evaluate for secondary intracranial injuries (Osborn. 2013). Repeat CT scans may be performed to monitor for cerebral edema. This brain swelling can lead to intracranial herniation syndromes which in turn may cause brain ischemia – either directly through compression of vascular structures, or indirectly due to increased intracranial pressure causing decreased brain perfusion, in accordance with the Monro–Kellie doctrine (Mokri, 2001). Posttraumatic vasospasm may occur leading to additional vascular compromise and ischemic injury.

NEUROIMAGING OF MILD TRAUMATIC BRAIN INJURY

Mild TBI, or concussion, accounts for over 75% of TBI cases (Centers for Disease Control and Prevention, 2003). As described in Chapters 12–15, symptoms of concussion include headache, confusion, fatigue, changes in sleep and behavior, neurosensory deficits, imbalance, and cognitive disturbance, which generally resolve over days to weeks (Carroll et al., 2004; McCrea et al., 2009; Mott et al., 2012). A minority of patients with mTBI, however, experience persistent symptoms and dysfunction.

Some patients with clinical features of mTBI will manifest visible abnormalities on neuroimaging, such as microhemorrhage. This group is commonly classified as having complicated mTBI (Williams et al., 1990). However, conventional neuroimaging is characteristically unrevealing in most patients with mTBI, including those with persistent symptoms (Hulkower et al., 2013). In fact, absence of visible indicators of brain trauma, such as hemorrhage and contusion, is a feature of most mTBI diagnostic criteria (McCrory et al., 2017).

Notwithstanding normal imaging findings, it is now generally recognized that persistent symptoms and dysfunction in mTBI arise from brain pathology below the detection threshold of standard imaging methods (Hulkower et al., 2013). Although evidence of progressive loss of brain volume over time has been quantified in mTBI patients (Zhou et al., 2013), it is advanced neuroimaging techniques that yield insight into microstructural and physiologic features of underlying brain pathology that offer approaches to evaluating such patients when conventional imaging is negative.

DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is an MRI technique that uses multidirectional magnetic field gradients to characterize the motion of water molecules within tissue. DTI is especially useful for examining the white matter of the brain. In a freely diffusible environment, such as in cerebrospinal fluid, water diffusion is essentially unrestricted (occurs equally in all directions) and is thus termed isotropic diffusion. White matter comprises bundles of axons packed closely together. Because the axolemma and myelin sheath present a relatively impermeable barrier to the free diffusion of water molecules, diffusion predominates along the long axis of the axons. This anisotropic motion of water molecules occurs in the intracellular compartment, but predominantly within the extracellular compartment. The movement of water along the different spatial gradient magnetic fields attenuates the MR signal of diffusing water protons in proportion to movement along the orientation of the gradient. Diffusion under a range of sensitizing directions can thus be modeled as a tensor or three-dimensional ellipsoid. From this model, we can derive parameters that describe the movement of water molecules within a voxel of interest.

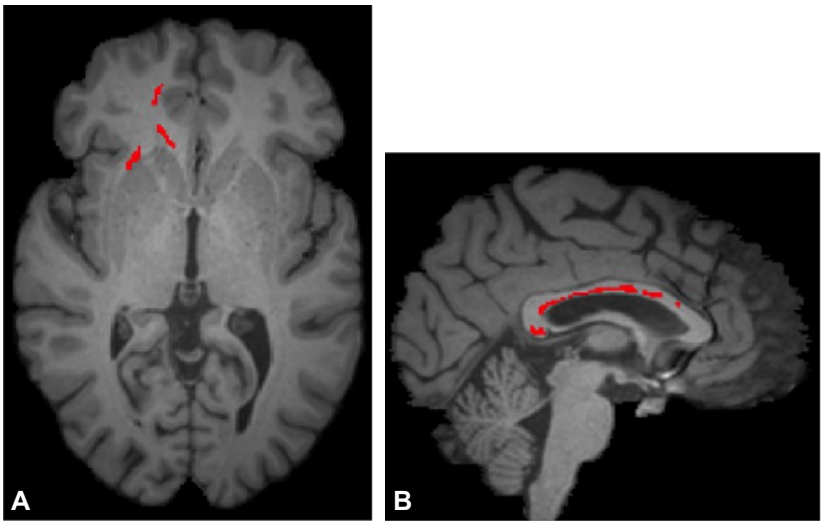

Fig. 21.3. (**A**) Diffusion tensor imaging abnormalities in a patient with mild traumatic brain injury, overlaid on structural imaging. Clusters of abnormally low fractional anisotropy (red) are shown within the right frontal lobe on axial T1-weighted images (**A**) and in body and splenium of the corpus callosum on sagittal T1-weighted images (**B**) (Suri et al., 2015). These regions reflect microstructural changes not visible on conventional magnetic resonance imaging.

Fractional anisotropy (FA) is a DTI parameter which measures the degree to which water molecules travel along the major axis of the ellipsoid. An FA value of 1 represents unidirectional motion along the major axis, while 0 represents completely isotropic motion. Mean diffusivity (MD), another DTI parameter, measures the magnitude of diffusion, independent of direction. Other parameters, such as radial diffusivity and axial diffusivity, characterize diffusion specifically along these demensions. Unlike conventional structural MR images used in clinical practice, DTI images generally require computational postprocessing, where diffusion values of a patient are compared to those of a control population. As individual brains vary in size and configuration, images must undergo "registration" into a common reference frame, typically that of a published brain atlas. This manipulation of the imaging data can introduce errors. Such registration errors can be reduced by performing registrations using the patient's brain as the reference frame, rather than a brain atlas (Suri et al., 2015) (Fig. 21.3).

FA is the diffusion parameter most widely studied in mTBI. It can discriminate mTBI patients from controls, despite differences in imaging and analysis methods and despite the absence of conventional imaging findings (Shenton et al., 2012; Hulkower et al., 2013). FA measurements may be extracted from anatomic regions of interest (ROI) or from white-matter tracts, defined using tractography methods (Fig. 21.4). Because the a priori choice of one or more ROI/tracts implies a specific hypothesis that the selected region will be the locus of injury, instances of injury outside the selected ROI or tracts will be missed.

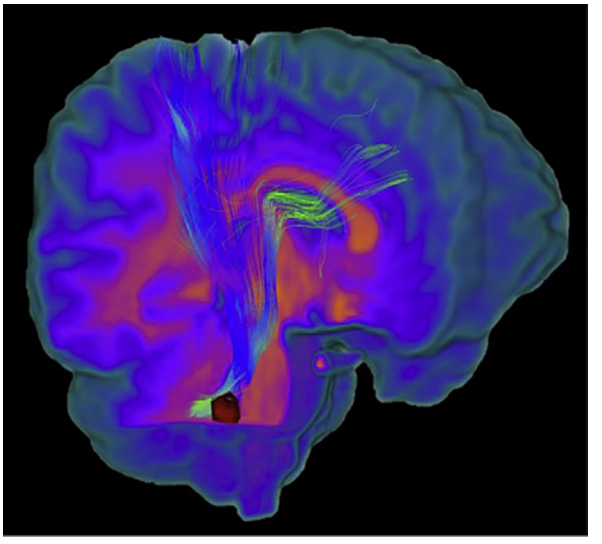

Fig. 21.4. Diffusion tensor imaging-based tractography in a patient with mild traumatic brain injury. Overlying the three-dimensional rendered imaging of the patient's T1-weighted image, fiber tracts generated from the patient's diffusion imaging emanate from a region of interest in the right middle cerebellar peduncle (red).

An alternate approach assesses the entire brain volume on a voxel-by-voxel (voxelwise) basis to determine the location of abnormalities, without a bias as to expected location. Whichever approach is employed, DTI parameter images can be used to compare groups in research studies, or to assess an individual in the context of a control group, whereby significant deviations indicate microstructural white-matter changes consistent with traumatic axonal injury (Arfanakis et al., 2002;

Inglese et al., 2005; Bazarian et al., 2007; Kraus et al., 2007; Niogi et al., 2008).

In addition to microstructural changes related to concussion, several studies have reported similar imaging abnormalities in the setting of repetitive subconcussive head injury. For example, amateur soccer players show a decline of FA relative to the amount of heading they do, in a dose-dependent fashion (Lipton et al., 2013). In a study of 12 adolescents who played ice hockey, rugby, and baseball, athletes had lower FA and higher MD compared to controls (Virji-Babul et al., 2013).

In two additional studies that evaluated DTI in 18 football players and 9 ice hockey/football players, respectively (Henry et al., 2011; Bazarian et al., 2012), the athletes demonstrated regions of higher FA and lower MD compared to controls. These results underscore the fact that, in patients with mTBI, values of FA and MD may deviate above or below values of a control group. These different directions of change may reflect timing in the dynamic process involved in evolution and recovery of white-matter injury. Higher FA, for example, may be the result of edema during the acute phase (Kimura-Ohba et al., 2016). Alternatively, persistent neuroinflammation or neuroplacticity, including remyelination during the chronic phase, could also result in increased FA (Wilde et al., 2008; Mayer et al., 2010; Strauss et al., 2016). Thus, although FA is a powerful tool to detect pathologic changes related to mTBI (including symptomatic concussion as well as repetitive subconcussive trauma), even in the setting of normal conventional imaging, its prognostic utility remains to be defined by further research.

BEYOND FA: NOVEL MR APPROACHES TO TISSUE CHARACTERIZATION

Most studies employing DTI in the study of concussion have reported effects on FA, with fewer reporting alteration of other DTI metrics. Notwithstanding the revolutionary insights into brain substrates of concussive and even subconcussive injury it has facilitated, DTI itself remains limited in its ability to characterize tissue microstructure, including the resolution tissue features such as crossing fibers and gray matter. Moreover, the nature of diffusion sensitization in DTI, relying on a single moderately high b-value, precludes the characterization of important tissue water pools such as “free” and intracellular water. Advanced techniques, which employ multiple b-values over a broader range and which leverage more complex mathematic approaches to characterize diffusion, are able to resolve and characterize important additional features of tissue microstructure (Shemesh et al., 2010; Zhang et al., 2012). Approaches such as diffusion kurtosis imaging (Jensen and Helpern, 2010) and neurite orientation density dispersion imaging (Zhang et al., 2012) are but two examples of advanced diffusion imaging techniques that hold promise for the characterization of microstructure and, it is hoped, more specific identification of pathologic mechanisms.

Several studies of concussion have employed advanced diffusion measurements and shown effects both consistent with those found with DTI as well as additional findings that may provide insight into underlying pathologic mechanisms (Stokum et al., 2015; Churchill et al., 2017; Mayer et al., 2017), which have also been explored in rodent models (Yu et al., 2017). Due to the small number of studies available, each employing a relatively small sample and unique design, future research will be required to evaluate the utility of advanced diffusion techniques for characterization of concussion-related pathology and patient prognosis.

In addition to diffusion, several quantitative MR methods hold promise for tissue characterization of concussion-related pathology by providing MR tissue contrast and quantitative metrics distinct from the T1- and T2-weighted contrasts used in conventional MRI. Examples include T1-rho (Gonyea et al., 2015), quantitative susceptibility mapping (QSM) (Chai et al., 2017), and magnetization transfer imaging (MTI). Each of these techniques yields a quantitative metric for tissue characterization. T1-rho characterizes one aspect of macromolecule concetration, QSM provides a metric of magnetic susceptibility that may reflect microhemmorhage and/or vascular phenomena, and MTI provides another macromolecular measure which is used to characterize myelin (Heath et al., 2018).

Although T1-rho holds much promise for the assessment of subclinical pathology, it has not been reported in concussion. QSM has been applied to discriminate mTBI patients from controls and the measure was related to symptom severity (Chai et al., 2017). A study using MTI (McGowan et al., 2000) found that, compared to controls, patients with mTBI have abnormalities in the splenium of the corpus callosum. In a study of all classes of TBI (Bagley et al., 2000), abnormal findings on MTI were found in 8 patients among regions of otherwise normal-appearing white matter (by conventional imaging); these patients all had persistent neurologic deficits. Future studies will be needed to determine how quantitative MR techniques may provide diagnostic and prognistic biomarkers for patients who have persistent symptoms after mTBI.

MAGNETIC RESONANCE SPECTROSCOPY

Magnetic resonance spectroscopy (MRS) provides noninvasive in vivo quantification of the abundance of chemical constituents of tissue and has been applied to

sports-related mTBI (Lin et al., 2012). Several sports populations have been studied, with metabolic alterations related to collision and concussion. These include elevation of choline (Manning et al., 2017), decline of *N*-acetyl aspartate, and alteration of neurotransmitter levels. Brain energetics in the wake of sports concussion has also been investigated using phosphoros-31 MRS (Sikoglu et al., 2015). An important limitation of MRS is its spatial resolution and field of view. Only few and relatively large brain regions can be interrogated within a reasonable imaging time. Synthesis of findings across studies that report alteration of different metabolites extracted from different brain regions in different patient populations is thus a significant impediment to delineating salient neurometabolic signatures of concussion-related pathology.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Functional MRI (fMRI) is an advanced MRI technique that allows for the evaluation of neural activity within the brain. This technique is based on the principle of neurovascular coupling of the nervous and cardiovascular systems. When an area of the brain is activated, the resultant increase in metabolic demand causes an increase in blood flow and volume localized to that region. Over several seconds, a localized increase in the ratio of oxygenated to deoxygenated hemoglobin, termed the blood oxygenated level-dependent (BOLD) effect, develops in the region. Rapid T2*-weighted imaging is used to capture this physiologic response. As the fraction of paramagnetic deoxygenated hemoglobin decreases, the MR signal becomes greater. However, on MRI scanners in clinical use, the magnitude of signal change is typically only 2% higher than the background signal. Many repetitions of the fMRI measurement are thus needed to achieve adequate statistical power. As with DTI, computationally intensive postprocessing of the data is necessary.

In a typical fMRI protocol, the patient alternately performs or rests from motor or cognitive tasks during a period of continuous imaging that spans many minutes. Voxelwise analysis of the brain is used to identify those voxels that exhibit signal change correlated with the timing of the switching between rest and tasks. Regions of significant activation are rendered in color on T1-weighted images of the subject. In addition to task-based fMRI, resting-state fMRI can be performed, in which the patient does not perform any task. Fluctuations of BOLD signals detected thus reflect baseline oscillations in neural activity, which occur in phases across nodes of a neural network, such as the default-mode network (Johnson et al., 2012; Zhu et al., 2015). The degree of correlation across a network shown by resting-state fMRI may be used to observe alterations in network activity under pathologic conditions, such as mTBI (Fig. 21.5).

Serial resting-state fMRI tests were performed on 8 Division I National Collegiate Athletic Association football players who suffered a concussion (Zhu et al., 2015). All had cognitive impairment with resolution of symptoms after approximately 2–6 days. However, compared to a control group, the resting-state fMRI results in this group of athletes showed disturbances in the default-mode network. Partial recovery was only noted on day 30, well beyond the time of symptom resolution.

An earlier study had evaluated a group of student-athletes with mTBI who then underwent fMRI in the subacute period after injury and after resolution of symptoms (Johnson et al., 2012). Those with mTBI showed alterations in their default-mode networks compared to controls. Additionally, in a study of younger football players (Abbas et al., 2015), a significant number of such athletes demonstrated disturbances in the default-mode network as compared to healthy athletic controls, which appears to show the cumulative effects of trauma, without symptomatology.

PERFUSION IMAGING: ARTERIAL SPIN LABELING

Arterial spin labeling (ASL) is an MRI technique that can be used to quantify cerebral blood flow within the brain without exogenous contrast media. This noninvasive technique magnetically labels water protons in the blood pool, outside the slice of brain to be imaged, by either saturating or inverting magnetization of blood water protons. Images are then acquired after a sufficient delay to allow perfusion of the tagged blood water protons into the head, but not long enough for complete longitudinal relaxation of such protons (Williams et al., 1992; Detre et al., 1994). Baseline imaging of the head is also obtained, without magnetic labeling of the blood. Subtraction of tagged from control images results in a set of images that demonstrate brain perfusion and can be related to cerebral blood flow through computational modeling.

ASL evaluations of the brain can be used to demonstrate altered cerebral blood flow in several disease states (Haller et al., 2016). After an mTBI event, individuals generally show decreased regional cerebral blood flow. For example, Ge et al. (2009) demonstrated decreased perfusion within the thalami in 21 patients after mTBI compared to controls. Wang et al. (2015), in a study of teenagers with sports-related mTBI or concussion, demonstrated lower regional cerebral blood flow up to 7 months after the injury (Fig. 21.6). In a study

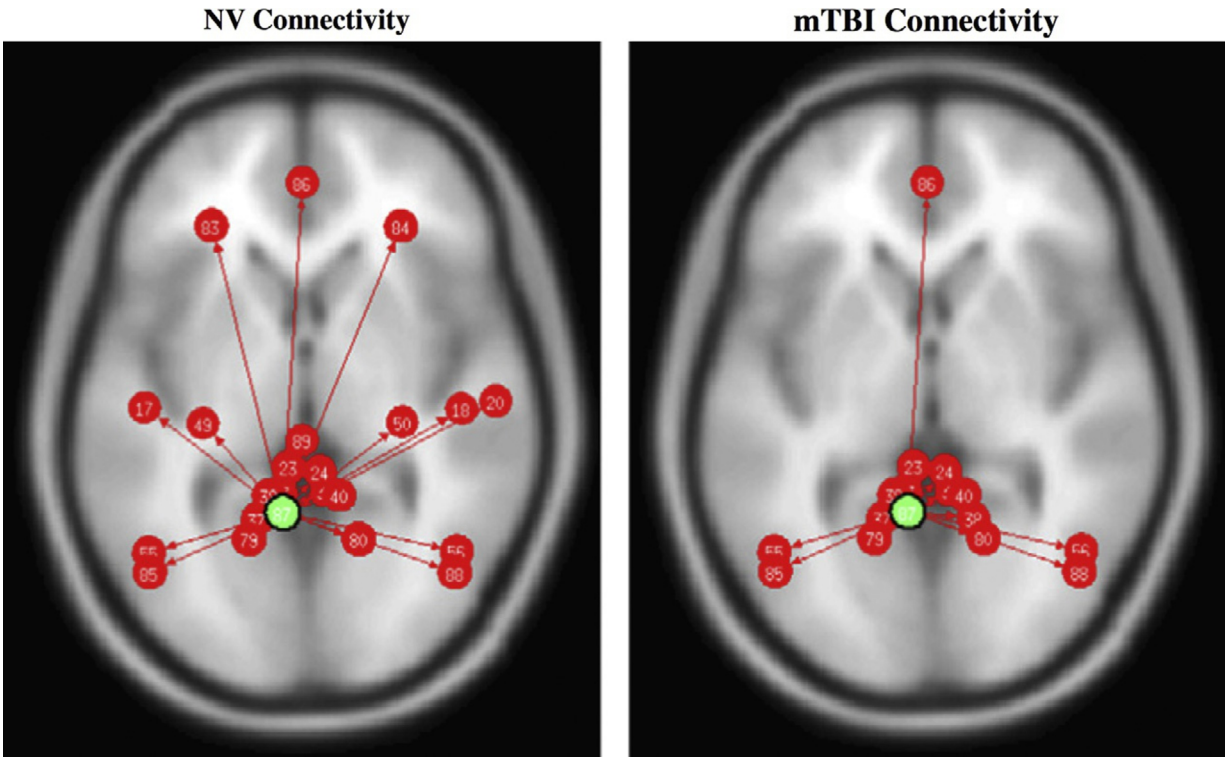

Fig. 21.5. A study by Johnson et al. (2012) demonstrates disruption of the default-mode network observed using functional magnetic resonance imaging The posterior cingulate cortex component of the default-mode network is shown to be intact in a normal volunteer (NV; left). Evaluation of a mild traumatic brain injury (mTBI) subject (right) demonstrates diminished functional connectivity to a number of locations in the bilateral frontal and temporal lobes. (Reproduced from Johnson B, Zhang K, Gay M, et al. (2012) Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. Neuroimage 59: 511–518.)

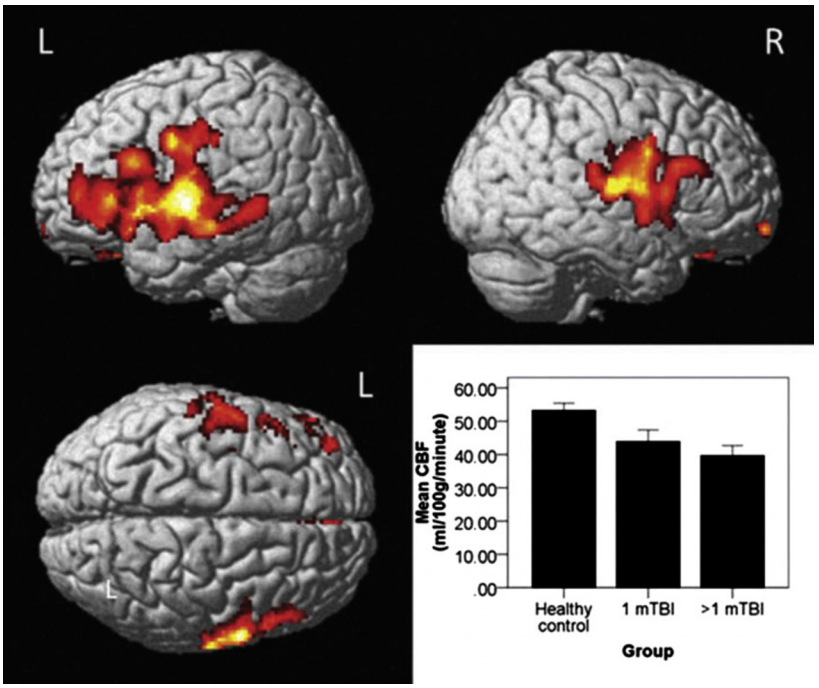

Fig. 21.6. Results of arterial spin labeling analysis in mild traumatic brain injury (mTBI) patients from Wang et al. (2015). When compared to a healthy control population, pediatric sports/recreation mTBI subjects demonstrated lower cerebral blood flow (CBF) in the bilateral frontotemporal regions despite normal structural imaging. (Reproduced from Wang Y, West JD, Bailey JN, et al. (2015) Decreased cerebral blood flow in chronic pediatric mild TBI: an MRI perfusion study. Dev Neuropsychol 40: 40–44.)

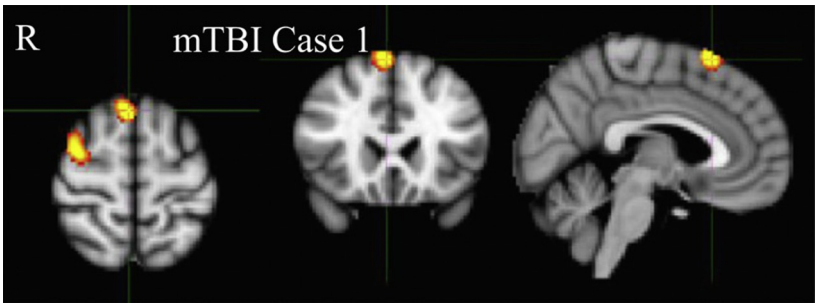

Fig. 21.7. Finding from Huang et al. (2014) demonstrating regions of slow (delta)-wave generation in the superior aspect of the right frontal lobe (yellow), identified using magnetoencephalogram superimposed on T1-weighted magnetic resonance imaging. These regions of delta-wave production may indicate areas of axonal injury.*mTBI*, mild traumatic brain injury. (Reproduced from Huang M-X, Nichols S, Baker DG, et al. (2014) Single-subject-based whole-brain MEG slow-wave imaging approach for detecting abnormality in patients with mild traumatic brain injury. NeuroImage: Clin 5: 109–119.)

of 44 college football players in which ASL was used to evaluate cerebral blood flow at different time points after injury, cerebral blood flow was lower in the earlier postinjury period, with values similar to those of controls by 1 month postinjury (Meier et al., 2015). However, a recent ASL study (Barlow et al., 2017) of symptomatic and asymptomatic postconcussive subjects showed a global increase in cerebral blood flow among symptomatic patients, and a global decrease in asymptomatic patients. Because recovery from mTBI is a dynamic process, further perfusion studies may help elucidate the relationship between cerebral blood flow and recovery from mTBI (Barlow et al., 2017).

MAGNETOENCEPHALOGRAPHY

Like fMRI, magnetoencephalography (MEG) is a functional imaging technique used to localize neuronal activity in the brain (Cohen, 1968, 1972; Sakkalis, 2011). However, rather than indirectly measuring such activity through coupling with the cardiovascular system, MEG directly measures neuronal activity using the magnetic field generated through the movement of electric charges within neurons. The magnetic fields generated by the brain are extremely weak compared to the extraneous man-made magnetic fields in our environment or the magnetic field of the earth. Therefore, heavily shielded multilayered rooms are needed to exclude such extraneous magnetic fields. Extremely sensitive magnetometers known as superconducting quantum interference devices (SQUIDs) are used to record the generated magnetic fields. Complex mathematics are used to integrate signal from many SQUIDs to determine the spatial location of the magnetic flux generator. Because the timeframe of measurement is on the order of milliseconds rather than seconds (as in fMRI), MEG can characterize the nature of neuronal responses to tasks and stimuli.

MEG studies have been performed with mTBI patients while in the resting state (Huang et al., 2014; Robb Swan et al., 2015; Alhourani et al., 2016). Injured areas of the brain generate delta waves, slow waves on the order of 1–4 Hz. Alpha waves (8–13 Hz), on the other hand, typically predominate in the relaxed awake state. Huang et al. (2014) evaluated 84 patients with mTBI who had persistent postconcussive symptoms; they had more regions of slow-wave abnormalities compared to controls. These were associated with areas in the prefrontal cortex responsible for a number of symptoms, including poor concentration and depressive symptoms (Huang et al., 2014; Robb Swan et al., 2015) (Fig. 21.7). Alhourani et al. (2016) evaluated 9 mTBI patients with MEG and observed disruption of the default-mode network in the resting state compared to controls.

MOLECULAR IMAGING: SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY

Single-photon emission computer tomography (SPECT) and positron emission tomography (PET) are functional imaging techniques that use radioactively labeled molecules (i.e., ligands) to evaluate regional blood flow and metabolic activity, respectively. In SPECT imaging, technetium 99m-labeled hexamethylpropylene amine oxime, a lipophilic molecule that crosses the blood–brain barrier, is typically used to assess cerebral blood flow, and thus infer neuronal activity through the principle of neurovascular coupling. Gamma photons are emitted and detected, with the resultant three-dimensional images registered to structural imaging for analysis. Technetium 99m has a relatively long half-life and is cost-effective. Thus, SPECT examinations are more readily accessible than PET examinations, which employ agents with much shorter half-lives. The longer half-life

allows for better acclimatization of a patient in the resting state before imaging takes place, which can help to decrease extraneous brain activity. Typically, an ROI is identified in which to evaluate cerebral blood flow, and compared to an ROI in an analogous part of the contralateral hemisphere. Calculation of relative cerebral blood flow can therefore have inherent bias if the head injury had a more global effect, where the comparison ROI may not represent normal tissue.

In general, when abnormalities in SPECT studies are present in patients with mTBI, hypoperfusion is often observed (Ichise et al., 1994; Jacobs et al., 1996; Hofman et al., 2001; Audenaert et al., 2003; Amen et al., 2011). This was seen in a study of 100 active and former professional football players with at least 3 years of active play. These players demonstrated areas of decreased perfusion in areas of the prefrontal, temporal, parietal, and occipital lobes, as well as in the cerebellum (Amen et al., 2011). One study demonstrated that negative findings on a SPECT examination during initial evaluations after trauma are associated with positive outcomes (Jacobs et al., 1996).

PET imaging of the brain is most widely performed to directly index glucose metabolism in the brain, using a radioactively labeled analog of glucose, 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG). As fluorine-18 undergoes decay, a positron is emitted and undergoes annihilation after collision with an electron. This produces two 511-keV photons emitted in opposite directions. Only simultaneous detection of such photons is recorded and used in imaging. The resultant images are registered to structural MRI for analysis. FDG PET imaging is more costly than SPECT. PET, however, affords better signal-to-noise ratio and spatial resolution. In general, hypometabolism is observed in mTBI patients who exhibit abnormalities on PET (Ruff et al., 1994; Provenzano et al., 2010; Peskind et al., 2011; Byrnes et al., 2013; Cross et al., 2015).

CONCLUSION

Conventional neuroimaging (CT, MRI) is important in the triage of selected patients who have experienced a traumatic injury to the head. A patient exhibiting a concerning clinical profile can quickly be assessed for primary and secondary intracranial injury, and a decision rapidly made whether neurosurgical intervention is needed. Sports present the potential for repeated concussion and TBI. In particular, the danger of reinjury to the brain before recovery is complete may confer risk for worse outcome. Second-impact syndrome, whereby a second relatively minor head trauma occurring before complete recovery of concussion results in loss of autoregulatory control, severe cerebral edema, and brain herniation (Cantu 1998), is an extreme example of such an adverse outcome.

At present, symptom reports and the clinical examination are the mainstays for diagnosing concussion and for assessing its resolution, including return-to-play determinations. Advanced neuroimaging techniques reveal abnormalities in concussion patients. FA, for example, has been repeatedly identified across many cohorts of mTBI patients, including studies that characterize individual patients (Shenton et al., 2012; Hulkower et al., 2013). For many, especially newer techniques, however, data are much less extensive. In any case, imaging findings currently serve as correlative information to supplement conventional clinical assessments. Prognostic utility of imaging markers for completeness of and time to recovery, however, is at present only suggestive. This is in large part because, notwithstanding numerous cross-sectional studies of neuroimaging in concussion, longitudinal studies that assess the relationship of imaging measures to outcomes are relatively few.

The advance of neuroimaging technology, only some of which is discussed in this chapter, seems unstoppable and many new and exciting developments are yet on and beyond the horizon. It is essential to recognize, however, that the greatest yield toward characterizing pathophysiology and improving assessment of patients with concussion may depend as much on implementation of neuroimaging in research studies as on the technology itself. Research studies must be designed and executed in a way that data can be integrated across multiple studies in order to yield power sufficient to support generalizable inferences. To this end, standardized data collection and reporting procedures are essential. The recently released Sport-Related Concussion Common Data Elements (https://www.commondataelements.ninds.nih.gov/SRC.aspx#tab=Data_Standards), for example, can guide standardized approaches to inclusion of neuroimaging in research studies, ultimately advancing the characterization of pathologic changes that confer future risk, providing targets for therapeutic intervention, and improving concussion management and outcomes for athletes.

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