

# The Role of Neuroimaging in Sport-Related Concussion

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## KEYWORDS

• Concussion • Neuroimaging • Sport-related

Individuals engaged in various sports and recreational physical activities are prone to injury. The Centers for Disease Control and Prevention estimates that approximately 1.1 million people with traumatic brain injury (TBI) are treated and released from emergency departments in the United States each year and an additional 235,000 are hospitalized for these injuries.<sup>1</sup> The most common TBI in athletes is concussion, a transient disturbance of neurologic function caused by trauma. Although the symptoms associated with concussion have been recognized for centuries, the term “post concussion syndrome” was described in the early part of the last century as the subjective posttraumatic syndrome caused by a direct blow to the head. Commonly, the course is self-limited, resolving usually within weeks of the incident. Indeed, 90% of athletes are symptom-free within 10 days.

The basis for the loss of consciousness following concussion has been variously hypothesized to result from changes in the reticular system (reticular theory), increased neuronal firing and cerebral excitability (convulsive theory), mechanical injury disrupting brain function (centripetal theory), and activation of cholinergic neurons resulting in suppression of behavioral responses (central to pontine cholinergic system theory), among others.<sup>2</sup> A number of changes, including alterations in neurotransmitter levels and disruption of neuronal membranes, have been described following traumatic injury to the brain.

Most concussive injuries are mild and resolve without long-standing sequelae. However, there is increasing evidence that concussion can affect cognitive function adversely and contribute to long-term disability in a proportion of patients. This

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problem is particularly significant in the young athlete. A number of studies indicate that concussion can have long-term sequelae including poor attention span, headache, impaired memory, behavioral problems, and learning difficulties.<sup>3</sup>

The challenge faced by the clinician taking care of this population is to determine when an athlete is fit to return to play and predict what long-term damage could result from single or repeated episodes of mild traumatic brain injury (mTBI). Among the dangers of returning too early to the sporting activity is the second-impact syndrome, which can be fatal. A number of guidelines have been proposed to help the sports medicine professional in this scenario. However, formulation of these guidelines has been hampered by a lack of objective tools to measure the structural damage to the brain and determine the pace of neurophysiological recovery in an individual case. Imaging studies have been evaluated as a tool with the potential to objectively assess damage resulting from TBI and develop individual-specific recovery plans. Most of the data available pertain to mild to moderate TBI in general, but are relevant to the injured athlete.

### **NEUROIMAGING FOLLOWING MILD TBI—AN OVERVIEW**

With the advent of ultrafast multislice computed tomography (CT) scanners, CT imaging can be completed in seconds and is still the modality of choice in emergency departments to look for macroscopic abnormalities associated with acute sports-related brain trauma. Magnetic resonance imaging (MRI) has greater contrast resolution than CT and can detect structural abnormalities earlier than CT. However, until recently, it has not been used in the acute setting because of its susceptibility to metal and motion-related artifact, incompatibility with certain life-support equipment within the scanner environment, long scan times, and decreased sensitivity in detecting skull fractures. These limitations have been addressed in the past decade. Scan times have become shorter and MRI-compatible equipment has been developed. In light of these developments, MRI is emerging as a possible alternative to CT in the acute setting. However, at present, in most institutions, the first imaging study performed in a patient with TBI is a CT scan. MRI is reserved for follow-up neuroimaging.

Traditionally, sequences used for the MRI have been designed to look at macroscopic structural damage. Newer sequences have been developed that have the potential to increase the sensitivity of MRI to detect both structural and functional abnormalities associated with TBI in the acute setting and subsequently in the period of rehabilitation. These newer techniques include susceptibility-weighted imaging, arterial spin labeling, diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), and magnetoencephalography (MEG). Quantitative MRI techniques like voxel-based morphometry (VBM) and brain segmentation algorithms also hold promise in objectively assessing changes following TBI. Advances in positron emission tomography (PET) and development of hybrid techniques like PET/MRI also have the potential to increase our understanding of changes in the microstructure and electrochemical alterations in the brain parenchyma following trauma. The use of these new techniques are especially relevant in cases where conventional CT and MRI sequences are unable to detect a macroscopic structural abnormality in the brain. Using these techniques, recent studies have looked at the brain that is “structurally normal” on conventional imaging, but manifests clinically as reduced responsiveness in the acute setting and delayed functional response on follow-up neuropsychological evaluation.

This article discusses some of the newer techniques and addresses their use in the acute setting and explores their potential role in long-term follow-up after mild to

moderate TBI. Also addressed are the challenges faced before some of these newer techniques can be incorporated into routine clinical management of the injured athlete.

## NEW TECHNIQUES IN NEUROIMAGING FOLLOWING BRAIN TRAUMA

The newer techniques described in this article can be broadly divided into structural and functional techniques (**Table 1**).

### *Susceptibility-Weighted Imaging*

Improvements in gradient echo imaging methods have increased our ability to detect the susceptibility-related effects of shear-related hemorrhagic injury. Susceptibility-weighted imaging (SWI) uses the paramagnetic property of blood products and increases visibility of microhemorrhages by accentuating signal dropout by rapid spin dephasing. SWI is extremely sensitive to iron and blood products and detects microhemorrhages where conventional MRI fails (**Fig. 1**). Similar to gradient echo images, SWI detects hemorrhage at all stages, because iron remains even after the fluid from blood is reabsorbed.

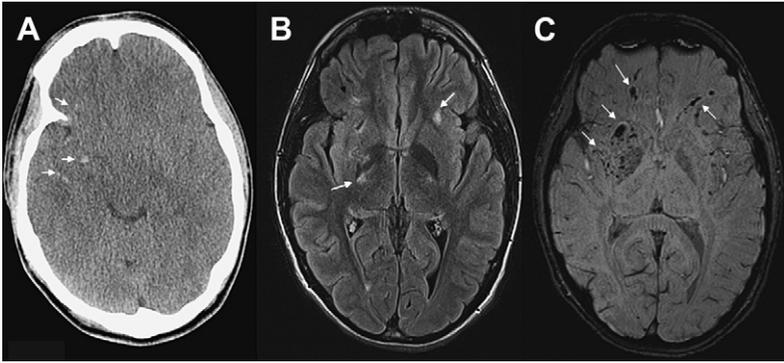
The technical aspects and clinical applications of SWI have been elaborated in detail by various investigators.<sup>4,5</sup> SWI is best used at higher field strengths, as the TE (time to echo) is much longer at low fields and acquisitions need to be longer. In addition, at higher field strengths, isotropic in-plane resolution can be obtained and the signal-to-noise ratio (SNR) is higher. The use of even higher field strengths can increase the resolution and SNR significantly. Another advantage of SWI over conventional gradient echo sequences is the ability to differentiate between hemorrhage and calcium and visualize vessel connectivity and microbleed location in relation to the vasculature and other structures in the brain. SWI is routinely used in the author's practice as part of the routine imaging protocol in patients with TBI, both at presentation and follow-up examinations. Automated and semi-automated methods of counting number of hemorrhages on SWI images have been described, but are not used routinely in the author's clinical practice.

In spite of its ability to detect intraparenchymal injury, the exact role of microhemorrhages on SWI images in determining prognosis is not completely clear. Most studies so far have indicated that the number and volume of SWI hemorrhagic lesions measured using automated methods in the injured brain may correlate with specific neuropsychological deficits on long-term follow-up.<sup>6</sup> Another study concluded that SWI findings rarely discriminated by outcome, when compared with T2-weighted and fluid-attenuated inversion-recovery (FLAIR) imaging.<sup>7</sup> It is important to point out that the foci of microhemorrhages in patients with TBI do not correlate directly with

**Table 1**

**Newer techniques in neuroimaging following traumatic brain injury**

<b>Structural Techniques</b>	<b>Functional Techniques</b>
Susceptibility-weighted imaging (SWI)	Magnetic resonance spectroscopy (MRS)
Diffusion-weighted imaging (DWI)	Arterial spin labeling (ASL)
Diffusion tensor imaging (DTI)	Magnetoencephalography (MEG)
Quantitative MRI techniques (eg, segmentation and voxel-based morphometry)	Single-emission computed tomography (SPECT) and positron emission tomography (PET)
	PET/MRI
	Functional MRI (fMRI)



**Fig. 1.** Susceptibility-weighted imaging: 16-year-old right-handed male who suffered a head injury while stunt riding a bike in an indoor park. (A) CT performed on day of admission shows small hyperdense acute hemorrhagic foci in the right temporal and inferior frontal lobe. (B) Axial FLAIR image on day 5 after injury shows foci of hyperintensity in the right temporal and both inferior frontal lobes indicating areas of white matter injury. (C) Axial SWI shows multiple foci of hypointensity, significantly greater than seen on the CT and FLAIR images, thereby indicating the true extent of the abnormality.

the neurologic impairment; instead, these are likely markers of a more severe injury and may indicate diffuse axonal injury (DAI).

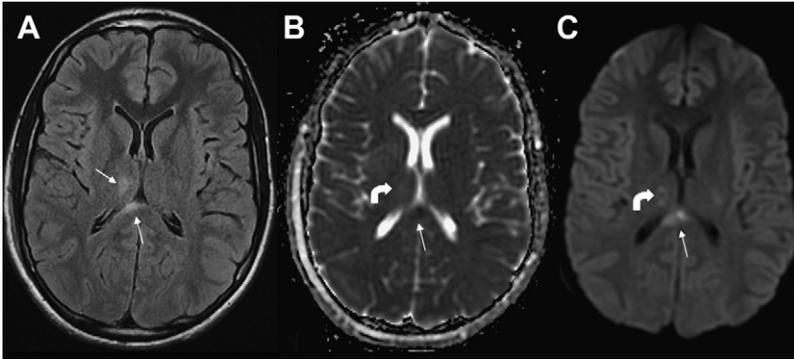
Another study investigated the impact of the field strengths of the magnets on the depiction of traumatic microbleeds by T2\*-weighted gradient echo MRI. This group concluded that, in clinical practice, MRI at 1.5 T seems to be adequate for this purpose in most cases. Based on their findings, they recommended that MRI at 3 T may be appropriate if there is a strong clinical suspicion of DAI, despite unremarkable routine MRI, and possibly if evidence of DAI is sought after a long interval from trauma.<sup>8</sup>

There is room for improvement in the technical aspects of acquiring the SWI sequence, such as standardization across scanner manufacturers, reducing acquisition times, and decreasing artifact around the skull base and improving acquisition in the spine.

### ***Diffusion-Weighted Imaging and Diffusion Tensor Imaging***

Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps have been used for lesion detection and as a predictor of outcome in adults with TBI. Few studies, however, have been reported in children.<sup>9</sup> The intracellular accumulation of water that occurs in cytotoxic edema is expressed as a reduction in the ADC (**Fig. 2A**).

Diffusion tensor imaging (DTI) provides measures of white matter integrity in the brain by tracking axonal tracts and their projections in the brain.<sup>10,11</sup> The first premise of DTI is that white matter tracts follow orderly paths in anteroposterior, lateral, and craniocaudal directions. The second principle used for DTI is the principle of anisotropy, which states that the diffusion rate of water molecules is dependent on the direction and integrity of the white matter tracts in a particular direction. Fractional anisotropy (FA) is a scalar value between 0 and 1 that describes the degree of anisotropy of a diffusion process. A value of 0 means that diffusion is isotropic, ie, free diffusion in all directions, and a value of 1 indicates that diffusion occurs only along one axis and is fully restricted along all other directions. Therefore, FA is a measure used in diffusion tensor imaging that is thought to reflect fiber density and integrity, axonal diameter, and myelination in white matter. Color coding the various axonal projections as a 2-dimensional representation produces a color FA map (**Fig. 3A**). The most commonly used convention for color

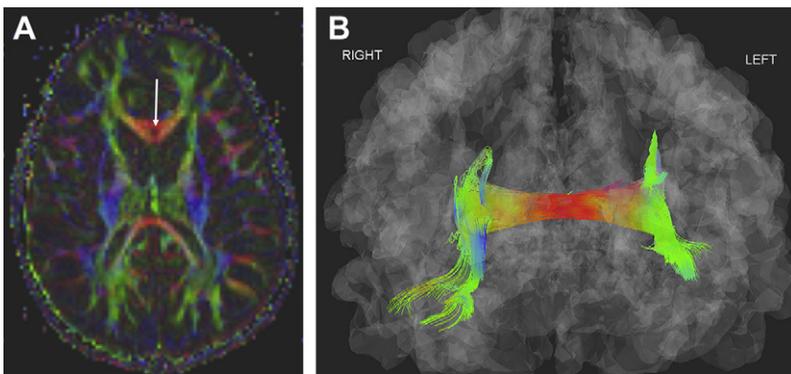


**Fig. 2.** Utility of diffusion-weighted imaging: 16-year-old male who sustained a TBI during a motocross competition when he fell while attempting to flip his bike in the air. MRI performed on day 3 after the accident. (A) Axial FLAIR image shows areas of hyperintensity in the splenium of the corpus callosum and right thalamus (*arrows*). (B) ADC map shows areas of decreased signal intensity (*arrows*) in the callosal splenium and right thalamus, thereby suggesting that the changes seen on FLAIR images is an acute process. (C) Trace diffusion image confirms restricted diffusion in the splenium (*arrows*). Note that the change in the right thalamus is of high signal intensity on the ADC map (*curved arrow*), indicating that this is an older injury.

coding the FA map is as follows: green represents anterior-posterior pathways, red color represents lateral pathways, and blue represents the craniocaudal pathways. These 2-dimensional maps can be used to track various axonal tracts of interest in a 3-dimensional (3D) representation, termed diffusion tractography (**Fig. 3B**). Specific tracts of interest following trauma include the corpus callosum, longitudinal fasciculus, cingulum bundle, and uncinate fasciculus.<sup>12,13</sup>

Recent studies have shown that there is significantly greater fractional anisotropy as a result of reduced radial diffusivity in the corpus callosum and several left hemisphere tracts following mTBI. The role of DTI has been studied in adults and adolescents.<sup>14–16</sup>

One such study was aimed at determining whether frontal white matter diffusion abnormalities can help predict acute executive function impairment after mild TBI.<sup>14</sup>



**Fig. 3.** Diffusion tensor imaging in a 15-year-old male following head trauma during snowboarding. (A) Color fractional anisotropy map displayed using the “red, green, blue” convention described in the text. (B) Same data reconstructed to provide a 3D tractography image that can be further analyzed to evaluate the integrity of each of the major tracts in the brain.

Based on DTI and standardized neuropsychological assessments, the investigators concluded that impaired executive function following mTBI is associated with axonal injury involving the dorsolateral prefrontal cortex.

In a similar study of acute mTBI involving adolescents, increased fractional anisotropy and decreased apparent diffusion coefficient and radial diffusivity correlated with the more intense post concussion symptoms and emotional distress that were seen in the mTBI group compared with the controls.<sup>17</sup> The role of DWI and ADC for outcome prediction has also been studied following pediatric TBI. One such study found that average total brain ADC value alone had the greatest ability to predict outcome, correctly predicting outcome in 84% of cases.<sup>9</sup> It is interesting that preliminary longitudinal data suggest that apparent diffusion coefficient and fractional anisotropy may normalize, at least partially, in several white matter tracts following a single-episode mTBI. These findings indicate that cytotoxic edema may be present during the semi-acute phase of mTBI and damage to axons affecting the intracellular ionic milieu, reflected as abnormal diffusion values.<sup>16</sup> These alterations may serve as potential biomarkers of recovery following brain injury. What is particularly relevant in this discussion of sports-related concussion is whether there is a more lasting change following repeated trauma. This question has not been addressed in large studies. The most attractive feature of this finding is that it is applicable even in brain regions that appear normal on conventional imaging. Early identification of young athletes at high risk for poor outcome may assist in aggressive clinical management following trauma.

In summary, DTI appears to have the potential to be more sensitive than conventional imaging methods in detecting subtle, but clinically relevant, changes following mTBI and may be critical in redefining the diagnosis, prognosis, and management of these patients.

### ***Quantitative MRI (Segmentation and Voxel-based Morphometry)***

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The differences in the MRI signal intensity of the gray and white matter permits segmentation of the brain parenchyma into 2 separate compartments. Similarly, the extra-axial spaces and the ventricles filled with cerebrospinal fluid (CSF) can also be separated. This segmentation enables volume calculation of the 3 different tissue-CSF compartments because the slice thickness of the scan and the distance between slices are known.<sup>18</sup> Such measurements enable accurate determination of qualitative and quantitative changes in specific brain areas following mild to moderate trauma.<sup>19,20</sup> One of the measures studied in patients following TBI is the ventricle-to-brain ratio (VBR). This ratio is the total volume of the ventricles divided by the total brain volume. Increased VBR indicates increasing atrophy, and is directly related to the severity of injury. It is reflective of global changes but may disproportionately reflect white matter volume loss compared with that of gray matter.<sup>21</sup>

Voxel-based morphometry (VBM) is a method of voxel-by-voxel analysis of 3D MRI data. In subjects following TBI, VBM has been used to look for sites where major differences occur in subjects with TBI compared with age-matched control subjects without damage. Voxel density in the gray and white matter is plotted on a standard 3D surface plot of the brain. In a study in young patients following moderate to severe brain injury, differences have been shown in the frontal and temporal regions, more so in the gray matter.<sup>22</sup> At present, VBM is a research tool that is not used in routine clinical practice in the author's center.

### ***Magnetic Resonance Spectroscopy***

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Magnetic resonance spectroscopy (MRS) has long been used as a noninvasive method to measure concentrations of various compounds in the brain within

a sampled region. Use of higher field strengths has increased our ability to accurately determine concentrations of a broader range of metabolites including neurotransmitters like glutamate, glutamine, gamma-amino butyric acid, and glycine. The value of MRS has been clearly documented in acute ischemic injury with the presence of lactate, an indicator of anaerobic metabolism, consistent with energy substrate depletion.<sup>23</sup>

More recently, the role of MRS in the evaluation of patients with TBI has been studied by a number of groups.<sup>24–26</sup> Preliminary findings in one study indicated significantly lower levels of gray matter glutamine and higher levels of white matter creatine (Cr) in subjects with mTBI relative to healthy controls.<sup>26</sup> Furthermore, Cr levels were predictive of executive function and emotional distress in the combined groups, thereby suggesting that change in levels of Cr, a critical component of the brain's energy metabolism, and glutamate, the brain's major neurotransmitter, may occur following mTBI. Moreover, the different pattern of results for gray and white matter suggests tissue-specific metabolic responses to mTBI. In a study of patients with severe TBI, supratentorial and infratentorial fractional anisotropy (FA), N-acetylaspartate-to-creatine (NAA/Cr) ratio in the pons, thalamus, and insula clearly separated the unfavorable outcome, favorable outcome, and control groups, with no overlap. Unfavorable outcome was predicted with up to 86% sensitivity and 97% specificity and these values were better than those obtained with DTI or MRS alone. These findings led the investigators to suggest that FA and NAA/Cr ratios hold potential as quantitative outcome-prediction tools at the subacute phase of TBI.<sup>27</sup>

In spite of the results of such studies, the evidence for MRS in prognostication is not yet sufficient for use in routine clinical practice in all patients undergoing MRI for evaluation of TBI.<sup>28</sup> The yield of applying newer techniques of obtaining and analyzing the MRS, like multivoxel acquisition and 2-dimensional correlation spectroscopy (2D-COSY), needs to be evaluated in the follow-up of athletes following brain injury.<sup>29</sup>

### ***Magnetoencephalography and TBI***

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Magnetoencephalography (MEG) is a noninvasive modality used to measure the neuromagnetic fields generated by activation of neurons. These fields are transmitted to the scalp and measured using sensors on the surface, generating data similar to standard encephalogram (EEG) data, but with fewer artifacts and better spatial resolution. Unlike other functional MRI techniques, MEG has the ability to detect rapid changes in neuronal activity, and this makes it possible to separate out the different components of a complex cognitive task like word comprehension. Small studies have looked at the use of MEG in TBI.<sup>30,31</sup> These studies suggest a role for MEG in the evaluation of patients with TBI, especially in conjunction with other modalities. At present, MEG is available in only a few centers across the world because of its relatively high cost. However, its increasing use in other conditions, such as epilepsy, may make this technique mainstream in the near future.

### ***Arterial Spin Labeling***

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Perfusion MRI can be performed noninvasively by labeling the hydrogen nuclei of the intravascular arterial water using 1 or 2 radiofrequency pulses. These pulses invert the longitudinal magnetization of arterial blood just upstream of the region of interest. This causes modification of the measurable magnetization and T1 relaxation time of the labeled blood. During acquisition, the signal obtained includes the measurable magnetization of the region of interest to which is added the magnetization from the labeled blood pool present in the explored volume. A second unlabeled acquisition serves as a reference to calculate the perfusion images. The advantage of being

able to assess perfusion and cerebral blood flow (CBF) without use of intravenous contrast medium and the relatively rapid acquisition times make it an attractive technique for use in the emergency care setting.

One study has demonstrated the hemodynamic impairment that can occur and persist in patients with mTBI, the extent of which is more severe in thalamic regions and correlates with neurocognitive dysfunction during the extended course of disease.<sup>32</sup> A more recent study demonstrated that in addition to global CBF reduction in subjects with TBI, there is more prominent regional hypoperfusion in the posterior cingulate cortices, the thalami, and multiple locations in the frontal cortices.<sup>33</sup> Diffuse injury was mainly associated with reduced CBF in the posterior cingulate cortices and the thalami, where the greatest volume losses were detected. In contrast, hypoperfusion in superior and middle frontal cortices was associated with focal lesions. These results suggest that structural lesions, both focal and diffuse, are the main contributors to the absolute CBF alterations found in chronic TBI and that CBF alterations as measured by the arterial spin labeling technique may serve as a tool to assess functioning neuronal volume.<sup>33</sup>

### ***SPECT, PET, and PET/MRI***

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Available data suggest that single-photon emission computed tomography (SPECT) in cases of mTBI may show lesions where no abnormalities are seen on structural imaging. This may be helpful in explaining the cause of persistent behavioral changes. However, some lesions seen on structural scans are not detected with SPECT. It has been suggested that an initial negative SPECT after TBI may be predictive of good clinical outcome, but the utility of an abnormal scan for prognostication is less clear.<sup>34</sup>

Cerebral ischemia is believed to be an important mechanism of secondary neuronal injury following TBI. Flow defects on the cerebral blood flow on positron emission tomography (PET) imaging have been shown to indicate areas of irreversible tissue damage (necrosis) in the chronic stage. Interestingly, the area of hypoperfusion surrounding the lesion partly resulted in tissue necrosis, but a large part of the hypoperfused tissue survived in the chronic stage.<sup>35</sup> Based on these findings, it can be hypothesized that there is some degree of impaired cerebral blood flow and metabolism around the area of contusion even in the subacute stage after TBI. The use of PET for studying cerebral blood flow is limited in the emergency setting by the logistics of moving the patient to the scanning area and tracer availability at short notice.

The development of an integrated PET/MR prototype system for brain imaging is the latest step in the evolution of PET. Early experience with this new imaging system suggests that MRI-based attenuation correction is feasible and high-resolution MRI and PET data can be fused without significant loss of performance of either imaging modality.<sup>36</sup> PET/MR combination might attain wider clinical application if the technology becomes cost-effective and more data emerge on its advantages compared with other modes of imaging. In the emergency setting, the drawbacks of this technique are similar to PET and MRI, with regard to logistics of getting the patient to the scanner and getting the tracer into the patient at the appropriate time.

### ***Functional MRI and TBI***

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Functional brain imaging identifies patterns of brain activation associated with specific cognitive or behavioral events. Neuronal function is inferred in functional MRI (fMRI) by the blood oxygen level dependent (BOLD) signal, which reflects magnetic field inhomogeneities caused by changes in the oxygenation state of hemoglobin. Neural activation results in a local increase in cerebral blood flow to the area out of proportion to the cerebral oxygen consumption, thereby

resulting in net reduction in the amount of deoxyhemoglobin. The paramagnetic property of deoxyhemoglobin as opposed to the diamagnetic property of oxygenated hemoglobin is responsible for the field inhomogeneities. The resultant BOLD signal is dependent upon the changes in cerebral blood flow, cerebral blood volume, and cerebral oxygen consumption.<sup>34</sup> The data obtained are reconstructed using statistical packages and co-registered with a structural MRI. At present, fMRI is used primarily as a research tool in the area of TBI. Although it is possible to obtain functional MRI studies on existing scanners with a few modifications, the analysis of the scans requires considerable expertise, both in the reconstruction and interpretation of the data. Further, there is a need for standardization of the activation tasks used in fMRI studies. Most fMRI tasks need the subject to perform an active task, thereby limiting its use to alert and cooperative patients. More recently, an emerging area of fMRI is aimed at mapping resting state connectivity or the default mode network.<sup>37,38</sup> Resting state networks refers to the temporal coherence between different brain regions indicated by spontaneous blood-oxygen-level dependent fluctuations in the absence of any active task performance, ie, when the brain is “at rest.” It is debatable whether this reflects consciously directed mental activity at rest or, alternatively, constitutes an intrinsic property of functional brain organization persisting in the absence of consciousness. Alterations in the resting state connectivity have been reported to occur in various forms of brain injury and may be especially relevant in light of the reticular theory invoked to explain the loss of consciousness following concussion.<sup>2</sup>

Currently available data indicate that the activation patterns in subjects following TBI may have significant differences compared with controls when performing cognitive activation tasks.<sup>39</sup> Changes have been reported in the right parietal and right dorsolateral frontal regions in performing a working memory task compared with control subjects after TBI within 1 month following injury.<sup>40</sup> The same group showed that the response to higher processing tasks in TBI suggested that these subjects do not have actual deficits in working memory ability, but they lose the ability to recruit additional neural resources during these tasks. They suggest that disturbances in catecholamine-mediated neural pathways that are needed for working memory function may be disrupted in these patients. Interestingly, when performing so-called “go-stop” tasks that require either a specific response to be made or no response depending on the stimulus, subjects with history of mTBI show reduced activation in the prefrontal cortex when no response was required and in the cingulate region when a response was indicated.<sup>41,42</sup> These changes may explain behavior and decisions made by the athlete on and off the field.

## SUMMARY

Some of the newer techniques described in this article are being increasingly used in the clinical assessment of patients following mild to moderate TBI. Other techniques are used in research, but may have clinical relevance, which needs to be proven by large-scale, well-designed studies that demonstrate a clear benefit in scanning these patients. Specifically, there is a need for large studies with a special emphasis on the effects of repeated head trauma in the young athlete. This is especially relevant in cases where conventional imaging does not demonstrate a macroscopic abnormality. The emphasis has to shift from identifying structural abnormalities on imaging studies to understanding the functional changes in the brain that may explain the long-term neuropsychological effects of concussion and mTBI.

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