A Critical Review of Neuroimaging Applications in Sports Concussion

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Abstract
While abnormalities related to concussion are typically not identified on traditional clinical neuroimaging (*i.e.*, computed tomography [CT] or magnetic resonance imaging [MRI]), more sophisticated neuroimaging techniques have the potential to reveal the complex neurometabolic processes related to concussion and its recovery. Clinically, these techniques may one day provide useful information to guide clinicians in the management and treatment of sports concussion. This article critically reviews the current state of the literature regarding neuroimaging and sports concussion, identifies challenges in the application of these techniques, and identifies areas for future research.

Introduction

Athletes participating in collision or contact sports are at high risk for concussion, and the incidence of sports-related head injury is estimated to be 1.6 to 3.8 million·yr^{-1} (5). Concussion involves traumatically-induced, complex, pathophysiological processes in the brain (14), which result in sudden neurological impairment and may or may not result in a loss of consciousness (31). Postconcussive symptoms may include difficulties with memory, concentration, dizziness, irritability, fatigue, anxiety, and headache. Evidence suggests that typical recovery from concussion is relatively rapid (*i.e.*, within approximately 7 d), involving no significant residual neurocognitive or subjective symptoms (4,30). Baseline and postinjury neurocognitive testing, sideline assessment (including balance testing), and symptom monitoring protocols currently are being used to evaluate, monitor, and direct clinical management of sports concussions, although currently there is no evidence to prove improved outcomes with any one of these approaches, either alone or in combination with others. Typically, no abnormalities are observed on radiological review of clinical structural neuroimaging. For this reason, standard clinical imaging techniques are not used for clinical decision-making in the evaluation of concussion, except when there is suspicion of an intracranial lesion (9). However, advances in neuroimaging technology may provide for greater sensitivity to concussion and may help elucidate the neuropathological cascade of concussion to help refine clinical management of concussion and ensure athletes' safety.

The investigation of sports-related concussion with neuroimaging is relatively new. Past reviews of the neuroimaging and sports-related concussion literature have focused on descriptions of different neuroimaging modalities, identification of advantages and disadvantages of each technique, and evaluation of their use with concussed athletes (9,11,21,32,34). This article is a critical review of prior investigations with recommendations for future research in order to encourage and support a better understanding of sports concussion and its management. For this article, a review of PubMed and Medline databases through June 2010 identified nine neuroimaging studies (Table) involving athletes with sports concussion (6–8,16,20,29,35,36,39), including four structural imaging studies (voxel-based morphometry [VBM] $N = 1$, diffusion tensor imaging [DTI] $N = 1$, magnetic resonance spectroscopy [MRS] $N = 2$) and seven functional imaging studies (functional magnetic resonance imaging [fMRI] $N = 7$).

Neuroimaging Modalities

Structural Magnetic Resonance Imaging (sMRI)

While computerized tomography (CT) historically has been utilized widely to identify fracture, intracranial hemorrhage, contusion, mass effect, and herniation related to head trauma (21), magnetic resonance imaging (MRI) offers superior visualization of brain structures in detecting traumatic lesions (24). Diffusion-weighted imaging (DWI) is particularly sensitive to shear injury (19). However, as noted previously, concussion is defined as a functional disturbance, and structural damage associated with concussion typically

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Table.
Summary of neuroimaging in sports concussion studies.

Study	N		Gender		Mean Age (yr)		Patient History of Multiple Concussions	PCS at Study (*N*)	Mean Concussion-Imaging Time Difference	# Times Scanned	Imaging Modality
	Patient	Control	Patient	Control	Patient	Control					
Chen *et al.* (2004)	16	8	16 M	8 M	26.9 ± 7.2	27.6 ± 5.2	15/16	15/16	4.7 months	1 or 2	fMRI
Jantzen *et al.* (2004)	4	4	4 M	4 M	20	20	Unknown	Unknown	Unknown	1	fMRI
Lovell *et al.* (2007)	28	13	''Largely male''		16.6 ± 2.4	18.3 ± 3.5	Some subjects[a]	Some subjects[a]	Time 1: 6.6 ± 4.7 d; Time 2: 35.1 d	2	fMRI
Chen *et al.* (2008a)	40	16	40 M	16 M	28.3 ± 6.6[b]	20 ± 1.2	Some subjects[a]	Some subjects[a]	6.0 ± 6.9 d[b]	1	fMRI VBM
Chen *et al.* (2008b)	9	6	9 M	6 M	31.7 ± 5.4[c]	20 ± 0.9	Unknown	5/9 at time 2	Time 1: 3 ± 2 months; Time 2: 14.7 ± 7.6 months[b]	2	fMRI
Vagnozzi *et al.* (2008)	14	5	9 M 5 F	Unknown	27 ± 4.8[d]		3/14	14/14	3, 4, 7, 15, 30, and 45 d	3–5	MRS
Henry *et al.* (2010)	12	12	Unknown		22.1 ± 0.8	23 ± 0.7	Some subjects[a]	Some subjects[a]	3.4 ± 1.9 d	1	MRS
Zhang *et al.* (2010)	15	15	21 M[d] 9 F		20.8 ± 1.7	21.3 ± 1.5	Unknown	Unknown	''Within 30 d''	1	fMRI DTI
Slobounov *et al.* (2010)[e]	15	15	21 M[d] 9 F		20.8 ± 1.7	21.3 ± 1.5	Unknown	Unknown	''Within 30 d''	1	fMRI

DTI = diffusion tensor imaging; F = female; fMRI = functional magnetic resonance imaging; PCS, postconcussion syndrome; M = male; MRS = magnetic resonance spectroscopy; VBM = voxel-based morphometry.

[a]Exact number unknown.

[b]Unweighted mean of three groups.

[c]Unweighted mean of two groups.

[d]Data not provided separately for patient and control groups.

[e]Same sample as Zhang *et al.* (2010).

is not identifiable on clinical MRI (22,23,27). As such, CT or MRI has not been utilized as part of standard clinical practice for diagnosis or management of sports concussion except when there is concern for intracranial injury.

Advances in quantitative morphometric MRI analyses allow measurement of grey and white matter density or volume differences (*e.g.*, VBM) that may identify regional structural damage that may be too subtle for standard clinical interpretation (2). Only one study to date has conducted quantitative MRI analysis, using VBM in conjunction with functional neuroimaging (fMRI), comparing athletes with and without concussion and with or without depression and healthy controls (7). They demonstrated reduced activation in the dorsolateral prefrontal cortex (DLPC), insular cortex, anterior cingulate cortex (ACC), and striatum, as well as attenuated deactivation in medial frontal and temporal regions dependent on the severity of depressive symptoms in concussed athletes. The extent of grey matter density loss also was dependent on severity of depressive symptoms, with reductions observed in the ACC, insula, DLPC, and parahippocampal gyrus. A group of nonconcussed athletes had significantly less grey matter bilaterally in the insula compared with control subjects. Additional MRI volumetric studies of concussion are needed to better determine the extent to which sMRI is sensitive to the heterogeneity of injury types, the implications of these measures for predicting recovery, and the degree to which sMRI might be sensitive to cognitive and emotional sequelae of concussion.

DTI

DTI is a relatively new MRI-based imaging technique that can generate exquisite structural images of brain white matter tracts via measurement of water molecule diffusion within white matter (3). Fractional anisotropy (FA), a measure of the relative directionality of water diffusion in axons, is used as a marker of white matter integrity, and has been demonstrated to be sensitive to white matter abnormalities following mild traumatic brain injury (mTBI) (18,26,37). DTI also can provide important information regarding grey matter integrity, particularly as it relates to gliosis and necrosis, which may be indicators of brain injury from concussion (33). There has been only one study to date in the sports-related concussion literature using DTI. Zhang and colleagues (2010) compared student-athletes who experienced recently a sport-related concussion with age-matched, healthy controls using both fMRI and DTI (39). Concussed athletes showed an abnormal, more disperse brain activation pattern with increased blood oxygen level dependent (BOLD) signal in the left DLPC during a spatial working memory task compared with controls. Additionally, no significant alterations in whole-brain or region of interest FA were observed, although there was larger variability of FA in the genu and body of the corpus callosum in concussed athletes. Decreased diffusivity, as reflected in left and right DLPC apparent diffusion coefficients (ADC), correlated significantly with percent change of fMRI BOLD signal in concussed athletes but not in healthy control subjects (39). The lack of consistency in findings between fMRI and DTI markers and their relation to sport concussion is not well understood and requires further investigation. Davis *et al.* (9) reported that there are prospective DTI studies of acute concussion in high-school athletes (University of Pittsburg) and collegiate athletes (University of North Carolina-Chapel Hill, University of Pittsburgh, and McGill University), and DTI studies of long-term effects of concussion in retired professional football players (University of North Carolina-Chapel Hill and National Football League MTBI Committee). The University of New Mexico Neuropsychology Research Team also has just begun a prospective acute DTI sports concussion study in collegiate athletics.

MRS

MRS is a noninvasive technique that measures neurometabolites via proton magnetic resonance (^{1}H-MR) spectroscopy. Neurometabolites that can be detected reliably with MRS include N-acetylaspartate (NAA; found in mitochondria and felt to be a marker of neuronal integrity), creatine (Cr; involves cellular energy metabolism), choline (a marker of membrane), myoinositol (found in glial cells), and lactate (a marker of anaerobic metabolism and indirect marker of ischemia and hypoxia) (11). Changes in NAA, choline, and Cr ratios demonstrated by MRS have been associated with individuals who have experienced traumatic brain injury (TBI) (13,38). Two studies have investigated sports-related concussion using MRS (16,36). Vagnozzi and colleagues (36) studied 14 individuals who sustained a sports-related concussion. They examined the subjects at 3 to 4, 15, and 30 d postinjury with MRS. Decreased NAA/Cr ratio was observed at 3 d following concussion, modest recovery at 15 d postinjury, and normalization of NAA/Cr ratio by 30 d postinjury. It is of interest that concussed athletes reported postconcussion symptom resolution by 3 d postinjury despite abnormal MRS findings. Further decrease in NAA/Cr was seen in an individual who experienced a second concussion before the 15-d study, and complete metabolic recovery was delayed until 45 d postinjury. Results suggest differences in recovery as determined by symptom report versus metabolic recording and that a second concussion that occurs prior to recovery from a first concussion can result in further metabolic compromise and delay the metabolic recovery period. Henry *et al.* (16) showed a significant decrease in NAA/Cr in prefrontal and primary motor cortices but not in hippocampi in concussed athletes compared with nonconcussed athletes. Additionally, decreased glutamate/Cr in primary motor cortices, but not in DLPC, was observed. In contrast to Vagnozzi *et al.* (36), Henry *et al.* found neurometabolic changes correlated temporally with resolution of self-report postconcussive symptoms.

fMRI

fMRI is a noninvasive technique that does not involve radiation exposure and can capture neuronal activation by measurement of changes in BOLD. By measuring changes in the state of oxygenation of hemoglobin (and thus signal intensity), it is assumed that brain regions associated with these changes represent the neural substrates of the task performed in the scanner (1). Seven studies have investigated sports-related concussion using fMRI (6–8,20,29,35,39), although two of those studies used the same research subjects (35,39). Six of the seven studies examined working memory, and two of the seven examined other neuropsychological functions, including sensorimotor coordination and visuospatial memory. Several recent review papers have discussed in greater detail fMRI findings from previous studies; to avoid redundancy, the reader is referred to those papers (9,34). Briefly, abnormal activation patterns of the DLPC during working memory tasks have been identified consistently across concussion studies. The working memory tasks varied between studies, and the pattern of activation in the DLPC (*i.e.*, increased vs decreased activation) also varied between studies. To date, it is unclear whether less activation indicates impaired working memory, whether greater activation of particular regions suggests a compensatory mechanism, or whether some combination of processes is occurring concurrently. Targeted research studies will be necessary in the future to address this question.

Chen *et al.* (8) reported a unique and important finding related to mood status. They found that the presence of depressive symptoms in concussed athletes was significantly related to fMRI activation on a working memory task and that concussed, nondepressed athletes performed comparably with healthy control subjects. No other studies reported depressive symptoms, suggesting that this may be an underlying factor that may account for some of the heterogeneous findings between studies. Thus far, fMRI has demonstrated the greatest clinical utility in determining return-to-baseline in brain functioning as it relates to resolution of postconcussion syndrome (PCS) symptoms, although this bias may be an artifact of the greater attention that has been given to fMRI.

Magnetoencephalograpy (MEG)/Magnetic Source Imaging (MSI)

MEG is an imaging technique used to measure the magnetic fields produced by electrical activity in the brain through the use of superconducting quantum interference devices (SQUID). See the Figure for a brief overview of MEG. When coupled with MRI, MSI provides a high-resolution anatomical/functional image. MEG abnormalities have been identified in adults with brain injuries with persistent (>1 yr) postconcussive symptoms (28). Integrated studies combining MEG with DTI have been found to be more sensitive

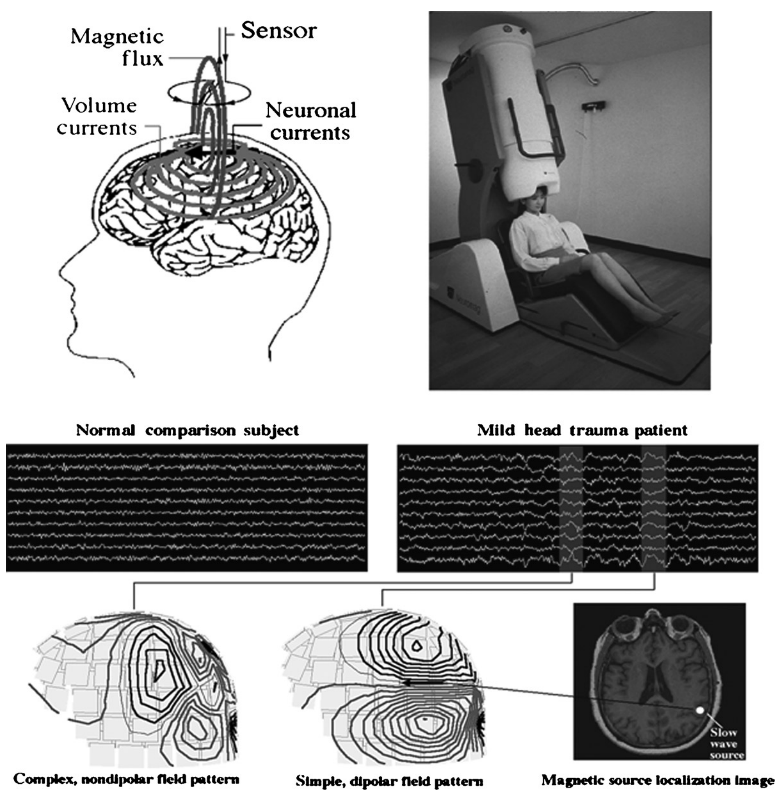

Figure: Basic principles of magnetoencephalography: currents flowing within the apical dendrites of pyramidal cells oriented parallel to the skull surface give rise to a magnetic field that can be measured outside of the head using supercooled sensors connected to superconducting quantum interference devices (SQUID). The sensors are arrayed within a head-shaped cryogenic vessel. During testing, the participant sits underneath the sensor unit. A 122-channel unit is pictured. The output of each sensor is a waveform that shows how the local magnetic flux changes in time. Representative data are shown for a normal comparison and patients with mild head trauma. A 6.8-s-long epoch of data is shown for 10 sensors over the left posterior temporal region. For the control participant, the bulk of activity is of low amplitude and high frequency. In contrast, the patient with head trauma displays prominent, large amplitude slow waves (1 to 6 Hz, each approximately 800 fT, peak-to-peak). Most slow waves have complicated magnetic field patterns as revealed by isofield contour maps that show multiple regions of emerging (gray contour lines) and entering flux (black contour lines). In contrast, some slow waves have a dipolar field pattern characterized by single regions of emerging and entering flux. The source location for the neuronal currents that contribute to dipolar slow waves can be inferred using mathematical techniques that identify the position, orientation, and time course for the best-fitting dipole source. This location can be plotted on a spatially aligned magnetic resonance image to generate a composite magnetic source localization images. (Reprinted from Lewine JD, *et al.* Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. J Head Trauma Rehabil 2007; 22(3):141–55. Copyright © Lippincott Williams and Wilkins. Used with permission.)

than conventional CT and MRI in detecting subtle neuronal injury in mTBI, with MEG being more sensitive than DTI in identifying individuals with mTBI (17). There are no published studies available to date utilizing MEG/MSI in sports-related concussion. The University of New Mexico Neuropsychology Research Team currently is investigating MEG/MSI correlates of sports concussion as part of a study involving traditional and computerized neuropsychological assessment approaches and comprehensive neuroimaging in collegiate athletes who sustain sports-related concussions at the University of New Mexico.

Single-Photon Emission CT (SPECT)

SPECT is an invasive method of measuring regional cerebral blood flow through the intravenous injection of a radioisotope, imaging extent and location of that radioisotope as it moves through brain vasculature (12). The utility of this method is limited because of the procedural complexity of SPECT and the risk of radiation exposure to otherwise healthy subjects. Further, SPECT is less helpful in assessing diffuse injury (*e.g.*, TBI) than focal injuries (*e.g.*, cerebrovascular accident, brain tumor). While SPECT has been used in the investigation of nonsports-related mTBI, no studies to date have utilized SPECT in the investigation of sports-related concussion.

Positron Emission Tomography (PET)

PET measures cerebral metabolism by brain imaging via PET scanner of radionuclides that are injected intravenously, cross the blood-brain barrier, and are distributed into brain cells. Similar to SPECT, limitations of this technology are the exposure to radio-labeled tracers, expense, and time consumption (12). No studies to date have utilized PET in the investigation of sport concussion, but it has been used in the investigation of nonsports-related mTBI.

Limitations of Current Research and Directions for Future Research

From this review, several limitations in the existing literature were identified. Areas for further research are suggested here:

1. *Neuroimaging modalities*. No neuroimaging studies have been reported utilizing PET, SPECT, or MEG/MSI in the sports concussion literature. Given that PET and SPECT have limited availability and involve exposure to radiation, it is unlikely that these modalities will be particularly useful in helping to better understand sport concussion, particularly in children/adolescents, although these modalities have proven useful in evaluating nonsports-related TBI (15). Given the temporal resolution superiority of MEG and the often-found impairments in information processing speed following concussion/mTBI, MSI may be a promising neuroimaging modality to use to better understand the pathology and recovery course of concussion. Quantitative sMRI (*i.e.*, VBM and region of interest MRI volumetric techniques) has so far been utilized little in the study of sport concussion. Presumably, this has been related to the lack of abnormal findings on clinical MRI in mTBI or concussion and the diffuse nature of mTBI. However, it is possible that regional susceptibility to brain injury or diffuse volumetric reductions may be demonstrated with quantitative or volumetric MRI measures. Only two studies used a combination of neuroimaging techniques (*i.e.*, fMRI/DTI, fMRI/VBM). The investigation and integration of multiple neuroimaging techniques with the same clinical populations may help to better clarify the brain abnormalities identified (17,28).
2. *Neuroimaging acquisition*. Studies vary as to when neuroimaging was obtained postinjury (*i.e.*, ranging from 3 d to 14 months). Only one study (20) included prospective preinjury neuroimaging to use as a baseline for comparison to postinjury status, and only three studies included multiple time points when neuroimaging monitoring occurred to document recovery (6,8,36). While obtaining preinjury neuroimaging is very expensive and difficult to accomplish, studies that include baseline preinjury neuroimaging and serial neuroimaging would be helpful in clarifying the time course of injury to recovery and would allow us to address the issue of differentiating premorbid risk factors for concussion from abnormality resulting from concussion.
3. *MRS*. Findings suggest that neurometabolic changes associated with concussion can be identified via MRS. However, the relationship between these neurometabolic concentration changes and clinical concussion pathology needs further clarification. For instance, the neurometabolic abnormalities discussed previously are ratios (*e.g.*, NAA/Cr). While there are valid reasons for using ratio measures to ensure measurement reliability in MRS, to what extent the metabolite abnormalities are due, for example, to changes in either NAA or Cr is unclear. In a study of mTBI (but not sports-related), lower levels of gray matter glutamate-glutamine and higher levels of white matter Cr-phosphocreatine were found (13), suggesting that the metabolic changes may be due to Cr increases rather than decreases in other metabolites. Further, there are varying findings regarding the relationship between neurometabolic changes and resolution of symptoms based on patient self-report. Further research is needed to understand the relationships between MRS metabolic changes, self-reported symptoms, and markers of concussion recovery before MRS can be considered a valid tool to assist in clinical and return-to-play decision-making.
4. *fMRI cognitive tasks*. While the majority of imaging studies that utilized fMRI primarily examined working memory, there is either inter-study inconsistency regarding task performance or similar performances between studies but with different activation patterns, making it difficult to determine the true nature of functional abnormalities. The consistent focus on working memory and motor tasks during fMRI may lead some to conclude prematurely that sports-related concussions are a disorder of

frontal network functioning. As such, future studies should examine other cognitive functions, guided by knowledge obtained through neuropsychological studies. Few of the neuroimaging studies related findings to neuropsychological batteries (36,39). Additional studies that involve neuroimaging and cognitive activation tasks and compare performance to traditional neuropsychological tasks may help clarify the relationships between neuroimaging findings and cognitive function/dysfunction associated with concussion. Additionally, although fMRI is the most studied of neuroimaging modalities in sports concussion, there appears to be a lack of methodological consistency between study groups. Nearly all (6/7) studies using fMRI utilized a block design method, which, although advantageous in several regards (*e.g.*, statistical power, easier implementation), also has several weaknesses and assumptions that must be met (*e.g.*, the BOLD effect remains constant across the epoch of interest). Only Chen *et al.* (6), the oldest of studies, used an event-related design, which also has unique advantages for studying the possibly subtle effects associated with concussion and recovery (*e.g.*, good estimation power, allows for post hoc trial sorting).

5. *Demographic factors*. There is some evidence in the literature that there may be gender differences in outcome or recovery from concussion (10). Gender was not reported or is unclear/unknown in two of the nine studies and is not a variable controlled for or specifically analyzed in any of the studies. Since there are marked individual differences in the gray-white matter composition of male versus female brains, it is essential that additional investigation is conducted to better understand sex differences in neuropathology and recovery in sports-related concussion. Additionally, there is a glaring restriction in the age of concussed subjects studied with neuroimaging (*i.e.*, mean ages 16.6 to 31.7 yr). It has been suggested that poorer outcome or atypical recovery may be associated with younger age (25), possibly from age-related differences in biomechanical properties of the musculoskeleture, head, brain, and pathophysiological responses. Further studies are needed to investigate concussion in younger populations, as childrens' participation in contact sports often begins in elementary school. Also, given the concerns about the long-term outcome from repeated concussion, neuroimaging studies are needed to study the long-term neuroanatomical consequences of concussion in older individuals who have complex sports concussion histories. Further, there is a lack of age, education, and gender norms for the various neuroimaging modalities, with which to compare concussed athletes. More research is necessary to simply establish the sensitivity and specificity of each method to concussive injury and the recovery process.
6. *Concussion-related factors*. Most studies did not indicate whether subjects had a prior history of concussion or included mixed samples where subjects had single and multiple concussions. Given that the effects of repeated concussions are not well understood, future neuroimaging studies that control for number of repeated concussions is critical to establishing the relative sensitivity and specificity of these measures. Further, only one study attempted to investigate the effects of repeated concussions within a short time frame (36). Additional studies are needed to better understand the temporal window of recovery from concussion and the effects of repeated concussions when there has not been full recovery. Disconcertingly, three of nine studies did not report subjective postconcussive symptoms at the time of neuroimaging, and the number of subjects with postconcussive symptoms was unclear in another three of nine studies. Only one study investigated the contribution of mood (39) and found differences in activation patterns on fMRI, as well as grey matter density on VBM, related to depression severity. The relationship of mood and neuroimaging correlates and recovery patterns of concussion requires further study.
7. *Motivation and effort.* Another important issue to assess in tasks involving cognitive functioning is that of motivation. Although it typically is assumed that athletes underreport symptoms, it also is possible that concussed athletes may not put forth sufficient effort on neuropsychological and fMRI tasks. Future studies should include assessment of motivation and effort in research designs to disentangle relationships between motivation, postconcussive depression, and neuropathology.

Conclusion

While advanced neuroimaging techniques have the potential to identify brain abnormalities related to concussion that are not appreciated with traditional clinical neuroimaging, the extent to which these techniques may be useful in guiding clinicians in the clinical management of sports concussion is unknown. We do not yet know the true clinical implications of neuroimaging results and must be cautious in our assessment of the meaning of imaging findings in relation to management of concussion. For example, does normalization on imaging mean that it is safe to return-to-play? To what extent do fMRI activation patterns have to be "abnormal" to rule out return-to-play? How should neuroimaging information be combined with other data to make decisions (*e.g.*, in the presence/absence of postconcussive symptoms, neurocognitive function)? For instance, even though imaging, particularly fMRI, may return to "normal," it is possible that the effort required to achieve that performance may be greater than expected in a healthy individual and so fMRI may not necessarily reflect true recovery. Additional normative studies are needed to better understand the sensitivity and specificity of neuroimaging modalities in sports-related concussion, repeated concussions, how neuroimaging findings are related to neurocognitive processes of sports concussion, and patient demographic factors (*e.g.*, age, gender, mood) in order to identify markers that can clarify the temporal resolution of concussion and predict outcome.

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References

1. Amaro E Jr, Barker GJ. Study design in fMRI: basic principles. *Brain Cogn*. 2006; 60(3):220–32.
2. Ashburner J, Friston KJ. Voxel-based morphometry — the methods. *Neuroimage*. 2000; 11(6 Pt 1):805–21.
3. Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis — a technical review. *NMR Biomed*. 2002; 15(7–8): 456–67.
4. Belanger HG, Vanderploeg RD. The neuropsychological impact of sports-related concussion: a meta-analysis. *J. Int. Neuropsychol. Soc.* 2005; 11(4):345–57.
5. Centers for Disease Control and Prevention (CDC). Nonfatal traumatic brain injuries from sports and recreation activities — United States, 2001–2005. *MMR Morb. Mortal. Wkly. Rep*. 2007; 56(29):733–7.
6. Chen J-K, Johnston KM, Frey S, *et al.* Functional abnormalities in symptomatic concussed athletes: an fMRI study. *Neuroimage*. 2004; 22(1):68–82.
7. Chen J-K, Johnston KM, Petrides M, Ptito A. Neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. *Arch. Gen. Psychiatry*. 2008; 65(1):81–9.
8. Chen J-K, Johnston KM, Petrides M, Ptito A. Recovery from mild head injury in sports: evidence from serial functional magnetic resonance imaging studies in male athletes. *Clin. J. Sport Med*. 2008; 18(3):241–7.
9. Davis GA, Iverson GL, Guskiewicz KM, *et al*. Contributions of neuroimaging, balance testing, electrophysiology and blood markers to the assessment of sport-related concussion. *Br. J. Sports Med*. 2009; 43(Suppl. 1):i36–45.
10. Dick RW. Is there a gender difference in concussion incidence and outcomes? *Br. J. Sports Med*. 2009; 43(Suppl. 1):i46–50.
11. DiFiori JP, Giza CC. New techniques in concussion imaging. *Curr. Sports Med. Rep*. 2009; 9(1):35–9.
12. Dougherty DD, Rauch SL, Fischman AJ. *Positron Emission Tomography and Single Photon Emission Computed Tomography*. Arlington (VA): American Psychiatric Publishing; 2004. p. 75–92.
13. Gasparovic C, Yeo R, Mannell M, *et al*. Neurometabolite concentrations in gray and white matter in mild traumatic brain injury: an 1H-magnetic resonance spectroscopy study. *J. Neurotrauma*. 2009; 26(10):1635–43.
14. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J. Athl. Train*. 2001; 36(3):228–35.
15. Granacher RP. *Traumatic Brain Injury: Methods for Clinical and Forensic Neuropsychiatric Assessment*, 2nd ed. Boca Raton (FL): CRC Press; 2008.
16. Henry LC, Tremblay S, Boulanger Y, *et al*. Neurometabolic changes in the acute phase after sports concussions correlate with symptom severity. *J. Neurotrauma*. 2010; 27(1):65–76.
17. Huang MX, Theilmann RJ, Robb A, *et al*. Integrated imaging approach with MEG and DTI to detect mild traumatic brain injury in military and civilian patients. *J. Neurotrauma*. 2009; 26(8):1213–26.
18. Hughes DG, Jackson A, Mason DL, *et al*. Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: correlation with neuropsychological tests and delayed recovery. *Neuroradiology*. 2004; 46(7):550–8.
19. Huisman TA, Sorensen AG, Hergan K, *et al*. Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. *J. Comput. Assist. Tomogr*. 2003; 27(1):5–11.
20. Jantzen KJ, Anderson B, Steinberg FL, Kelso JA. A prospective functional MR imaging study of mild traumatic brain injury in college football players. *AJNR Am. J. Neuroradiol*. 2004; 25(5):738–45.
21. Johnston KM, Ptito A, Chankowsky J, Chen JK. New frontiers in diagnostic imaging in concussive head injury. *Clin. J. Sport Med*. 2001; 11(3):166–75.
22. Jordan BD. Acute and chronic brain injury in United States National Team Soccer Players. *Am. J. Sports Med*. 1996; 24(5):704–5.
23. Jordan BD, Zimmerman RD. Magnetic resonance imaging in amateur boxers. *Arch. Neurol*. 1988; 45(11):1207–8.
24. Kelly AB, Zimmerman RD, Snow RB, *et al*. Head trauma: comparison of MR and CT-experience in 100 patients. *AJNR Am. J. Neuroradiol*. 1988; 9(4):699–708.
25. Kirkwood MW, Yeates KO, Wilson PE. Pediatric sport-related concussion: a review of the clinical management of an oft-neglected population. *Pediatrics*. 2006; 117(4):1359–71.
26. Le Bihan D, Mangin JF, Poupon C, *et al*. Diffusion tensor imaging: concepts and applications. *J. Magn. Reson. Imaging*. 2001; 13(4): 534–46.
27. Levin HS, Lippold SC, Goldman A, *et al*. Neurobehavioral functioning and magnetic resonance imaging findings in young boxers. *J. Neurosurg*. 1987; 67(5):657–67.
28. Lewine JD, Davis JT, Bigler ED, *et al*. Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. *J. Head Trauma. Rehabil*. 2007; 22(3):141–55.
29. Lovell MR, Pardini JE, Welling J, *et al*. Functional brain abnormalities are related to recovery and time return-to-play in athletes. *Neurosurgery*. 2007; 61(2):352–9.
30. McCrea M, Guskiewicz KM, Marshall SW, *et al*. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA*. 2003; 290(19):2556–63.
31. McCrory P, Meeuwisse W, Johnston K, *et al*. Consensus statement on concussion in sport 3rd international conference on concussion in sport held in Zurich, November 2008. *Clin. J. Sport Med*. 2009; 19(3): 185–200.
32. Mendez CV, Hurley RA, Lassonde M, *et al*. Mild traumatic brain injury: neuroimaging of sports-related concussion. *J. Neuropsychiatry Clin. Neurosci*. 2005; 17(3):297–303.
33. Mukherjee P, Miller JH, Shimony JS, *et al*. Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. *AJNR Am. J. Neuroradiol*. 2002; 23(9):1445–56.
34. Ptito A, Chen JK, Johnston KM. Contributions of functional magnetic resonance imaging (fMRI) to sport concussion evaluation. *NeuroRehabilitation*. 2007; 22(3):217–27.
35. Slobounov SM, Zhang K, Pennell D, *et al*. Functional abnormalities in normally appearing athletes following mild traumatic brain injury: a functional MRI study. *Exp. Brain Res*. 2010; 202(2):341–54.
36. Vagnozzi R, Signoretti S, Tavazzi B, *et al*. Temporal window of metabolic brain vulnerability to concussion: a pilot 1H-magnetic resonance spectroscopic study in concussed athletes — part III. *Neurosurgery*. 2008; 62(6):1286–95.
37. Wilde EA, McCauley SR, Hunter JV, *et al*. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology*. 2008; 70(12):948–55.
38. Yeo RA, Phillips JP, Jung RE, *et al*. Magnetic resonance spectroscopy detects brain injury and predicts cognitive functioning in children with brain injuries. *J. Neurotrauma*. 2006; 23(10):1427–35.
39. Zhang K, Johnson B, Pennell D, *et al*. Are functional deficits in concussed individuals consistent with white matter structural alterations: combined fMRI and DTI study. *Exp. Brain Res*. 2010; 204(1):57–70.