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# A Systematic Review of Diffusion Tensor Imaging Findings in Sports-Related Concussion

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## Abstract

Sports-related concussion (SRC) is typically associated with functional, as opposed to structural, injury. The results of traditional structural neuroimaging techniques used to assess SRC tend to be normal in many athletes, and are only clinically helpful in ruling out a more serious injury. Diffusion tensor imaging (DTI) has increasingly been touted as a method offering greater clinical potential in mild traumatic brain injury (mTBI). Despite this, the utility of DTI as a clinical tool for diagnosing and managing SRC has received considerably less attention than it has in the general TBI research literature. The aim of this article is to conduct a systematic review of DTI in SRC, and to provide a focus and overview of research findings using this MRI technique in SRC. A systematic review of articles published in the English language, up to February 2012, was retrieved via PsycINFO®, MEDLINE®, EMBASE, SPORTDiscus™, Scopus, Web of Science, and Informit; using the key search terms: diffusion tensor imaging, diffusion magnetic resonance imaging, diffusion weighted MRI, diffusion MRI, fractional anisotropy, tractography, apparent diffusion coefficient, magnetic resonance imaging, mild traumatic brain injury, mTBI, traumatic brain injury, concussion, sport, athletic and athlete. Observational, cohort, correlation, cross-sectional and longitudinal studies were all included in the current review. Results of the review found eight articles that met inclusion criteria, which included data on 214 athletes and 96 controls. Seven of eight studies reported some type of DTI abnormality, although the neuroanatomical sites involved varied. Although considerable methodological variations exist across studies, the current review suggests that DTI may possess adequate diagnostic sensitivity to detect SRC in affected athletes. Further longitudinal studies are required to demonstrate its discriminative validity and prognostic capacity within this field.

**Key words:** MRI; neural injury; TBI

## Introduction

WITH THE WORLDWIDE POPULARITY OF SPORTS involving contact or collision, there is an imperative to focus efforts on the better detection, prevention, and treatment of the potentially damaging neurological, social, and psychological effects of sports-related traumatic brain injury (sports-related concussion [SRC]). Although the neuropsychology of SRC is reasonably well documented, the pathophysiology is not well understood, even though the incidence of SRC is high and increasing.<sup>1</sup>

It is a well-established notion that the majority of SRCs tend to fall at the mild end of the traumatic brain injury (TBI) continuum.<sup>2</sup> Although SRC can result in overt problems such as acute headache, dizziness, confusion, and nausea, in many instances the signs of

concussion are more covert, manifesting as mild cognitive deficits<sup>3</sup> that may not be detected via traditional clinical assessment.

Structural neuroimaging is one method typically used to establish pathophysiological diagnosis of SRC, albeit that it focuses on only one of the multi-faceted presentations of the condition.<sup>4,5</sup> Ideally it informs acute clinical management post-injury, and may also be predictive of functional recovery at chronic stages.<sup>6</sup> However, because of the nature of SRC, which involves functional rather than structural injury, results of traditional structural neuroimaging techniques (i.e., CT, and MRI) are predominantly normal in many athletes.<sup>7,8</sup> These conventional structural imaging techniques may, therefore, have little utility in diagnosing or assessing SRC, beyond ruling out a more serious injury, such as intracranial hemorrhage or small cerebral contusions,<sup>9</sup> and do not

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adequately detect more subtle or even widespread microstructural traumatic axonal injury (TAI), such as those that may be observed in SRC. As a result, conventional CT and MRI have not reliably correlated with patient symptoms of SRC and are inconsistent in predicting functional outcome following mild TBI (mTBI).<sup>10,11</sup> Advances in neuroimaging technology and the improved capacity of neuroimaging techniques to examine tissue at a microstructural level is required, and is especially important in cases of chronic post-concussive symptoms.<sup>12</sup>

Diffusion tensor imaging (DTI) is a less conventional and relatively new MRI modality that provides noninvasive, *in vivo* indices of tissue microstructure. Characterization of the microstructure of white matter connections is achieved by assessing the degree of water diffusion in the brain.<sup>13–15</sup> DTI exploits the fact that myelin sheaths and cell membranes of white matter tracts hinder the movement of water molecules.<sup>12,16</sup> Although DTI has been used primarily as a research method for assessing structure and function following TBI of all severities, it has increasingly been touted as a method offering great clinical potential, as well as holding some promise as a means of predicting recovery (i.e., prognosis) in cases of mTBI.<sup>12</sup> A growing body of literature suggests that certain DTI parameters may serve as a biomarker for microstructural white matter changes in mTBI at both acute and chronic stages.<sup>6,17</sup> DTI may be a promising approach for characterizing microscopic damage to specific white matter pathways following mTBI. If DTI can reliably detect subtle, but clinically relevant, changes in brain microstructure in ways that exceed the capabilities of conventional imaging methods, it may be crucial in redefining the diagnosis, prognosis, and management of mTBI patients.

### Application of DTI in TBI

Although DTI has been used primarily as a research method for assessing structure and function following TBI of all severities, it has increasingly been touted as a method offering great clinical potential, as well as holding some promise as a means of predicting recovery (i.e., prognosis) in cases of mTBI.<sup>12</sup>

In the acute stage of a traumatic lesion, the axonal swelling is believed to increase fractional anisotropy (FA) and decrease apparent diffusion coefficient (ADC). In the chronic stage, this effect appears to reverse as the membrane degradation and cellular lysis allow more space for water to diffuse, increasing ADC and decreasing FA.<sup>17</sup>

### DTI analysis methods in TBI

**Whole brain distributional analysis.** In this approach, a histogram of the diffusion MR parameter (such as the mean diffusivity) is calculated for every voxel in the entire brain. In previous approaches,<sup>18</sup> a set of three Gaussians is fitted to the histogram, to represent three distinct compartments: 1) “tissue,” 2) non-tissue and CSF, and 3) partial volume voxels containing both tissue and non-tissue/CSF contributions to the signal. The “tissue” Gaussian is used to infer the diffusion properties of the brain, typically by characterizing the peak height, peak location, and the width of the Gaussian.

From a practical standpoint, the approach is simple to implement, as no user interaction is required, and the fact that the measurement is “global” means that there is no need to correct for multiple comparisons, as would be needed in voxel-based or forms of region of interest (ROI)-based analyses, and there is no need for *a priori* hypotheses relating to anatomical location of group differences. On the other hand, any information on the location of damage is lost and any

changes are averaged across the whole brain. Therefore, one can miss subtle effects that may be detected by other analysis methods. For a more detailed discussion of the pros and cons of histogram analysis, the reader is referred to Cercignani.<sup>19</sup>

**Whole brain voxel-based analysis.** Whole brain voxel-based DTI analysis also assesses the entire brain volume in the absence of *a priori* hypotheses pertaining to anatomical location but, in contrast to histogram analyses, tries to identify the specific locations of any group differences. There are two main approaches used in the neurotrauma literature: 1) those based on voxel-based morphometry approaches,<sup>20</sup> in which the data sets from individuals are first aligned, then smoothed before statistical inferences are drawn at each voxel of the smoothed image; and 2) those based on skeleton-projection-based approaches<sup>21</sup> in which, after alignment, a skeleton of the mean of the aligned images is derived and the data are projected onto this skeleton to correct for residual misalignment.

One of the limitations of this method is the difficulty associated with assigning significant cluster attributes to a single tract,<sup>22–24</sup> in addition to issues with choice of smoothing kernel (in the first method),<sup>20</sup> heterogeneity of statistical power (in the second method),<sup>25</sup> and other biases that avoid the detection of pathology.<sup>26</sup>

Despite this shortcoming, DTI in mTBI cases has indicated microstructural alteration in comparison with controls,<sup>27,28</sup> with reduced FA detected in the genu of corpus callosum, posterior limb of internal capsule, superior longitudinal fasciculus, superior fronto-occipital fasciculus, and centrum semiovale in the mTBI group. Further, FA values within the corpus callosum, posterior limb of the internal capsule, superior longitudinal fasciculus, corticospinal tract, superior fronto-occipital fasciculus, and inferior occipitofrontal fasciculus, are negatively correlated with severity of injury as determined by Glasgow Coma Scale (GCS) scores.<sup>29</sup> However, as noted previously, the association between DTI indices and injury severity or other measures of impairment relies upon whether imaging is performed during the acute or the more chronic phase of TBI recovery.

**ROI analysis.** With the ROI approach, the anatomical structures of interest to be compared across groups are predetermined. TBI samples typically show lower ADC and higher FA values during the acute stage of injury when compared with controls using ROI methods.<sup>30</sup> Analysis of ROIs has also demonstrated that FA values of the genu, stem, and splenium of the corpus callosum, and the columns of the fornix, were lower in patients with TBI than in healthy controls.<sup>31</sup> Attentional control has also been shown to positively correlate with FA in the anterior part of the left corona radiata, and FA in the uncinate fasciculus positively correlated with memory performance in TBI samples.<sup>32</sup> The advantage is that the method is transparent and readily interpretable, and by definition requires less correction for multiple comparison than a whole-brain voxel-by-voxel search. As several voxels are averaged with the ROI, this approach will confer greater sensitivity than voxel-by-voxel searches. The disadvantages are the laborious nature, and the inability to detect changes that were not previously hypothesized. Moreover, it is well known that there is subjectivity in hand-drawn ROI placement,<sup>26</sup> which can confound analyses, although using atlas-defined ROIs can ameliorate this problem. Maximum sensitivity will be had when the size of the ROI matches the size of the abnormality. If the ROI is too large, for example, subtle effects will be missed.

**In vivo tractography.** *In vivo* tractography provides “virtual dissections” or an architectural representation of the major white

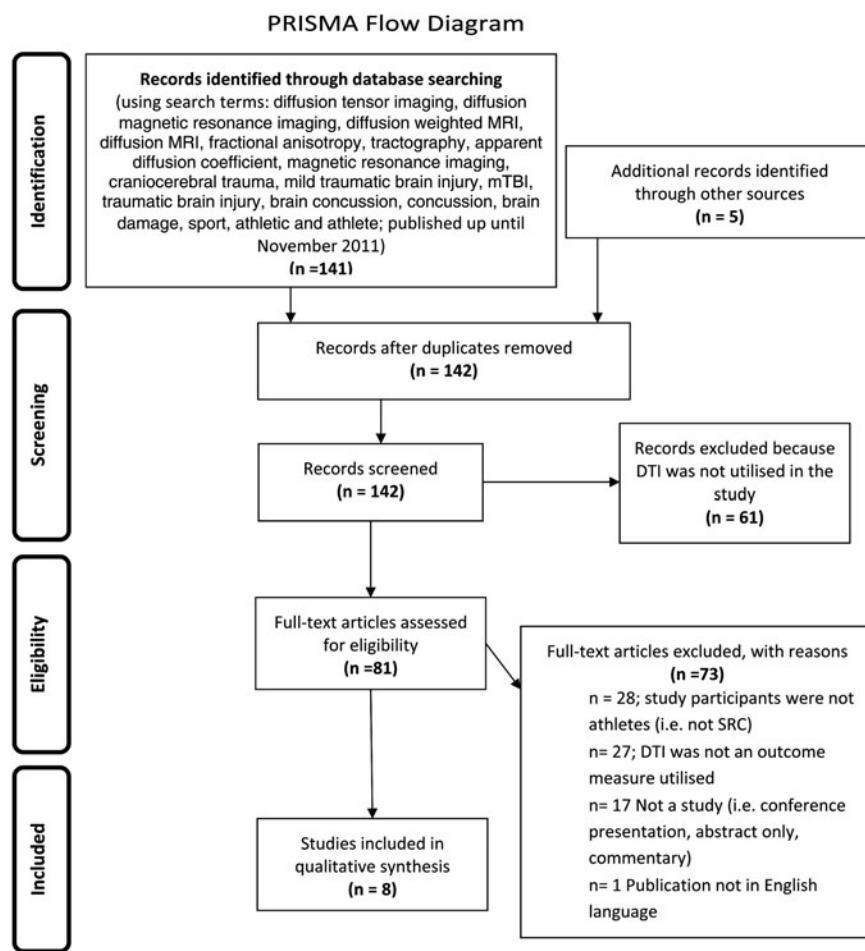


FIG. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

matter pathways.<sup>33</sup> Unfortunately, many of the TBI studies that have used tractography have limitations, including single case studies,<sup>33–35</sup> assessing a limited number of tracts such as the corpus callosum<sup>31,36</sup> or including only moderate/severe TBI cases.<sup>37</sup>

The tractography-based approach may be more sensitive in revealing FA differences than the voxel-based or small-ROI-based approach, as many more averages of the parameter of interest are used in deriving a mean value for the tract. This notion is supported by the findings of Keedwell and colleagues<sup>38</sup> who reported highly significant tract-specific results, whereas the tract-based spatial statistics revealed no significant results. Further, Kanaan and colleagues<sup>39</sup> reported differences using tract-based approaches that were not observed with ROI-based approaches. Moreover, for white matter pathways that take a tortuous route in and out of the plane of the screen, a tractography-based definition of an ROI will clearly be superior to a hand-drawn approach. The downsides are shared with those of ROI-based approaches, in that unexpected differences will not be revealed. As with the non-tractography ROI-based approaches, if the effects are highly localized (such as to a small portion of a tract), then averaging over the whole tract may obscure these differences.

Given that SRCs are typically in the mild range of TBIs,<sup>2</sup> and the abovementioned results are from DTI studies in more general mTBI samples, it follows that this imaging technique may be useful in the detection and management of the unique sequelae associated with SRC. What is particularly relevant in terms of SRC is whether

there are more lasting or cumulative changes that are measurable using DTI following repeated head trauma. The current systematic review examines the growing literature on the use of DTI with SRC in children and adults.

## Objectives

In the current review, studies that used DTI to investigate brain injuries in athletes were considered. The aim of this review was to systematically evaluate the currently available evidence on the utility of DTI in the diagnosis and prognosis of SRC, and to determine whether the promising findings within general mTBI groups translate to SRC in athlete samples. To examine this question, observational, cohort, correlation, cross-sectional, and longitudinal studies were all included in the current review.

## Methods

The review was conducted in three stages:

In stage 1, articles were retrieved via online database searching, hand-searching reference lists, and performing cited reference searches (see Fig. 1). The online databases of PsycINFO®, MEDLINE®, EMBASE, SPORTDiscus™, Scopus, Web of Science, Informit, dissertations, and theses were searched. Keywords and combinations of these words were used to search the databases comprehensively: diffusion tensor imaging, diffusion magnetic resonance imaging, diffusion weighted MRI, diffusion MRI,

TABLE 1. QUALITY ASSESSMENT RATING RESULTS

Quality Assessment Rating Criteria Questions	Cubon et al (2011) <sup>42</sup>	Zhang et al (2010) <sup>47</sup>	Chappell et al (2006) <sup>43</sup>	Zhang et al (2006) <sup>44</sup>	Zhang et al (2003) <sup>45</sup>	Henry et al (2011) <sup>46</sup>	Bazarian et al (2012) <sup>48</sup>	Maugans et al (2012) <sup>1</sup>
1. Was the research question clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the selection of study subjects/patients free from bias?	Y	Y	Y	N	N	Y	Y	Y
3. Were study groups comparable?	Y	Y	N	N	N	Y	N	Y
4. Was method of handling withdrawals described?	Y	Y	Y	Y	Y	Y	Y	Y
5. Was blinding used to prevent introduction of bias?	N	N	N	N	N	N	Y	Y
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Y	Y	Y	Y	Y	Y	Y	Y
7. Were outcomes clearly defined and the measurements valid and reliable?	Y	Y	Y	Y	Y	Y	Y	Y
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?	Y	Y	Y	Y	Y	Y	Y	Y
9. Were conclusions supported by results with biases and limitations taken into consideration?	Y	N	N	Y	N	Y	Y	Y
10. Is bias due to study's funding or sponsorship unlikely?	Y	N	N	N	Y	Y	N	Y
<b>Overall Quality Rating</b>	<b>P</b>	<b>P</b>	<b>O</b>	<b>O</b>	<b>O</b>	<b>P</b>	<b>O</b>	<b>P</b>

Y, yes; N, no; P, positive; O, neutral.

fractional anisotropy, tractography, apparent diffusion coefficient, magnetic resonance imaging, craniocerebral trauma, mild traumatic brain injury, mTBI, traumatic brain injury, brain concussion, concussion, brain damage, sport, athletic, and athlete. Articles were limited to those that were published in English-language journals up to February 2012, although several articles reported later in 2012 that were part of a special issue on mTBI (*Brain Imaging and Behavior*, June, 2012) were also reviewed. The reference lists of articles retrieved for inclusion in the review were hand searched to identify other relevant articles. Key articles retrieved via online databases and through hand searching reference lists were also used for further searches using the Web of Science Cited Reference function. The results of cited reference searches were narrowed using the key words diffusion tensor imaging or DTI; concussion or sports-related concussion; sport; and athletic or athlete. This was undertaken to capture the most relevant articles for further evaluation and critical appraisal.

During stage 2, the titles and abstracts of articles were reviewed to assess eligibility for inclusion in this review. Articles were regarded as relevant, and warranting inclusion in the review if they were experimental studies using diffusion tensor imaging to determine the presence (or absence) of neurological abnormality in concussed athletic samples. Studies were included whether they were conducted with acute or long-term concussed athletes (i.e., there were no restrictions placed on time elapsed since injury) and whether or not they also used other measures of neurological function (i.e., conventional MRI, CT, symptom checklist, balance testing, or neuropsychological testing). Where there was uncertainty about whether a study should be included based on the review of the title and abstract, the full article was retrieved.

In stage 3, all retrieved articles were independently assessed for quality using a standardized quality assessment checklist selected for its generic comprehensiveness and currency.<sup>40</sup> The methodological quality of the included studies was scored according to the criteria lists developed for both primary research and review articles.<sup>40</sup> The criteria list included questions pertaining to both study relevance and validity. Validity questions considered a number of dimensions including: the research question and aims; participant and control selection criteria; prevention or acknowledgement of

potential biases; exposure and intervening factors; appropriateness of statistical analyses; and whether conclusions were supported by results. The criteria answer format included designation of studies as positive, neutral, or negative. A study qualified for a positive score if: 1) it included an appropriate selection of study participants and matched controls, 2) intervention(s) were described in detail, and 3) the measures used were valid and reliable. Negative criteria were assigned to studies in which at least 6 of the 10 validity questions were not met. The neutral criteria were assigned to studies that had not fully met the positive criteria abovementioned, but nevertheless offered some valid information.

The checklist included such items as whether the research question was clearly stated, whether the selection of study subjects/patients was free from bias, whether the study groups were comparable, was the method of handling withdrawals described, was blinding used to prevent introduction of bias, were interventions or procedures and any comparison(s) described in detail, were outcomes clearly defined and the measurements valid and reliable, were statistical analyses appropriate for the study design and type of outcome indicators, were conclusions supported by the results with biases and limitations taken into consideration, and was the potential bias caused by the study's funding or sponsorship disclosed (see Table 1).

#### Data extraction

Initially, one reviewer extracted data from the identified studies, including 1) participant demographics (athletes and control subjects), 2) characteristics of participants (sport, exposure to concussion, concussive history), 3) DTI paradigms (technique and data extraction), 3) time lapsed (acute versus delayed assessment), 4) anatomical structures studied, 5) results of the study, and 6) study comments (see Tables 2–7 for data extraction results).

#### Methodological quality assessment

Three reviewers (A.G., F.K.-L., and A.H.) independently scored the included articles according to the quality assessment criteria using the checklists described previously. Consistency was attained

TABLE 2. STUDY CHARACTERISTICS

Ref	Athletes	N	Sex Girls M F	Age Range	Time lapsed post-SRC Mean SD	PCS v delayed onset of symptoms	Method for diagnosis of SRC	SRC severity (rating scale; GCS, PTA, LOC)	SRC symptoms	Concussion definition	Concussion history	Level of play	Sports involved	Follow up period (if any)		
Cubon et al (2011) <sup>2</sup>	10 (TBI: 5) 10 (TBI: 5)	10	10 S: 17–22 C: 18–23	S: 19.7 (1.6) C: 20.4 (1.8)	115 days; TBI: >1yr	104 days	Prolonged PCS	None of the subjects demon- strated symptomatol- ogy warrant- ing assessment by GCS.	Individual data included with in the article	Vienna 1st CIS Group	Majority had a his- tory of prior conc. (Mean = 3; SD = 1.4)	Varsity	Football, Hockey, Lacrosse, Rugby, Wrestling, Soccer, Pole Vault	N/A		
Zhang et al (2010) <sup>7</sup>	15	15	70% 30%	18–21	S: 20.8 (1.7) C: 21.3 (1.5)	30 days +/- - 2 days	NR	asymptomatic	Initial diagno- sis made on the field by a certified train- er. Cantu Data Driven Revised Con- cussion Grad- ing Guide- lines, 2006	Cantu Guide- lines made clinically w/in 7–10 days	asymptomatic NP tests and inclusion cri- teria: com- plaints of loss of concentra- tion, dizziness, fatigue, head- ache, irritabil- ity, visual disturbances, and light sen- sitivity	NR	Collegiate	Rugby, Hockey, Soccer	N/A	
Chappell et al (2006) <sup>3</sup>	81	12	all nil	S: 20–42 C: 22–31	median: S: 28 C: 25.5	NR	NR	NR	NR	NR	NR	NR	Boxing	N/A		
Zhang et al (2006) <sup>4</sup>	49	19	all nil	S: 30+/- 4.5yrs C: 32+/-9.5yrs	NR	NR	“all subjects were free of neurological disease”	NR	NR	NR	NR	NR	Professional	Boxing	• Two boxers had repeat studies within 1 and 2 years, re- spectively. • Both re- peated stud- ies showed decreased decreased trackable fi- bers in the whole brain and corpus callosum compared with their initial scans. N/A	
Zhang et al (2003) <sup>5</sup>	24	14	all nil	S: 21–52 C: 23–45	S: 32.3 (7.2) C: 32.2 (7.3)	NR	NR	NR	NR	NR	NR	NR	Professional	Boxing	All results demonstrated on initial Ax were observed at F/U	
Henry et al (2011) <sup>6</sup>	16	8	all nil	NR	S: 22.08 (1.72) C: 22.81 (1.53)	Initial: < 5 days mean = 81.92	Initial: SD = 46.74 h: F/U: 0.41 mths; Crd F/U: 10.29 mths h: F/U: mean = 6.375 mths; Crd F/U: 18.24 mths	14/16 subjects self- reported Sk on ini- tial imaging. NR at F/U.	Intervarsity sports team's physician and physiothera- pists	American Academy of Neurology Quality Stan- dards Subcommittee and Neurology AAo (1997)	1 conc.= 8 2 conc.= 6 3 conc.= 2	NR	Recorded us- ing PCSC, in- dividual total symptoms score reported but not the specific symp- toms	university level in- tersity sports	Football	

(continued)

TABLE 2. (CONTINUED)

Ref	Athletes	N		Sex		Age		Time lapsed post-SRC		PCS v delayed onset of symptoms	Method for diagnosis of SRC	SRC severity (rating scale; GCS, PTA, LOC)	SRC symptoms	Concussion definition	Concussion history	Level of play	Sports involved	Follow up period (if any)
		Males	Females	M	F	Range	Mean	SD	Mean									
Bazarian et al (2012) <sup>48</sup>	7	6	14	1	S: 16-18 C: 16-35	S: 17.17 (0.75) C: 23.00 (6.54)	<72 hrs	N/A (n=1)	NR	NR	No significant change from pre-season results	NR but no conc. 1 month prior to recruitment to the study.	NR	Subjects were considered to have suffered a concussion if they incurred an injury resulting in witnessed LOC <20 min, transient amnesia or confusion.	High School	Hockey (n=4) Football (n=5)	Study design=3mth FU	
Maugens et al (2012) <sup>1</sup>	12	12	18	6	S: 11-15 C: NR	S: 13.41 (1.24) C: NR	1st: <72hrs 2nd: 14-days 3rd: >30days	1st: 44.75hrs (19.48) 2nd: NR 3rd: 70 days (46.10)	NR	NR	Licenced healthcare professional in accordance with the International Conference on "Local neurological injury" and "pathology in Concussion in Sport."	<72hrs: mean 27.83 (6.86); 3 days: mean 11.17 (4.41); 30 days: mean 3.78 (1.24);	Zurich (3rd CIS Group)	0 conc. = 9 1 conc. = 3 (greater than one year ago)	High School	Foothall	Two follow-up time periods: 14 days and greater than 30 days post-injury	

PCS, post-concussion symptoms; SRC, sports-related concussion; GCS, Glasgow Coma Scale; PTA, post-traumatic amnesia; LOC, loss of consciousness; TBI, traumatic brain injury; S, subject group; C, control group; yr, year; CIS, concussion in sport; N/A, not applicable; NR, not reported; PCS, post-concussion symptoms; SRC, sports-related concussion; GCS, Glasgow Coma Scale; PTA, post-traumatic amnesia; LOC, loss of consciousness; TBI, traumatic brain injury; S, subject group; C, control group; conc., concussion; Ax, assessment; CIS, concussion in sport; NA, not applicable; NR, not reported.

TABLE 3. STUDY CHARACTERISTICS

Refs	Anatomical structures examined	Other outcomes measured
Cubon et al (2011) <sup>42</sup>	<ul style="list-style-type: none"> <li>• sagittal stratum (including the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus);</li> <li>• retro lenticular part of the internal capsule;</li> <li>• posterior thalamic radiation (including the optic radiation);</li> <li>• acoustic radiation;</li> <li>• superior longitudinal fasciculus.</li> </ul>	<ul style="list-style-type: none"> <li>• Neuropsychological testing &amp; concussion history (Princeton Uni Concussion Program protocol).</li> <li>• ImPACT.</li> </ul>
Zhang et al (2010) <sup>47</sup>	<ul style="list-style-type: none"> <li>• Corpus Callosum (genu, body, and splenium);</li> <li>• Right hippocampus;</li> <li>• Bilateral dorso-lateral prefrontal cortex (DL-PFC);</li> <li>• Precuneus;</li> <li>• Primary Visual Cortex (V1).</li> </ul>	<ul style="list-style-type: none"> <li>• Post Concussion Symptoms Checklist.</li> <li>• fMRI BOLD.</li> <li>• Neuropsychological assessment battery - HAVLT, Stroop, TMT, SDMT, &amp; ImPACT.</li> </ul>
Chappell et al (2006) <sup>43</sup>	<ul style="list-style-type: none"> <li>• splenium;</li> <li>• cortical regions located laterally and dorsolaterally in both the frontal and posterior lobes;</li> <li>• midbrain;</li> <li>• internal capsule (including the posterior limb);</li> <li>• putamen/globus pallidus;</li> <li>• medial temporal lobe;</li> <li>• inferior frontooccipital fasciculus;</li> <li>• inferior longitudinal fasciculus;</li> <li>• cerebral peduncle/ corticobulbar/corticospinal tracts.</li> </ul>	<ul style="list-style-type: none"> <li>• Conventional MRI demonstrated “negative or nonspecific findings”, including cavum septum pellucidum, subcortical WM disease and periventricular WM disease.</li> </ul>
Zhang et al (2006) <sup>44</sup>	<ul style="list-style-type: none"> <li>• Corpus Callosum (genu, splenium);</li> <li>• Internal Captule (anterior &amp; posterior).</li> </ul>	<ul style="list-style-type: none"> <li>• Conventional MRI (42/49 normal; 7 dominated by nonspecific WM disease)</li> </ul>
Zhang et al (2003) <sup>45</sup>	Non-specific, whole brain analysis	<ul style="list-style-type: none"> <li>• Conventional MRI</li> </ul>
Henry et al (2011) <sup>46</sup>	Non-specific, whole brain analysis	<ul style="list-style-type: none"> <li>• Post Concussion Symptoms Checklist</li> </ul>
Bazarian et al (2012) <sup>48</sup>	Non-specific, whole brain analysis	<ul style="list-style-type: none"> <li>• Post Concussion Symptoms Checklist.</li> <li>• ImPACT.</li> </ul>
Maugans et al (2012) <sup>1</sup>	<ul style="list-style-type: none"> <li>• Corpus Callosum (genu, body, and splenium);</li> <li>• bilateral, anterior limb of the internal capsule;</li> <li>• posterior limb of the internal capsule.</li> </ul>	<ul style="list-style-type: none"> <li>• ImPACT.</li> <li>• T1 MRI.</li> <li>• Susceptibility Weighted MRI.</li> <li>• Proton magnetic resonance spectroscopy.</li> <li>• Phase contrast angiography.</li> </ul>

Uni, university; ImPACT, Immediate Post-Concussion Assessment and Cognitive Testing; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; BOLD, blood-oxygen-level-dependent; HAVLT, Hopkins auditory verbal learning test; TMT, trail making test; SDMT, symbol digit modalities test; WM, white matter.

without further discussion across four of eight articles. The specifics pertaining to rating inconsistencies among the four other articles were resolved via discussion between the lead author (A.G.) and each individual reviewer (F.K-L. and A.H.) to obtain a consensus agreement.

## Results

A total of 146 articles were identified using the search strategy outlined in Figure 1. The initial search strategy was extremely liberal, in order to capture all possible articles for inclusion in this review. Of identified citations, 142 were screened following removal of duplicates, with 81 retrieved and screened for eligibility. Because of the nature of the initial liberal approach to searching for relevant articles, 61 were immediately identified as not meeting criteria, as they had not used DTI. Of the remaining 81 articles, 28 were excluded on the basis that the participants were not athletes (i.e., they were not SRC cases), 27 studies on closer inspection also had not used DTI as an outcome measure, 17 were not research studies (i.e., conference presentation, abstract only, commentary), and one publication was not in English. The final outcome fol-

lowing this screening process resulted in the inclusion of eight articles for this review.

A total of 55 review articles on DTI in TBI samples were also identified through the current search strategy. Of these, only nine reviews were focused on SRC, with all but one providing only a brief overview. In addition to this, a Master's level dissertation was also identified but not included in the current review, as no manuscript of this work had been published in a peer-reviewed journal.

The quality assessment resulted in four studies with positive study quality ratings and four with neutral quality study ratings. None of the identified studies were rated with negative quality ratings when assessed against the pre-specified standardized criteria.<sup>40</sup> The neutral rating was assigned to studies because of participant selection bias and the use of control groups that were not comparable (see Table 1 for the quality assessment results).

The quality assessment of the one review article identified that met inclusion criteria, Davis and colleagues,<sup>41</sup> was assigned a neutral review quality rating because of the absence of a description of how the authors appraised the quality of the studies included in their review, making replication of their review impossible.

TABLE 4. POSSIBLE CORRELATION BETWEEN DTI RESULTS AND OTHER METHODOLOGIES

Refs	Other methods	Results of other methods	DTI findings	Correlation with DTI findings		DTI analysis (A, BI, B2, C or D)	Abnormalities detected	
				DTI	DTI		DTI	Other methods
Cubon et al. (2011) <sup>42</sup>	NP testing SCAT/SCAT2 ImPACT NP Ax	The ImPACT and NP data demonstrated normal ( $n = 3$ ) and abnormal ( $n = 6$ ) findings. Persistent PCSx were reported in all subjects.	LH: MD changes in sagittal stratum, retroolentical part of the IC, posterior thalamic radiation, acoustic radiation and SLF.	ImPACT was not considered "specific enough to cognitively target the brain region identified with MD differences."	All subjects revealed persistent PCSx and showed a lack of WM fiber tract integrity despite the NP Ax results.	B2	Yes	Yes
Zhang, Johnson et al. (2010) <sup>47</sup>	PCSx fMRI BOLD with VRSN NP Testing	There was a positive correlation between ADC and % change of fMRI BOLD signals at DL-PFC in SRC subjects. No significant differences on NP testing reported.	There were slight but significant differences in ADC at both left DL-PFC and right DL-PFC.	DL-PFC abnormalities across both MR modalities.	DL-PFC abnormalities across both MR modalities.	B2, C, D	Yes	Yes
Chappell et al. (2006) <sup>43</sup>	MRI	"Negative or nonspecific findings," including cavum septum pellucidum, subcortical WM disease, and periventricular WM disease	Increased ADC and/or decreased FA in the IC, putamen, medial temporal lobe, inferior frontooccipital and inferior longitudinal fasciculus, and the cerebral peduncle/corticobulbar/corticospinal tracts.	Limited, if any correlation between MR modality findings.	Increased ADC and/or decreased FA in the CC and posterior limb of IC.	B1	Yes	Yes
Zhang et al. (2006) <sup>44</sup>	MRI	42/49 normal; 7 dominated by nonspecific WM disease	BDav increased and FA decreased significantly in the CC and posterior limb of IC.	BDav was increased by 2.6% in all the boxers and in 2.4% of boxers with normal results on MR imaging.	BDav was increased by 2.6% in all the boxers and in 2.4% of boxers with normal results on MR imaging.	C, D	Yes	Yes
Zhang et al. (2003) <sup>45</sup>	MRI	11 abnormal results on MRI; 8 with volume loss greater than age, 5 had a CSP and 4 with nonspecific WM disease (Note: some subjects had more than one abnormality).	Five cases with high BDav values.	Of the five cases with high BDav, only one had negative MR findings, three of the other four demonstrated CSP.	Of the five cases with high BDav, only one had negative MR findings, three of the other four demonstrated CSP.	A, C, D	Yes	Yes

TABLE 4. (CONTINUED)

Refs	Other methods	Results of other methods	DTI findings	Correlation with DTI findings	Abnormalities detected	
					(A, B1, B2, C or D)	DTI
Henry et al. (2011) <sup>46</sup>	PCSSx	Increase in reported Sx in the concussed sample.	FA increases in the CC and CST. MD decreases in ventral portions of the CST and body of the CC.	Number of regions demonstrating elevated FA level did not differ with respect to the total symptom score.	B1	Yes N/A
Bazarian et al. (2012) <sup>48</sup>	PCSSx NP Test (SAC) ImPACT	Increase in reported Sx in the concussed sample. Poor cognitive performance in verbal and visual memory and reaction time.	FA and MD demonstrated both increases and decreases in athletes between pre- and post-season.	The increase in PCSSx “correlated strongly” with the proportion of significant change in FA.	B1	Yes NR Yes
			Most of the ROIs (voxels) experienced an increase in FA and decreases in MD.	WM changes in the right corona radiata and right inferior longitudinal fasciculus could underlie the poor cognitive performance (specifically, verbal memory). Involvement of the inferior longitudinal fasciculus was also speculated to have implications in the poor visual memory.	C	Yes
Maugans et al. (2012) <sup>1</sup>	ImPACT T1 MRI SWI MRS MR PCA	Initial ImPACT PCSSx and RT scores significantly differed, but this resolved at 14 days post-injury.	There were no significant differences detected.	All other modalities detected at least some abnormality post-injury, whereas DTI did not.	No C	Yes No No No No

DTI, diffusion tensor imaging; NP, neuropsychological; ImPACT, Immediate Post-Concussion Assessment Tool; Ax, assessment; RT, reaction time; VRSN, virtual reality spatial navigation task; PCSSx, Post Concussive Symptoms Checklist; SAC, Standardized Assessment of Concussion; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MR PCA, phase contrast angiography; LH, left hemisphere; WM, white matter; FA, fractional anisotropy; MD, mean diffusivity; ADC, apparent diffusion coefficient; BDav, brain diffusivity average; NR, not explicitly reported; DL-PFC, dorsolateral prefrontal cortex; IC, internal capsule; SLF, superior longitudinal fasciculus; CC, corpus callosum; CST, corticospinal tract; SRC, sports-related concussion; CSP, cavum septum pellucidum; DTI Analysis Method A, voxel-based approach; B, region of interest; B1, statistical parametric mapping (SPM) / voxel-based statistics (VBM); B2, tract-based spatial statistics (TBSS); C, tractography; ROI, region of interest.

TABLE 5. STUDY RESULTS

Refs	Major findings	Studies strengths	Anatomical structures examined	Other outcomes measured
Cubon et al (2011) <sup>42</sup>	<ul style="list-style-type: none"> <li>MD may be a more sensitive measure than FA, particularly for detecting minor DAI.</li> <li>With increasing injury severity, FA may be a better marker for structural abnormalities.</li> <li>A lack of structural integrity located in the left temporal lobe, where association and projection fibers running anterior-posterior and superoposterior merge or cross.</li> <li>The most significant cluster spans the retroレンellular part of the internal capsule and the posterior thalamic radiation.</li> <li>DTI may serve as a biomarker for concussion, and thus may provide an objective diagnostic tool to help determine the severity of injury, and to manage concussions, particularly with regard to return-to-play decisions.</li> </ul>	<ul style="list-style-type: none"> <li>No information pertaining to:</li> <li>MD in individuals with sport-related concussion who experience persistent symptoms from an injury that did not warrant assessment by the GCS.</li> <li>The severe TBI control group had small numbers, so only qualitative data, from which limited conclusions can be drawn.</li> <li>Between-subject variability in the testing time intervals post-injury, and in the testing time intervals from date of DTI scan. This may in fact be an explanation for the insignificant correlations of MD with neurocognitive (NP) testing measures.</li> <li>Similarly, there was no relationship between MD and concussion history, although self-report of concussions is inherently troublesome, as athletes often minimize symptoms and do not report their injuries.</li> <li>Study not designed to target a particular brain region with specialised neuropsychological tests, therefore limited correlations can be drawn.</li> </ul>	<ul style="list-style-type: none"> <li>sagittal stratum (including the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus); retroレンellular part of the internal capsule; posterior thalamic radiation (including the optic radiation); superior</li> </ul>	<ul style="list-style-type: none"> <li>Neuropsychological testing &amp; concussion history (Princeton Uni Concussion Program protocol).</li> <li>ImPACT.</li> </ul>
Zhang et al (2010) <sup>43</sup>	<ul style="list-style-type: none"> <li>Slight but significant differences in ADC at both left DL-PFC and right DL-PFC, indicating decreased diffusivity in SRC subjects.</li> <li>Positive correlation between ADC and % change of fMRI BOLD signals at DL-PFC in SRC subjects, but not in normal controls.</li> </ul>	<ul style="list-style-type: none"> <li>Young sample. Age group (18-21 years)</li> </ul>	<ul style="list-style-type: none"> <li>Corpus Callosum (genu, body, and splenium); Right hippocampus; Bilateral dorso-lateral prefrontal cortex (DL-PFC); Precuneus; Primary Visual Cortex (V1).</li> </ul>	<ul style="list-style-type: none"> <li>Post Concussion Symptoms Checklist.</li> <li>fMRI BOLD.</li> <li>Neuropsychological assessment battery Snoop, TMT, SDMT, &amp; ImPACT.</li> </ul>
Chappell et al (2006) <sup>44</sup>	<ul style="list-style-type: none"> <li>Increases in the ADC and decreases in FA were identified in deep white matter (WM).</li> <li>Decreases in ADC in cortical gray matter (GM).</li> <li>Increases and decreases in ADC, and decreases in FA; localised in the internal capsule, putamen, medial temporal lobe, inferior fronto-occipital and inferior longitudinal fasciculus, cerebral peduncle, and corticospinal tract.</li> <li>Identified regions with smaller ADCs, comprised of both CSF and GM.</li> <li>The ADC values in all clusters with CSF &amp; GM were higher than those which are predominantly WM and were lower for the boxes than for controls.</li> <li>There was a strong correlation in the cerebellum of the boxes with age, which was not apparent in controls.</li> <li>DTI's ability to identify microstructural abnormalities makes it an important diagnostic tool.</li> </ul>	<ul style="list-style-type: none"> <li>Subjects were not scanned because of recent known trauma.</li> </ul>	<ul style="list-style-type: none"> <li>splenium;</li> <li>cortical regions located laterally and dorsolaterally in both the frontal and posterior lobes;</li> <li>midbrain;</li> <li>internal capsule (including the posterior limb);</li> <li>putamen/globus pallidus;</li> <li>medial temporal lobe;</li> <li>inferior fronto-occipital fasci</li> </ul>	<ul style="list-style-type: none"> <li>Conventional MRI demonstrated "negative or nonspecific findings", including cavum septum pellucidum, subcortical WM disease and periventricular WM disease.</li> </ul>
Zhang et al (2006) <sup>44</sup>	<ul style="list-style-type: none"> <li>A significant difference in diffusion and anisotropy measurements in all the boxes compared with the healthy control subjects.</li> <li>BDav increased and FA decreased significantly in the corpus callosum and posterior limb of internal capsule.</li> <li>FA and Dav inversely correlated in regions of the corpus callosum and posterior limb of internal capsule.</li> <li>BDav also robustly correlated with both FA and Dav in the splenium of corpus callosum in boxes.</li> <li>Increased BDav and the decreased FA in the CC and IC may represent preclinical signs of subtle brain injury in professional boxers.</li> <li>Conventional MRI: Forty-two (86%) boxers had a normal clinical MR imaging; four (8%) had focal or diffuse nonspecific subcortical white matter disease or periventricular white matter disease, mostly in the frontal and parietal lobes; one (2%) had chronic hemorrhage; one (2%) had all the above; and one (2%) had a cavum septum pellucidum.</li> <li>BDav was increased by 2.6% in all the boxers and in 2.4% of boxers with normal results on MR imaging.</li> <li>The splenium of the corpus callosum had the highest anisotropy measured by FA, followed by genu in both boxers and healthy control subjects.</li> <li>Regional diffusion anisotropy demonstrated decreased anisotropy in the genu of the corpus callosum (6.2%), splenium of corpus callosum (3.2%), anterior limb of the internal capsule (3.8%), and posterior limb of the internal capsule (5.4%) in the boxers compared to controls.</li> <li>DTI-based tractography showed less tractable white matter fibers in the CC as well as the whole brain in boxers compared with healthy control subjects.</li> <li>The CC is more susceptible to the damage caused by boxing.</li> </ul>	<ul style="list-style-type: none"> <li>No information pertaining to:</li> <li>duration of participation in contact sport (as a proxy for exposure);</li> <li>last brain injury;</li> <li>retirement.</li> </ul>	<ul style="list-style-type: none"> <li>Corpus Callosum (genu, splenium); Internal Capsule (anterior &amp; posterior).</li> </ul>	<ul style="list-style-type: none"> <li>Conventional MRI (42/49 normal; 7 dominated by nonspecific WM disease)</li> </ul>

(continued)

TABLE 5. (CONTINUED)

Ref	Major findings	Studies strengths	Anatomical structures examined		Other outcomes measured
			Study comments		
Zhang et al (2003) <sup>5</sup>	<ul style="list-style-type: none"> <li>Thirteen boxers had BDav values more than two SD above the controls' mean.</li> <li>Five boxers had BDav values more than four SD above the controls' mean.</li> <li>DTI can reveal early pathologic changes in the cellular and microvascular structures of the brain in boxers.</li> <li>The most common MR finding in the boxer group was volume loss inappropriate to age followed by cavum septum pellucidum, subcortical white matter disease, and periventricular white matter disease.</li> </ul>	<ul style="list-style-type: none"> <li>Individual data reported on BDav, widened distribution &amp; MR findings.</li> <li>The most common MR finding in the boxer group was volume loss inappropriate to age followed by cavum septum pellucidum, subcortical white matter disease, and periventricular white matter disease.</li> </ul>	<ul style="list-style-type: none"> <li>"Acute &amp; chronic phase" data for all concussed and control subjects.</li> <li>Inclusion criteria controlled for:           <ul style="list-style-type: none"> <li>o alcohol and/or substance abuse;</li> <li>o psychiatric illness;</li> <li>o learning disability;</li> <li>o neurological disorders;</li> <li>o seizure disorder;</li> <li>o central nervous system neoplasm;</li> <li>o brain tumor</li> </ul> </li> <li>TBI unrelated to contact sports.</li> </ul>	<ul style="list-style-type: none"> <li>As mTBI is diffuse and heterogeneous, a VBA approach may lack the sensitivity to identify all alterations, because only those injured brain areas that are common to the experimental group will be detected.</li> <li>Likewise, from a clinical standpoint, it has not been established that VBA has enough statistical power for legitimate single-subject analysis.</li> <li>From a technical standpoint, VBA requires spatial normalization, which can introduce error if it is inaccurate, leading to false positive results due to poor alignment.</li> <li>Because VBA requires spatial smoothing to allow each subject's brain to fit into a common space, there is further loss of sensitivity, leaving only changes in large tracts detectable.</li> <li>The "chronic" phase comparison between concussed group and control group approx. 12 months different.</li> <li>Half of the subjects possess a history of multiple concussions, so it is not possible to determine whether these results are a reflection of the acute damage, the past history of head injury or a combination of both.</li> <li>There are similar issues associated with interpreting the "chronic phase" data.</li> <li>The severity of the current concussion differed across subjects, no data was reported according to severity, although numbers were too small to analyse between group differences based on severity.</li> </ul>	<ul style="list-style-type: none"> <li>Non-specific, whole brain analysis</li> <li>Post Concussion Symptom Checklist</li> </ul>
Henry et al (2011) <sup>46</sup>	<ul style="list-style-type: none"> <li>Prominent FA increases were detected in the corpus callosum, as well as throughout the corticospinal tract (CST) in the concussed group.</li> <li>Within the right hemisphere, underlying primary motor and sensory cortices containing ventrally through the CST to the level of the thalamus, demonstrated elevated FA values.</li> <li>The left hemisphere showed only sparse changes in FA in the dorsal regions immediately underlying the primary motor and sensory cortices.</li> <li>AD demonstrated a main effect of group at the dorsal end of the CST underlying the primary motor cortex in the right hemisphere in the same areas showing higher FA values.</li> <li>Concussed athletes showed greater AD values than control athletes.</li> <li>MD demonstrated significant differences along the CST and CC.</li> <li>A main effect of group seen in the body of the CC, ventral portions of the CST; concussed group &gt; control group.</li> <li>Results of the individual analyses reveal that while every concussed athlete showed increased FA in at least one area, some athletes were more affected than others, according to the number of clusters affected.</li> <li>"more concussed athletes" (presumably greater severity) had elevated FA at the second cluster along the CST (nearest the corpus callosum) at both time points.</li> <li>At an individual level the number of regions showing elevated FA levels did not differ with respect to the total symptom score, however the number of regions showing elevated FA values differed significantly according to the number of previously reported concussions (this was only found to be statistically significant in those reporting &gt; 3 conc.).</li> <li>Individual analysis of MD revealed elevation within the CC, in the concussed group.</li> <li>Significantly higher FA and AD values and lower MD values along the CST and in the CC in concussed than in nonconcussed athletes at both the acute and chronic time points.</li> <li>The WM underlying the primary motor and primary sensory cortical areas exhibited most damage.</li> </ul>	<ul style="list-style-type: none"> <li>Small sample; concussed athlete n=1.</li> <li>The control group is arguably not equivalent in age.</li> <li>Exclusion criteria for only one month previous is a short time frame.</li> <li>There is no indication of educational attainment which may be an important variable to consider in this age sample.</li> <li>No data on the history of previous concussions.</li> <li>Did the two groups have similar preseason data? i.e. can the changes be attributed to the subconcussive blows sustained during the season?</li> <li>Baseline effort/validity measures not considered.</li> <li>The SHB group improved on cognitive testing - practice effect, relative change indices not taken into consideration.</li> <li>Image misrepresentation, residual spatial mismatching may have contributed to false-positive errors in the controls.</li> </ul>	<ul style="list-style-type: none"> <li>Non specific, whole brain analysis</li> <li>Post Concussion Symptom Checklist</li> <li>ImPACT.</li> </ul>		
Bazarian et al (2012) <sup>48</sup>	<ul style="list-style-type: none"> <li>The concussed athlete had the largest proportion of WM voxels with a statistically significant preseason to postinjury change, with 3.19% of his WM voxels showing significant changes in FA and 3.44% in MD.</li> <li>FA and MD changes colocalized to the right corona radiata and right inferior longitudinal fasciculus.</li> <li>FA and MD changes in both directions (increased and decreased) were detected postseason compared to preseason.</li> <li>Primarily observed increases in FA and decreases in MD values in both the acute and chronic time points.</li> <li>The WM underlying the primary motor and primary sensory cortical areas exhibited most damage.</li> </ul>	<ul style="list-style-type: none"> <li>Preseason and post-season analysis correlated with data pertaining to the number of subconcussive blows sustained.</li> </ul>	<ul style="list-style-type: none"> <li>Small sample; concussed athlete n=1.</li> <li>The control group is arguably not equivalent in age.</li> <li>Exclusion criteria for only one month previous is a short time frame.</li> <li>There is no indication of educational attainment which may be an important variable to consider in this age sample.</li> <li>No data on the history of previous concussions.</li> <li>Did the two groups have similar preseason data? i.e. can the changes be attributed to the subconcussive blows sustained during the season?</li> <li>Baseline effort/validity measures not considered.</li> <li>The SHB group improved on cognitive testing - practice effect, relative change indices not taken into consideration.</li> <li>Image misrepresentation, residual spatial mismatching may have contributed to false-positive errors in the controls.</li> </ul>	<ul style="list-style-type: none"> <li>Corpus Callosum (genu, body, and splenium); bilateral; anterior limb of the internal capsule; posterior limb of the internal capsule.</li> <li>Proton magnetic resonance spectroscopy.</li> <li>Phase contrast angiography.</li> </ul>	
Maugans et al (2012) <sup>1</sup>	<ul style="list-style-type: none"> <li>There were no significant differences in FA, trace, axial diffusivity or radial diffusivity over time for any of the ROI.</li> <li>There were no group differences in the DII metrics for any of the ROI at the initial study time-point.</li> <li>ImPACT results demonstrated initial post-injury total symptoms score differed significantly and resolved at the day 14 follow-up. Reaction time composite scores were significantly different at initial and 14-day follow up and had returned to control levels by the final testing session.</li> </ul>	<ul style="list-style-type: none"> <li>Age range 11-15 years.</li> <li>Post-injury assessment utilized a number of methods of assessment (i.e., ImPACT, TI MRI, SWI, DII, MRS, CBF).</li> <li>Confined follow-up period (the maximum follow-up post-injury approx. 30 days).</li> <li>Two outliers (1. large post-injury symptom reporting; 2. large time lapse between 1st and 2nd follow-up periods).</li> </ul>	<ul style="list-style-type: none"> <li>Corpus Callosum (genu, body, and splenium); bilateral; anterior limb of the internal capsule; posterior limb of the internal capsule.</li> <li>Proton magnetic resonance spectroscopy.</li> <li>Phase contrast angiography.</li> </ul>	<ul style="list-style-type: none"> <li>Corpus Callosum (genu, body, and splenium); bilateral; anterior limb of the internal capsule; posterior limb of the internal capsule.</li> <li>Proton magnetic resonance spectroscopy.</li> <li>Phase contrast angiography.</li> </ul>	

MD, mean diffusivity; FA, fractional anisotropy; ADC, apparent diffusion coefficient; DAI, diffuse axonal injury; DTI, diffusion tensor imaging; GCS, Glasgow Coma Scale; DL-PFC, dorsolateral prefrontal cortex; SRC, sports-related concussion; MRI, functional magnetic resonance imaging; BOLD, blood-oxygen-level-dependent; mTBI, mild traumatic brain injury; NP, neuropsychological; CSF, cerebrospinal fluid; BDav, brain diffusivity average; FA, fractional anisotropy; CC, corpus callosum; IC, internal capsule; DTI, diffusion tensor imaging; ROI, region of interest; DTI, diffusion tensor imaging; ImPACT, ImPACT Post-Concussion Assessment and Cognitive Testing; MRS, magnetic resonance spectroscopy; SWI, susceptibility weighted imaging; MRI, magnetic resonance imaging; SRC, sports-related concussion; DTI, diffusion tensor imaging; GCS, Glasgow Coma Scale; DL-PFC, dorsolateral prefrontal cortex; BOLD, blood-oxygen-level-dependent; mTBI, mild traumatic brain injury; NP, neuropsychological; CSF, cerebrospinal fluid; BDav, brain diffusivity average; FA, fractional anisotropy; CC, corpus callosum; IC, internal capsule; DTI, diffusion tensor imaging; ROI, region of interest; DTI, diffusion tensor imaging; ImPACT, ImPACT Post-Concussion Assessment and Cognitive Testing; MRS, magnetic resonance spectroscopy; SWI, susceptibility weighted imaging; MRI, magnetic resonance imaging.

TABLE 6. DTI STUDY CHARACTERISTICS

Ref	MR specifications	Acquisition voxel size (mm) reconstruction voxel size (mm)	No. directions	Duration of DTI sequence	No. ROIs
Cubon et al (2011) <sup>42</sup>	Siemens Allegra 3.0 T head-only MRI; 3.0(s)	Eddy-current compensated double spin-echo, echo-planar pulse sequence. Diffusion encoding vectors were uniformly distributed through space using an electrostatic model. Diffusion scanning parameters were as follows: TR/TE=10sec/95 msec, matrix size 96x128 in plane (6/8 pf zero-filled to 128x128), 66 axial slices, voxel size 1.718/75.1/78/75mm in plane, slice thickness 2.5mm. Diffusion images were acquired using 60 distinct gradient directions and a b-value of 1000 sec/mm <sup>2</sup> , in addition to two volumes with no diffusion weighting (b=0). All diffusion scans were run three times and averaged.	60	High resolution T1-weighted structural images using a gradient echo pulse sequence (MP-RAGE parameters: TR/TE/TR=2.5 sec/4.38 msec/1.1 sec, matrix size 160x256x256 interpolated to 160x512x512, giving a final voxel size of 1x0.5x0.5mm <sup>3</sup> .	Whole brain
Zhang et al (2010) <sup>47</sup>	3.0 Tesla Siemens Trio whole-body scanner using a 12 channel head coil.	fMRI, DTI, T1, and T2 anatomical images were acquired in the axial plane parallel with the Anterior and Posterior Commissure axis covering the entire brain. Two-dimensional 20 direction echo planar DTI (1.8 9 1.8 9 3 mm resolution, TE=93 ms, TR = 6,500 ms, EPI factor=128, 47 slices, iPAT = GRAPPA, acceleration factor = 2, NSA = 4). Three-dimensional isotropic T1-weighted magnetization prepared rapid gradient echo (MP-RAGE; 0.9 0.9 0.9 mm resolution, TE = 3.46 ms, TR = 2,300 ms, TI = 900 ms, flip angle = 9, 160 slices, iPAT = none, NSA = 1). Two-dimensional T2-weighted fast spin echo (0.7 9 0.7 9 5 mm resolution, TE = 90 ms, TR = 6,000 ms, flip angles = 90, 120, ETL = 18, 30 slices, iPAT = GRAPPA, acceleration factor = 2, NSA = 1). Identical two-dimensional blood oxygen level-dependent (BOLD) echo planar fMRI images obtained for each experimental task (3.1 9 3.1 9 5 mm resolution, TE = 25 ms, TR = 2,000 ms, EPI factor = 64, flip angle = 79, 30 slices, iPAT = none, NSA = 1).	20	NR	ROI analysis of the CC was chosen as a primary ROI and subdivided into the genu, body, and splenium; (R) hippocampus, (L) & (R) dorso-lateral prefrontal cortex (DL-PFC), Precuneus and Primary Visual Cortex (V1).
Chappell et al (2006) <sup>43</sup>	2×GE 1.5-T MRI scanners	MRIs scanners with 22 mT/m gradient strength. A quadrature head coil was used, and in all cases the section thickness was 5 mm, with no intersection gaps. A 2D spin-echo EPI acquisition was used with TE/TR = 100 ms/12 s. An acquisition matrix of 128×128×30 and 1.7×1.7×5 mm <sup>3</sup> voxels in 26 gradient directions with direction-dependent b values between 815 and 1152 s/mm <sup>2</sup> , and six acquisitions with no diffusion weighting, was used.	26	The total acquisition time was 6 min 24 s.	Whole brain
Zhang et al (2006) <sup>43</sup>	GE, 1.5-T MRI scanners with a quadrature head coil	Axial T1-weighted (repetition time [TR]/echo time [TE] 500 ms/minimum), axial T2-weighted (TR/TE, 4000 ms/102 ms); fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time [TI], 10,000/162/2200 ms; matrix, 256x192), and diffusion-weighted imaging (TR/TE, 10,500 ms/minimum; matrix, 128x128; section thickness, 5 mm). There were no gaps between the sections. Single shot, echo-planar DTI sequence. DTI protocol, the maximum b-value per axis was 820s/mm <sup>2</sup> . Using TR/TE, 12,000 s/100 ms, 30 contiguous sections with 5-mm thickness covering the entire brain were acquired. The FOV was 22 cm and imaging acquisition matrix was 128x128.	26	NR	CC [genu & splenium] & IC [anterior & posterior]
Zhang et al (2003) <sup>45</sup>	GE, 1.5-T MRI scanners with a quadrature head coil	Imaging parameters were: axial T1-weighted imaging (TR/TE, 500/14), axial T2-weighted imaging (TR/TE, 4000/102), fluidattenuated inversion recovery imaging (TR/TE, 10500/106; matrix, 128x128). For all imaging protocols, section thickness was 0.5 cm, (no intersection gap); field of view, 22 cm; and number of excitations, 1.	30	NR	Not specified

(continued)

TABLE 6. (CONTINUED)

Ref/s	MR specifications	Acquisition voxel size (mm) reconstruction voxel size (mm)	No. directions	Duration of DTI sequence	No. ROIs
Henry et al (2011) <sup>46</sup>	3T Siemens Trio whole-body MRI system	Diffusion weighting gradients applied in 64 directions with b values of 0 and 700 sec/mm <sup>2</sup> and four averages in each direction, repetition time of 12,800 msec, echo time of 101 msec, field of view of 256×256 mm <sup>3</sup> , matrix size of 128×128 with partial Fourier reconstructed to 668, slice thickness of 2 mm with 0.6-mm gaps, and 75 slices. 3D T1-weighted images of corresponding subjects were also acquired with an inversion recovery rapid gradient echo sequence. Acquisition parameters were as follows: TI/TR/TE = 500/2500/3.83 msec; flip angle = 15 degrees; slice thickness = 0.9 mm, with an acquisition matrix of 256×256×256.	64	Total scan time was 28 min (15 min DTI).	Whole brain, voxel-based analysis
Bazarian et al (2012) <sup>48</sup>	3T Siemens Trio	Acquired using a single-shot spin-echo planar imaging sequence with repetition time/echo time = 800/89 ms, isotropic voxel 2×2×2 mm <sup>3</sup> , iPAT (Generalized Autocalibrating Partially Parallel Acquisition) acceleration factor = 2, 60 directions of diffusion weighting with one average, b = 700 s/mm <sup>2</sup> , one non-diffusion-weighted image (b=0), with 10 averages. The wild bootstrap permutation test, assess each voxel, if there is no lesion at that spatial location, measured FA/MD at either the pre- or postseizure acquisition should fall into the normal range of the empirical distribution of WB samples. Furthermore, by comparing distributions of FA/MD from longitudinal data sets of the same patient, a valid statistical comparison can be constructed to detect subject-specific DTI changes. Distributions of DTI parameters, such as FA, are not necessarily Gaussian. To address this issue, a permutation test is applied at each voxel to conduct nonparametric comparisons between empirical distributions from the WB sampling. The permutation test can be applied to any summary statistic without any assumption about the statistical model. In the WB permutation test frame, the permutation test was not only used to construct a more accurate statistical comparison but also used to correct multiple comparison issues based on the maximal statistics correction method.	60	10mins	Whole brain, voxel-based analysis; with additional ROIs in external capsule, CC & IC (posterior & anterior limb)
Maugans et al (2012) <sup>1</sup>	3T Phillips Achieva	Magnetic Resonance system with an eight channel phased array head coil. Utilised fractional anisotropy, trace, axial diffusivity and radial diffusivity.	NR	NR	CC (genu, splenium & body) & bilateral IC (posterior & anterior limbs)

ROIs, regions of interest; T, tesla; MRI, magnetic resonance imaging; DTI, diffusion tensor imaging; TR, repetition time; TE, echo time; FA, fractional anisotropy; MD, mean diffusivity; FMR, functional magnetic resonance imaging; EPI, echo planar imaging; GRAPPA, generalized auto calibrating partial parallel acquisition techniques; iPAT, integrated parallel acquisition techniques; MP-RAGE, magnetization prepared rapid gradient echo; ETL, echo train length; NSA, number of signal averages; FOV, field of view; WB, wildbootstrapping; min, minute; MS, millisecond; CC, corpus callosum; IC, internal capsule; (L), left; (R), right; mm<sup>2</sup>, millimeters squared; mm<sup>3</sup> millimeters cubed.

TABLE 7. DTI STUDY CHARACTERISTICS

Refs	Post-processing steps	DTI analysis methodology
Cubon et al (2011) <sup>42</sup>	Eddy current correction, motion correction and averaging of the three sets of 60 diffusion directions using software from FMRIB's Diffusion Toolbox (FDT). The TBSS image analysis technique reduces the alignment issues of traditional voxel-wise analyses, and reduces the limitations of a priori defined region-of-interest analyses that may dilute or eliminate detection of small structural lesions post-concussion.	FA & MD, using WM skeleton tract-based spatial statistics (TBSS).
Zhang et al (2010) <sup>47</sup>	The DTI images were eddy current corrected, in order to remove the artifacts from motion and eddy-current-induced distortion. A white matter tract skeleton was constructed as the template using data from all the subjects. Each subject's main tracts were registered to that template to form an average white matter atlas. TBSS toolboxes generated atlas for the control and patient groups, and performed a statistical analysis for differences. Obtained DTI data were corrected for multiple comparisons. The algorithm was implemented in SPM software package.	Whole-brain voxel-wise statistical analysis of the FA data was carried out using TBSS (tract-based spatial statistics). FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET; FA data were then aligned into a common space using the nonlinear registration tool FNIRT, which uses a b-spline representation of the registration warp field, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics.
Chappell et al (2006) <sup>43</sup>	In SPM, each brain is first warped, or normalized, to a standard template such that any given voxel (with fixed coordinates) will represent the same part of the brain in every subject. After smoothing with an 8-mm FWHM Gaussian kernel, the general linear model analyzed the variance of measurement at each voxel. To be able to separate voxels with increased ADC (or FA) from those with decreased ADC (or FA), two one-tailed t-tests were performed on both ADC and FA. Since the MR images were collected on two different MRI scanners, any scanner effect was also removed from the results by using analysis of covariance (ANCOVA), with the scanner treated as a confounding variable. Once the statistically significant clusters had been identified, the coordinates of the most significant voxel in each cluster were used to identify that voxel as being within the WM or gray matter (GM). This was achieved by using the predefined WM/GM templates of a normal brain in the FreeSurfer software, and then checked against the segmented images of each of the subjects as produced by SPM5. The appropriate average ADC or FA values for the boxes and the controls at each cluster maximum were then tabulated.	Statistical parametric mapping (SPM), using the SPM2 package, was used in the analysis.
Zhang et al (2006) <sup>44</sup>	A computer program was used to calculate the global BDav from the diffusion distribution histograms of each participant. This program distributed the pixels into 250 bins with a bin width of 0.02 (10 cm <sup>2</sup> /s). This histogram was fitted to a triple Gaussian curve using commercial software. The average diffusion constant (Dav) and diffusion anisotropy maps (FA) were then calculated pixel by pixel.	No further information beyond the post-processing steps was described.
Zhang et al (2003) <sup>45</sup>	This program distributed the pixels into 250 bins with a bin width of 0.02 10 5 cm <sup>2</sup> /s. This histogram was then fitted to a triple Gaussian curve by using commercial software.	No further information beyond the post-processing steps was described.
Henry et al (2011) <sup>46</sup>	Extracerebral tissues were removed from the 3D structural MRIs using iMagic Pro 2.0 software followed by manual editing. Edited scans were linearly registered to a high-resolution single-subject brain template image using FLIRT software. Each 3D structural image was warped to the MDT using a 3D fluid registration algorithm that allows large deformations while guaranteeing diffeomorphisms. Jacobian matrices representing local volume expansions or contractions relative to the template image were calculated from the deformation fields for each subject. From the diffusion-weighted images, voxel-wise diffusion tensors were generated with MedINRIA. Log-euclidean tensor de-noising was used to eliminate singular, negative definite, or rank-deficient tensors. Deformation fields from the nonlinear registration of TI-weighted images were applied to the diffusion tensor images to warp them to a common space. The finite strain (FS) method was applied.	Voxelwise 2×2 repeated-measures analysis of variance (ANOVA) using SPM8 to the derived scalar images (FA, AD, and MD), with a significance threshold of .01 divided by the number of derived scalar images computed for a final significance threshold of .003 in order to be conservative in our estimate of significant differences, and to account for the use of multiple comparisons.
Bazarian et al (2012) <sup>48</sup>	Postprocessing and statistical analysis were conducted using a custom software package developed in C++ and Matlab (Mathworks, Natick, MA, USA), as well as public domain image processing tools. DTI images were processed in three steps: (a) correction for eddy current and susceptibility artifacts followed by 12 degrees-of-freedom affine linear registrations between two longitudinal DTI data sets using the FLIRT tool in the FSL package (FMRIB, Oxford University). (b) WB sampling of DTI data followed by tensor calculation to generate bootstrap samples of FA/MD and (c) voxel-wise permutation tests between bootstrap samples of FA/MD of pre- and postseizure to detect significant changes of FA/MD associated with concussion. All ROIs were drawn using the Type II Johns Hopkins White Matter Parcellation Atlas. Using the DTIStudio software package, a dual-contrast Large Deformation Diffeomorphic Metric Mapping method, in which both the FA image and the b=0 image were used for nonlinear registration simultaneously, was used to transform the JHU WMPA into individual subject's native space. The binary masks for five ROIs were then automatically generated.	An optimized WB implementation was applied for generating WB samples. Modified Matlab code based on the SnIPM toolbox ( <a href="http://www.sph.umich.edu/hi-stat/SnIPM">www.sph.umich.edu/hi-stat/SnIPM</a> ) was used to perform the permutation test, and a corrected P value of .01 was selected as the significant level to further reduce the false-positive ratio.
Maagans et al (2012)	DTI Studio was used for evaluation of the regions of interest.	DTI Studio was used for evaluation of the regions of interest.

TBSS, tract-based spatial statistics; FA, fractional anisotropy; ADC, apparent diffusion coefficient; BDav, brain diffusivity average; MRI, functional magnetic resonance imaging; fMRI, magnetic resonance imaging; WM, white matter; GM, gray matter; MRI, magnetic resonance imaging; MDT, minimal deformation target; FA, fractional anisotropy; MD, mean diffusivity; ROIs, regions of interest; DTI, diffusion tensor imaging; SPM, statistical parametric mapping; WM, white matter; GM, gray matter; MRI, magnetic resonance imaging; MD, mean diffusivity; ROIs, regions of interest; DTI, diffusion tensor imaging; SPM, statistical nonparametric mapping; WB, wild bootstrapping; DTI Studio, regions of interest.

A total of 214 athletes participated across the eight studies, with the results of 96 “neurologically intact” control participants also reported. One study also included two moderate TBI and three severe TBI patients as a means of exploring the effects of severity on DTI data.<sup>42</sup> Four of eight studies involved only male samples.<sup>43–46</sup> Of the four studies<sup>1,42,47,48</sup> that included a mixture of both genders, one<sup>42</sup> included a 50:50 split, and another<sup>48</sup> had one female as a control subject in their sample. Another comprised nine males and three females,<sup>1</sup> whereas another<sup>47</sup> reported a 70:30 (male:female) ratio for their overall sample but did not report whether the ratio was consistent across study groups. In total, 284 males and 26 females were represented in the overall sample, and sex differences in findings were not fully explored. In terms of the sports represented, three studies involved a strict cohort of boxers,<sup>43–45</sup> whereas the other five samples included a mixed sample of contact sport athletes<sup>1,42,46–48</sup> (see Tables 2–4).

Findings within subject groups and across studies varied greatly with both increases and decreases in FA, and mean diffusivity (MD) measures reported. There was a trend across studies for ADC to increase post-SRC.<sup>43–45</sup> The detected changes within voxels were located in a variety of neuroanatomical regions, with the corpus callosum,<sup>44,49</sup> internal capsule,<sup>42–44</sup> the inferior longitudinal fasciculus,<sup>42,43</sup> and superior longitudinal fasciculus<sup>42</sup> the most common regions identified. In contrast, Maugans and colleagues<sup>1</sup> who also included the corpus callosum and internal capsules as ROIs, found no significant differences between the concussed sample and age-matched controls. Three studies used a whole brain analysis method<sup>45,46,48</sup> (see Table 5).

Although it is well recognized that concussion history, injury dynamics and severity, and clinical presentations in SRC samples are heterogeneous, the lack of reporting of detailed individual versus group data was notable (only two out of eight studies reported individual data;<sup>1,20</sup> see Tables 2–4). This was particularly evident in terms of concussion severity, history of previous concussion, and reported post-concussion symptoms, all of which provide important information that could be correlated with the individual’s DTI results. The difficulty with recall bias in obtaining valid retrospective data on the number and nature of the SRCs has been noted previously.<sup>50</sup> Only Maugans et al<sup>1</sup> reported individual data on number of previous concussions. Information pertaining to the exposure levels, such as years of play, position played, and number of bouts (in the boxing cases) were also often absent. Therefore, it is not known in some cases whether the DTI data acquired represent the sequelae of the current concussion, a previous history of concussions, or a combination of both. In all but one study that recorded the number of subconcussive hits sustained during a season,<sup>48</sup> there was no indication of the level of prior exposure to head trauma. Even in the one study that reported on the subconcussive hits, there was no prior history reported and the recording of the subconcussive hits relied on self-reported information, which has its own limitations. This is understandable, however, given that reporting of past subconcussive blows to the head would likely be even less reliable or valid than reports of past diagnosable concussions. Nonetheless, in examining current concussion or subconcussive blows to the head, often it is not known what the previous history might be.

The MR demographics (manufacturer and magnet strength, head coil channels), data acquisition (e.g., number of directions) and post-processing procedures also varied considerably across studies (see Tables 6 and 7). Given this variation, it is not surprising that there is limited convergence of the results. Attempting to interpret the extent to which these methodological variations across studies contribute to the variation observed in the results is quite complicated, particularly, as noted previously, given that concussion is heterogeneous with respect to injury, depending upon where the injury occurred.

Three studies examined the acute effects of SRC,<sup>1,46,48</sup> and one of these also conducted a 2 week and >1 month follow-up,<sup>1</sup> whereas another conducted a 6 month follow-up examination,<sup>46</sup> one study at the subacute phase<sup>47</sup> and one study at the chronic (and still symptomatic) phase.<sup>42</sup> Three studies did not report on the time lapse between injury and DTI examination.<sup>43–45</sup>

Repeated or follow-up DTI was only conducted in three of the eight identified studies,<sup>1,44,46</sup> but in one of those studies only 2 of the subjects in the sample of 49 (~4%) had follow-up imaging.<sup>44</sup> The results of these two cases demonstrated a decrease in trackable fibers in the whole brain and corpus callosum compared with the results of the initial scans.<sup>44</sup> However, interpretation of this result is limited because there were no control subjects imaged serially during the same time period, and therefore the possibility that the effects are caused by experimental instability cannot be excluded. A more comprehensive study reported follow-up results for both concussed and control samples.<sup>46</sup> The results of this study reported increased FA in dorsal regions of both corticospinal tracts and the corpus callosum in concussed athletes at the acute and chronic (6 months) time points compared to non-concussed controls. Additionally, elevated axial diffusivity (AD) values in the right corticospinal tract and decrease in MD values in the corticospinal tracts and the corpus callosum across both time points were also observed in the concussed group compared with the controls.<sup>46</sup> There was no report on the possible time × group effect (i.e., did the magnitude of group differences change with time). In contrast to these results, Maugans and colleagues,<sup>1</sup> who included the corpus callosum (genu, body, and splenium) and internal capsule (anterior or posterior limb) as regions of interest, found no significant difference across DTI metrics in concussed 11–15-year-olds compared with age-matched controls at 3, 14, and 30 days post-injury. Interestingly the authors reported group differences at 3 days post-injury on reaction time and total symptoms score on a computerized neuropsychological test that resolved at the 14 day follow-up, which arguably refutes any suggestion that the participants may not have sustained a concussion.

## Discussion

This review identified only eight studies published through February 2012 that have used DTI within SRC samples. Following quality assessment of these studies, four were given a positive quality rating and four a neutral quality rating, with no study receiving a negative quality rating.<sup>40</sup> With the exception of one study in adolescents,<sup>1</sup> each of the other seven studies investigating DTI in athlete samples reported some type of DTI abnormality; however, the anatomical location was inconsistent. This variance in location is not surprising in view of the heterogeneity of concussion, in addition to the variability in these studies between time of injury and DTI scanning. Some regions, such as the corpus callosum, internal capsule, and longitudinal fasciculus, are reported more often than others, which may further suggest the vulnerability of these structures to axonal injury in concussion.

### Acute phase

**Diagnostic potential of DTI in SRC.** In the general mTBI literature, DTI has been touted as more sensitive than other imaging techniques to the subtle changes observed post-injury. This advance in MRI acquisition and analysis may make it possible to better characterize the extent of brain abnormalities in mTBI within days of injury.<sup>12</sup>

The results of the current review suggest that DTI is also a more sensitive method of detecting change in SRC than are conventional

MRI techniques. All studies examining concussion in the acute stages that were included in this review identified significant group changes in their samples, suggesting that DTI can identify microstructural white matter abnormalities, and that therefore it is a potentially important diagnostic tool. Four studies<sup>43–45,47</sup> found nonspecific white matter and periventricular changes on conventional MRI techniques, which were quantified in much greater detail by using DTI.

**Prognostic potential of DTI in SRC.** At the current time, data are limited regarding the prognostic ability of DTI in any concussion sample. Although follow-up data have been published, there has been no published longitudinal study conducted with SRC samples that correlated initial DTI results with long-term outcomes. For example, whether or not an observed change in FA in the acute phase following injury or, for that matter, at any time over the course of recovery is predictive of poorer outcome requires far more investigation.

#### *Subacute/chronic phase*

**Further diagnostic potential of DTI in SRC.** Some study results included in the current review suggest that, as is the case in the acute phase, DTI is a more sensitive method of detecting change even weeks to months post-injury in concussed individuals compared with conventional MRI techniques. All studies in this review examining SRC in the subacute and chronic stages identified significant group differences in DTI indices in their samples.

**Further prognostic potential of DTI in SRC.** As is the case in the acute phase post-injury, data are limited regarding the prognostic ability of DTI data collected in the subacute or chronic stages of recovery in concussion samples of any kind. Many of the identified DTI studies of SRC either examined subjects acutely after injury, or at a chronic time point. Again, there has been no published longitudinal study conducted with SRC samples that correlates subacute or chronic DTI indices with any long-term outcomes. In particular, the implications of early increases or subsequent decreases in FA, or reduced MD, for poorer outcome, remain unclear.

Only one study in the current review reported follow-up imaging on their SRC sample,<sup>46</sup> whereas another reported follow-up imaging in only a small minority of their overall sample ( $n=2$ ).<sup>44</sup> This has also been identified as a shortcoming in the general mTBI literature, where studies that have tended to include both acute and chronic time points either have a small number of subjects,<sup>51</sup> consist of separate acute and chronic groups not followed longitudinally,<sup>11</sup> consisted of separate cohorts of acutely and chronically injured patients,<sup>52</sup> or only had neuropsychological testing and no imaging at chronic phase follow-up.<sup>53,54</sup> As such, it is difficult to ascertain how DTI metrics change as the injury progresses or recovers. Of note is that 15–30% of mTBI (not necessarily SRC) patients develop chronic post-concussion syndrome,<sup>55,56</sup> and longitudinal studies will be critical in determining whether or not DTI can help predict which patients continue to experience chronic symptoms. A longitudinal study that investigates the course of injury over time would provide important information regarding the staging, progression, and, possibly, recovery and reversal of brain injury over time (see review by Shenton and colleagues<sup>12</sup>).

Although cross-sectional DTI studies have been conducted,<sup>57–59</sup> there is currently insufficient cross-sectional normative data for any DTI index in athlete samples, and no data on variables related to simply participating in contact sport. Basic research on these var-

iables is also critical if we are to judge the value of DTI in detecting or predicting persistent effects of SRC or recovery. Data on the test-retest reliability of DTI indices in concussed and non-concussed participants at various ages is also critical in judging clinically significant change.<sup>60</sup> The inclusion of pre-participation and post-injury DTI data would be ideal, and better longitudinal quantification of both concussive and subconcussive head trauma would help clarify the very diverse findings and the DTI-neuropsychological outcome links.

Despite the small number of studies examining DTI in samples of concussed athletes, considerable variability with respect to the magnetic field strength, time period of scanning post-concussion, brain regions examined, methods of data acquisition and the post-processing techniques employed are apparent. The obvious methodological variations could easily account for the diverse findings, however most of the studies (seven out of eight) have reported radiological evidence of subtle brain injury in SRC. Surprisingly, the only study where nonsignificant DTI findings were observed used a sample of 12 11–15-year-olds. This may reflect the rapid maturation that occurs through this age range; therefore, the greatest spread of data may have been observed in this sample, and, as such, detection of group differences was more difficult.

Arguably the greatest limitation of this body of work to date is the absence of exposure/concussion history details and information on the severity of injury. A number of points are worth elaboration. First, a large amount of important individual information is inherently lost in group data analysis. The absence of individual data in combination with the small sample sizes in the majority of the identified studies in this review is a large limitation for generalizing these results. Second, without adequate history of exposure (i.e., a proxy measure for subconcussive blows) and a history of previous SRCs, it is not possible to accurately determine whether the DTI abnormalities observed are a consequence of the most recent concussion, a culmination of previous concussions, or a combination of both. Third, injury severity information was only presented in one study,<sup>42</sup> which limits the potential conclusion that can be drawn regarding the sensitivity of DTI in detecting changes post-SRC. This is a particularly important point when considering the results of those studies that used mixed (i.e., participants recruited from varying sports) samples, as exposure, cause, and severity of injury can vary considerably across sports. For example, it is acknowledged that boxing (where the aim of participation is to deliver knockout blows to an opponent's head and body), is a considerably different sport leading to different injury etiology than that of other contact/collision sports, such as American football, in which concussive injuries may be the result of unintentional/innocuous incidents.<sup>61</sup> In view of this distinction, the ability to make a comparison between the results in boxing samples and those in other collision sports is limited, and pooling data across sports appears unjustified. A further limitation to this body of work is the absence of any information pertaining to the mechanism of injury, that is, the site of impact and nature of the cause of the SRC (e.g., whiplash, blow to forehead). This level of detail would have been useful to correlate with the findings on DTI.

A number of further limitations exist that require consideration in interpreting these data. First, four studies were identified as possessing control groups that were not comparable.<sup>43–45,48</sup> This presents a considerable limitation to interpretation of any observed group differences, because such differences may be unrelated to the variable of interest (in this case, SRC). Second, within the field of SRC, it is known that gender differences are apparent in terms of susceptibility and recovery from concussive injury.<sup>62–65</sup> Therefore,

it is likely that merging male and female data introduces another variable that is hidden in discussing group data.

In addition, there is no agreement as to the best method to analyse DTI data (i.e., post-processing procedures).<sup>19</sup> This is not surprising, given that the field is in its relative infancy, and that novel methods are developed rapidly in this field. Comparing data extraction and processing methods head-to-head and determining their relative strengths in test-retest reliability and concurrent or predictive validity is certainly indicated as another important fundamental step in understanding the value of DTI. The predominant focus on cross-sectional studies has in its very nature limitations in terms of its ability to judge DTI's value in predicting outcome. This limitation and other factors noted previously argue strongly for the necessity for longitudinal research that follows athletes during the initial recovery period and the long term, especially in cases of recurrent concussion. Such data would provide important insights into individual differences in acute stage profiles, and also into factors that predict neuropsychological, psychiatric, or behavioral outcomes, and, possibly, the mechanisms that subserve the adjustment to or reversal of damage in what appear to be more resilient athletes.

## Conclusion

The review identified eight studies that have used DTI in concussed athletes. The need for further investigation is apparent; however, one of the most attractive features of DTI in the SRC context is the potential for early identification of athletes with unresolved concussions who are at high risk for poor outcome, which may assist in more specific and effective clinical management. Uniformity in terms of methodology would certainly enable greater interpretation of the data across studies. As it is anticipated that there will be a proliferation of research employing this imaging technique within the field of sports concussion, developing an understanding of the fundamental mathematical characteristics of the various DTI indices and developing a consensus in the field regarding the most reliable and valid extraction and processing techniques is certainly recommended. Further systematic investigation will provide more information on this imaging technique for the diagnosis of SRC, monitoring the course of recovery (i.e., prognosis), and informing the management of athletes with single and recurrent SRC.

## Author Disclosure Statement

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