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REVIEW ARTICLE

Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review

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Abstract This review seeks to summarize diffusion tensor imaging (DTI) studies that have evaluated structural changes attributed to the mechanisms of mild traumatic brain injury (mTBI) in adult civilian, military, and athlete populations. Articles from 2002 to 2016 were retrieved from PubMed/MEDLINE, EBSCOhost, and Google Scholar, using a Boolean search string containing the following terms: "diffusion tensor imaging", "diffusion imaging", "DTI", "white matter", "concussion", "mild traumatic brain injury", "mTBI", "traumatic brain injury", and "TBI". We added studies not identified by this method that were found via manually-searched reference lists. We identified 86 eligible studies from English-language journals using, adult, human samples. Studies were evaluated based on duration between injury and DTI assessment, categorized as acute, subacute/chronic, remote mTBI, and repetitive brain trauma considerations. Since changes in brain structure after mTBI can also be affected by other co-occurring medical and demographic factors, we also briefly review DTI studies that have addressed socioeconomic status factors (SES), major depressive disorder (MDD), and attention-deficit hyperactivity disorder (ADHD). The review describes population-specific risks and the complications of clinical versus pathophysiological outcomes of mTBI. We had anticipated that the distinct population groups (civilian, military, and athlete) would require separate consideration, and various aspects of the study characteristics supported this. In general, study results suggested widespread but inconsistent differences in white matter diffusion metrics (primarily fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD], and axial diffusivity [AD]) following mTBI/concussion. Inspection of study designs and results revealed potential explanations for discrepant DTI findings, such as control group variability, analytic techniques, the manner in which regional differences were reported, and the presence or absence of persistent functional disturbances. DTI research in adult mTBI would benefit from more standardized imaging and analytic approaches. We also found significant overlap in white matter abnormalities reported in mTBI with those commonly affected by SES or the presence of MDD and ADHD. We conclude that DTI is sensitive to a wide range of group differences in diffusion metrics, but that it currently lacks the specificity necessary for meaningful clinical application. Properly controlled longitudinal studies with consistent and standardized functional outcomes are needed before establishing the utility of DTI in the clinical management of mTBI and concussion.

Keywords Mild traumatic brain injury · mTBI · Diffusion tensor imaging · DTI · Concussion · Sport-related concussion · Military TBI · Systematic review

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Scope of the review

Traumatic brain injuries (TBI) are an international public health concern. They occur secondary to multiple mechanisms including motor vehicle accidents, falls, athletic collisions, blast-related trauma in military theatre, and abuse or assault (Langlois et al. 2004). Brain injuries are classified on a continuum as mild,

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moderate, or severe based on degree of neurological impairment and structural imaging findings (DeCuypere and Klimo 2012). This review focuses on mild traumatic brain injuries (mTBIs), often also referred to as concussions, in adult civilians, military personnel, and athletes. Other reviews have examined neuroimaging findings in mTBI and concussion, as well (Davis et al. 2009; Mendez et al. 2015; Prabhu 2011; Pulsipher et al. 2011; Ptito et al. 2007; Bigler 2013; Eierud et al. 2014; Shenton et al. 2012). The primary goal of the current review is to critically analyze diffusion tensor imaging (DTI) studies that investigated structural changes attributed to the mechanisms of mTBI acutely, subacutely, or remotely, and to briefly review DTI studies of other medical and demographic influences (e.g., ADHD, depression, and socioeconomic factors) to gain a better understanding of imaging biomarkers potentially unique to brain trauma. In doing so, we will also describe population-specific risks and the importance of considering factors that may complicate both clinical (i.e., symptom expression) and pathophysiological (i.e. microstructural white matter differences) outcomes of mTBI in adults.

Epidemiology and terminology

Inconsistent definitions, injury underreporting (particularly for mTBI), and difficulty establishing effective monitoring systems all complicate epidemiological estimates of TBI prevalence (Roozenbeek et al. 2013). The Centers for Disease Control reported that 1.7 million Americans per year sustained a TBI between 2002 and 2006 (Faul et al. 2010). An estimated 80% of all TBIs are mild and were associated with a Glasgow Coma Scale score of 13 or greater, indicating largely intact neurological functioning (Servadei et al. 2001). Athletes and military personnel represent unique populations that often receive medical attention for their injuries, including TBI, from medical professionals outside of traditional hospital or emergency department settings. Indeed, when taking into account these different care pathways and the high degree of underreporting in sport-related TBI, incidence estimates approach 4 million per year in the United States (Langlois et al. 2006; McCrea et al. 2004). The Defense and Veterans Brain Injury Center (2016) reported that 344,030 servicemen sustained at least one TBI in the U.S. military between 2000 and 2015–82.3% of whom met criteria for mild TBI, similar to CDC estimates of the rate of mild versus moderate or severe TBI in civilian samples. However, these figures do not take into account servicemen and servicewomen who sustained multiple TBIs in the military and, thus, likely underestimated the true number of military-related brain injuries.

Despite representing only a small subset of the general population, athletes and military servicemen require special consideration because they are regularly exposed to potential TBI risk and are often demographically more homogeneous than the general, civilian population. This key difference between these populations and the general civilian population is not trivial. While the majority of the civilian population is at risk for single-event brain injuries that allow for resolution of both clinical symptoms and physiological dysfunction over time, athletes and military personnel undergo the TBI recovery process in the context of real or perceived pressures to return to an environment where additional brain injury may occur.

"Mild TBI" (mTBI) and "concussion" are often used interchangeably. "Concussion" is used more commonly in sports medicine settings, while more traditional medical settings prefer mTBI (Tator 2009). Some have contended that concussion represents a distinct, milder form of mTBI (i.e. all concussions are mTBIs, but all mTBIs are not concussions) (Harmon et al. 2013). Definitions of concussion and mTBI has evolved over time and readers are directed to Bodin et al. (2012) for a more comprehensive review of classifications for concussion and mTBI. There is general agreement that a transient alteration of brain function induced by traumatic forces transmitted to the brain that lead to complex, pathophysiological changes with or without loss of consciousness best defines these injuries (Harmon et al. 2013; McCrory et al. 2013; Brain Injury Association of America 2015). Concussion is currently a clinical diagnosis because a sensitive and specific diagnostic biomarker, or panel of biomarkers, has not yet been identified or validated (Zetterberg et al. 2013; Jeter et al. 2013).

Clinical and pathophysiological correlates

Concussion symptoms fall into several domains including physical/somatic, insomnia/sleep-related, emotional/mood, and cognitive (Iverson et al. 2015; Joyce et al. 2014; Kontos et al. 2012), as well as difficulties with postural stability and dysfunction of the visual and vestibular systems (Collins et al. 1999; Alves et al. 1987; Van Kampen et al. 2006), (Kleffelgaard et al. 2011; Guskiewicz et al. 1996) (Galetta et al. 2012; Mucha et al. 2014; Kontos et al. 2016).

The clinical syndromes associated with these injuries are the result of complex pathophysiological processes. The acute neurophysiological reactions that set these processes in place are reviewed extensively by Giza, Hovda, and Barkhoudarian (for a more detailed description see Giza and Hovda 2001, 2014, and Barkhoudarian et al. 2011). These authors have described the concept of a "neurometabolic cascade of concussion" based primarily on the results of preclinical studies. Concussive injury also leads to a period of decreased cerebral blood flow, rendering the brain ill-equipped to meet the energy demands required for restoring homeostasis. This so-called "energy crisis" creates a potential window of vulnerability within which the brain is susceptible to compounded injury effects if further neuronal stress or damage is

sustained (Lazzarino et al. 2012; Asken et al. 2016b). One key unanswered question pertaining to pathophysiological processes of concussion in humans is the degree to which these neurometabolic alterations might occur following single or repetitive subclinical brain insults that do not produce overt symptomatology, but might complicate attribution and interpretation of findings in cross-sectional research using modalities such as DTI. This is a particularly important consideration for athletes and certain military service members exposed to frequent subclinical head impacts, who may return to situations with high risk of head impacts after *clinically* recovering from injury but while *physiological* recovery is likely still ongoing (McCrea et al. 2015).

Clinical management would be aided by physiological or structural biomarkers of mTBI, particularly in determining at what point pathophysiological processes caused by the injury-inducing forces resolve. This would allow for more targeted and individualized treatment approaches. However, the clinical presentations and pathophysiological processes referenced in many definitions of concussion and mTBI represent related but not completely overlapping constructs. Selecting research samples on the basis of symptoms alone will produce highly heterogeneous groups since symptoms may be due to multiple factors (Gouvier et al. 1988; Lees-Haley and Brown 1993; Iverson and Lange 2003; Lange et al. 2011; Asken et al. 2016a), thus complicating data interpretation intended to link structure and function after mTBI.

Susceptibility of white matter

In addition to altered neurotransmitter release and metabolic dysfunction, the biomechanical forces of concussive injury result in damage to elements of the neuronal microstructure. Adams, Gennarelli, and colleagues coined the term "diffuse axonal injury", or DAI, after describing widely distributed axonal pathology in TBI cases, including those following more mild instances of rapid acceleration and deceleration (Adams et al. 1982; Gennarelli et al. 1982). Axons are particularly susceptible to injury due to their complex organizational arrangements and the limitations of their viscoelastic properties. They are sufficiently ductile to withstand slow developing stretch mechanisms and are able to return to their original shape and length when such forces are removed (Johnson et al. 2013b). However, more rapid deformation, such as those created by typical TBI-mechanisms (e.g. motor vehicle accidents, abrupt blows to the head, etc.), damages the axonal cytoskeleton, leads to loss of elasticity, and impairs axon transport functions (Smith and Meaney 2000).

Axonal deformation rarely leads to complete nerve disconnection ("primary axotomy"), though subsequent processes can still cause neuron death. Microstructural studies indicate cytoskeletal disruption can lead to axonal swelling and neurofilament accumulation. In some instances immunoreactive changes to the neuron begin but subside. In other cases, these changes progress, neurons accumulate more neurofilament, and areas of reactive swelling can ultimately cause focal disconnections ("secondary axotomy") (Christman et al. 1994). Importantly, even neurons that avoid disconnection may be less elastic and more brittle after injury, leaving them potentially susceptible to outright disconnection if reinjured in subsequent shear-strain events. Mechanical deformation precipitates the excitotoxic release of neurotransmitters, which researchers indicate can cause secondary damage to cell microstructure (Pettus and Povlishock 1996). Microtubule damage from stretch mechanisms has also been linked to axon transport dysfunction, which may lead to proteomic and neurochemical abnormalities at the synaptic junction (Büki and Povlishock 2006). The role that repetitive brain trauma plays in damaging white matter is a focus of considerable interest, not only for its structural implications for network disruption, but also as a potential mechanism of misfolded tau accumulation, an essential microtubule-stabilizing protein associated with general axonal function. Advanced neuroimaging tools capable of detecting these white matter microstructural changes may provide better insight to the subtle abnormalities described in the basic science literature on mTBI and concussion. Evidence for disruption of axonal flow is demonstrated by buildup of beta-amyloid at the site of axonal swelling (Smith and Meaney 2000; Johnson et al. 2013b).

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a specific diffusion weighted imaging (DWI) technique, use of which has gained significant momentum over the past decade due to its purported ability to sensitively detect white matter changes resulting from TBI pathophysiology. DWI is based on Brownian motion, a molecular diffusion principle describing the random motion of molecules within a given medium (Einstein 1956). In the brain, this concept applies to the movement of water molecules within different types of tissue (e.g., gray versus white matter). Sensitivity of conventional imaging modalities like CT and MRI are limited to detecting macroscopic brain changes, while DTI quantifies diffusion characteristics within microscopic nerve fiber bundles and is thought to represent the structural integrity of axons. The basic principles are predicated upon the assumed restriction of directional movement as water molecules flow along an axon. A three-dimensional, spherical "tensor" is created within a brain voxel, essentially describing the shape of the water diffusion map (ellipsoid). Basser, Le Bihan, and colleagues developed and described the physical properties underlying diffusion imaging methods (Basser et al. 1994; Le Bihan 1991).

Fractional anisotropy (FA) and mean diffusivity (MD) are among the most common quantifications of water diffusion and will be the main focus of this review. FA describes the degree of uniformity in direction of water flow on a scale of 0 to 1. An FA of 0 refers to complete isotropic, or unrestricted, movement in all directions and is believed to be best represented by relatively unbounded mediums such as cerebrospinal fluid (CSF). Conversely, an FA value of 1 describes complete anisotropic, or restricted, movement in a single direction. In the brain, axonal cytoarchitecture provides restriction as water diffuses along the neuron. Shenton et al. (2012) described FA as representing the "shape" of the ellipsoid; greater flow in one direction will elongate the ellipse in that direction. MD, on the other hand, represents the "size" of the ellipsoid tensor and is typically inversely related to FA. MD is based on the average of the three principal diffusion directions – the axial direction (direction of primary movement), and two radial axes (perpendicular to the primary movement direction). MD provides an index of the average rate of diffusion in all directions within a voxel, with its coordinate space oriented such that one axis is collinear with the largest direction of diffusion within a voxel (which better accounts for inter-voxel microstructure differences). The apparent diffusion coefficient (ADC) is conceptually similar to MD and is the average of the diffusion measured in the x, y, and z, directions and does not take into account diffusion differences within voxel microstructure. Other common diffusion metrics include the subcomponents of MD – axial diffusivity (AD) and radial diffusivity (RD) – which animal models suggest provide evidence of axonal and myelin pathology, respectively (Song et al. 2003).

There are four commonly used analytical techniques in DTI research: whole-brain histogram analysis, voxel-based analysis (VBA), region of interest (ROI) analysis, and tractography. Niogi and Mukherjee (2010) described each method, with their strengths and weaknesses, in more detail. In general, choosing a particular analytical technique requires consideration of sample size, labor intensity, inter-rater reliability, image registration accuracy and consistency, and corrections for multiple comparisons. It is important to remember that DTI provides quantification of water diffusion properties in the brain, which is believed to *indirectly* indicate white matter integrity and the presence of pathological changes. DTI outcome variability is non-specific and many factors can potentially cause alterations to FA and MD values beyond mTBI and concussion. Assaf and Pasternak (2008) further described two key DTI limitations. The first is reliance upon the assumption that the probability of water displacement within white matter follows a "normal" or Gaussian distribution; they noted that the compartmentalization and restriction of movement in white matter confounds this assumption. A second limitation is the averaging of diffusion properties within a single brain voxel that contains tens of thousands of axons and glial cells within an extracellular matrix. The distribution and orientation of fibers within a voxel is often not uniform, and the DTI model may misrepresent the tensor within a voxel where two or more fiber systems pass and/or cross each other. Despite these limitations, DTI is highly regarded as an innovative means of measuring the microstructural changes associated with mTBI and concussion.

Population-specific considerations – exposure to repetitive brain trauma

Niogi and Mukherjee (2010) stated, "DTI has great potential to help identify the subclinical axonal injury neuropathology that is thought to be common in mTBI." Subclinical effects are an important consideration within the context of repetitive brain trauma, especially the subclinical head impacts common to collision sports and, to a somewhat lesser degree, military service. In this context, the term "subclinical" refers to head impacts that do not produce symptoms but are common to certain sports and military activities. There are numerous attributional complications when interpreting the acute or subacute microstructural effects of a diagnosed mTBI in a collision sport athlete who, conceivably, has sustained innumerable subclinical impacts before (and perhaps after) a concussion event (Broglio et al. 2013; Gysland et al. 2012). Evidence described below from collision sport athletes and military personnel with blast exposure implies that subclinical impacts may still impart axonal injury detectable by DTI even in the absence of clinically observed symptoms. This finding highlights the importance of proper control group comparisons, as well as the need to exercise caution when attributing a distinct causal mechanism to observed differences in DTI outcomes.

Review methodology

Articles were retrieved via online data base searching and hand-searching reference lists. PubMed/MEDLINE was first searched using the "All Fields" criteria and the following keywords: "diffusion tensor imaging" OR "DTI" OR "diffusion imaging" OR "white matter" AND "concussion" OR "mild traumatic brain injury" OR "mTBI" or "traumatic brain injury" OR "TBI." These search criteria were then applied to EBSCOhost Web Databases which did not result in the addition of any unique, eligible studies. The resulting PRISMA flow diagram (Fig. 1) represents the process of article identification beginning with the initial PubMed/MEDLINE search.

Articles were limited to those involving human samples that were published in English-language journals beginning in 2002 and ending on January 31, 2016. Search terms similar

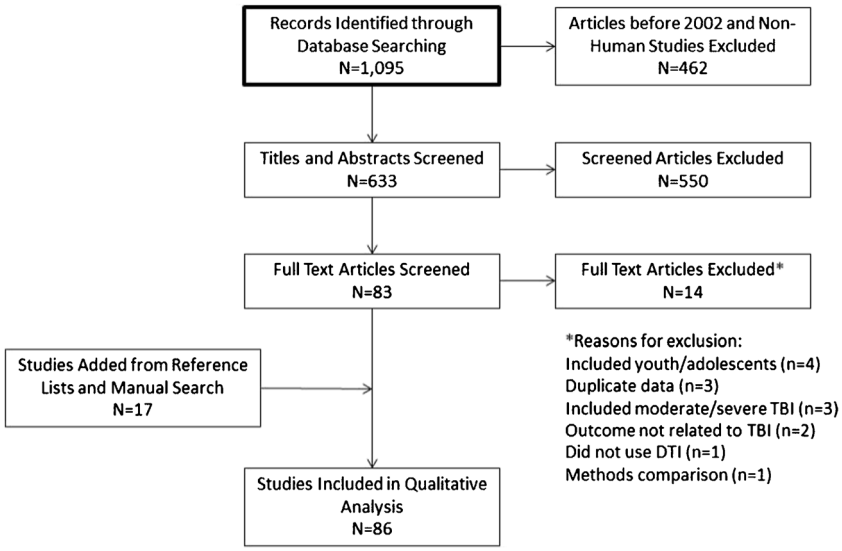

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) diagram of search strategy and admitted articles

to those described above, as well as population-specific modifiers (sport-related, athlete, military, blast, etc.) were also used to manually search Google Scholar for additional potential articles. Titles and abstracts of articles were screened to assess for eligibility for full-text screening. Primary reasons for exclusion included: not using DTI, inclusion of moderate to severe TBI participants, inclusion of youth/adolescent participants, focus on methodological comparisons, and duplicate datasets. Lastly, reference lists from previously published review papers on DTI and concussion/mTBI were specifically targeted for hand-searching in addition to the reference lists from studies determined eligible for our qualitative analysis. A total of 86 articles met inclusion criteria for this review.

Considerations of repetitive subclinical brain trauma history in the populations at highest risk are important when studying pathophysiological changes, and we have structured the following review of DTI literature accordingly. The delineated time frames (i.e. "Acute," "Subacute/Chronic," and "Remote History") were chosen arbitrarily and studies within each section largely represent the mean or median time between mTBI and assessment. In some cases, studies overlapped time frames due to the high variability in time between mTBI and imaging. In our review, Tables 1, 2, and 3 provide more specific information on the interval between injury and neuroimaging. If a study employed multiple assessment points, we describe findings within the section corresponding to the first assessment time point in the study. Our review focuses on reported structural findings within each time frame, and does not provide distinct results with regard to various clinical endpoints. We restricted our review of the mTBI literature to studies examining mTBI only (excluding moderate and severe) in adults (18 and older) since the developing brain may respond differently to the effects mTBI or concussion.

DTI findings in civilian mTBI

Acute (DTI within approximately 2–3 weeks of injury)

Arfanakis et al. (2002) investigated a small group of individuals less than 24 h after sustaining an mTBI and found lower FA within the internal capsule (IC) and corpus callosum (CC) compared to controls. Later studies corroborated this finding in larger samples imaged acutely after injury, noting lower FA in the IC, CC, and parts of the limbic system, as well as findings of both higher and lower MD in the splenium of the CC (sCC) (Huisman et al. 2004; Zhu et al. 2014; Veeramuthu et al. 2015; Inglese et al. 2005; Miles et al. 2008). Toth and colleagues' data suggests acute abnormalities may resolve over time based on decreased MD and increased FA values in the CC, CR, and IC after approximately one month (Toth et al. 2013). In contrast, there is evidence these acute changes persist months after injury based on longitudinal findings from Veeramuthu et al. (2015) who described within-group FA decline from day-of-injury to six months post-mTBI in the corona radiata (CR), anterior limb of the IC (ALIC), cingulum, superior longitudinal fasciculus (SLF), optic radiations (OR), and genu of the CC (gCC). However, there were significant discrepancies in education level between the mTBI (11.5 years) and control groups (15.6 years), possibly affecting long-term comparisons. Of note, 77% of subjects had loss of consciousness (LOC) at time of injury, considered by many to indicate greater injury severity. Lipton and colleagues also reported longitudinal data, but with inconsistent findings indicating that a majority of their participants showed both higher and lower than normal FA values in sporadic locations (Lipton et al. 2012).

Yuh et al. (2014) demonstrated a potential effect of injury severity based on conventional neuroimaging findings. Their study included 76 mTBI patients (67% with LOC), 32 of

Table 1 Summary of DTI literature review findings in adult civilian mTBI

Injury phase	First author	Year	N (Experimental)	Age mean (SD)	N (Control)	Age mean (SD)	Time since injury	Analytical method	Selected results
Acute	Arfanakis	2002	5 (2F, 3 M)	35.6 (14.8)	10 (5F, 5 M)	28.9 (7.6)	<24 h	ROI	↓FA in IC, CC
	Huisman	2004	20 (5F, 15 M)	31 (10)	15 (?F,? M)	35 (10)	≤ 7 d	ROI	↓ADC in sCC; ↓FA in sCC, IC
	Inglese	2005	46 (17F, 29 M)	36 (r 18–58)	29 (14F, 15 M)	35 (r 18–61)	G1: 4d (r 1-10d) G2: 5.7y (r 0.6-31y)	WB, ROI	↓FA and ↑MD in sCC, IC
	Bazarian	2007	6 (4F, 8 M for whole sample)	21.7 (r 18–31)	TC – 6 (4F, 8 M for whole sample)	21.7 (r 18–31)	<4 h	WB, ROI	No FA differences
	Miles	2008	17 (6F, 11 M)	33.4 (r 18–58)	29 (14F, 15 M)	35 (r 18–61)	4.1d (r 1-10d)	ROI	On average, ↓FA and ↑MD in mTBI across centra semiovala, CC, and IC
	Lipton	2009	20 (11F, 9 M)	33.4 (8.3)	20 (11F, 9 M)	34.2 (9.3)	2-14d	VBA	↓FA in 15 voxel clusters
	Mayer	2010	22 (14F, 8 M)	27.4 (7.4)	21 (sex-matched)	Age-matched	≤ 20d	ROI	↑FA and ↓RD in gCC, CR, UF
	Wilde and McCauley	2012	7 (2F, 5 M)	24.8 (7.5)	None (longitudinal)	n/a	T1: 0-48 h T2: 49-96 h T3: 97-144 h T4: 145-192 h	ROI	↑FA in cingulum; AD, RD, ADC variable
	Lipton	2012	T1: 34 (19F, 15 M) T2: 16 (?F,? M) T3: 10 (?F,? M)	34.9 (11.5)	30 (14F, 16 M)	37.3 (11.0)	T1: 2-14d T2: ~3 m T3: ~6 m	Individual Enhanced Z-Score	T1: 32/34 mTBI with regions of ↓FA and ↑FA T2: 14/16 mTBI with regions of ↓FA and 15/16 with ↑FA T3: 7/10 mTBI with regions of ↓FA and 10/10 with ↑FA
	Ling	2012	28 (12F, 16 M)	28.2 (10.6)	28 (12F, 16 M)	27.4 (10.2)	15.6d (4.3d)	ROI, VBA, TBSS	No multivariate group effect in any ROI
	Toth	2013	14 (5F, 9 M)	34.9 (18.4)	14 (5F, 9 M)	35.8 (18.5)	T1: <72 h (r 12-72 h) T2: ~1 m (r 28-43d)	TBSS	T1: ↓FA and ↑MD in "several white matter tracts…" compared to controls T2: ↓FA in right hemisphere compared to controls T1- > T2: ↓MD and ↑FA in CC, CR, and IC over time in mTBI group
	Yuh	2014	76 (26F, 50 M)	32 (10.5)	50 (18F, 32 M)	28.7 (9.2)	11.2d (3.3d)	WB, VBA, ROI	↓FA in IC, EC, gCC, UF, ACR
	Ilvesmaki	2014	75 (30F, 45 M)	37.2 (12)	TC – 40 (20F, 20 M)	r 18–60	48.1 h (45.5 h)	WB, TBSS	No group differences in FA, ADC, AD, RD
	Hasan	2014	36 (13F, 23 M)	29.0 (8.4)	37 (10F, 27 M)	29.4 (9.2)	T1: 21.2 h (11.6 h) T2: 98d (16d)	WB, ROI	No between/within group differences in FA, MD
	Zhu	2014	12 (2F, 10 M)	35.7 (r 19–50)	13 (sex-matched)	Age-matched	5.5d (2.3d)	WB, VBA, TBSS	↓FA in CC, limbic, all lobes
	Veeramuthu	2015	61 (7F, 54 M)	27.1 (8.6	19 (?F,? M)	Age-matched	T1: 10 h (4.3 h) T2: 6.1 m (0.1 m)	TBSS, ROI	T1- > T2: mTBI ↓FA in CR, IC, cingulum, SLF, OR, gCC
	Wang	2016	47 (15F, 32 M)	30.0 (6.8)	37 (16F, 21 M)	31.4 (8.7)	<7d	TBSS, ROI, GAMMA	↑FA in MCP and pontine crossing tract
	Wilde	2016	79 (24F, 55 M)	29.6 (8.8)	TC – 64 (17F, 47 M)	28.8 (8.5)	T1: 25.9 h (12.3) T2: 94.4d (8.7d)	ROI	T1: LOC correlated to FA and MD; no FA differences at T1 or T2
Subacute / Chronic	Rutgers	2007	21 (9F, 12 M)	32 (9)	11 (3F, 8 M)	Age-matched	med. 5.5 m (r 0.1–109.3 m)	WB	Regions of ↓FA in cingulum, CC
	Niogi	2008	34 (16F, 18 M)	37.4 (r 16–61)	26 (7F, 19 M)	28.3 (r 17–58)	>1 m (r 1-65 m)	ROI	↓FA in ACR, UF, gCC, cingulum, ILF
	Messé	2010	23 (6F, 17 M)	30.6 (8.6)	23 (12F, 11 M)	30.0 (8.4)	T1: 17.2d (7.2d) T2: 3-4 m	VBA, TBSS	Poor outcome ↑MD in fMaj, fMin, IFOF, ILF; no FA, AD, RD differences
	Warner	2010	24 (7F, 17 M)	27.2 (11.4)	n/a	n/a	T1: 2.2d (2.4d) T2: 7.7 m (1.9 m)	Tractography	T1: no correlation of WM and GM T2: WM (FA) correlated to cortical GM volume

Table 1 (continued)

Injury phase	First author	Year	N (Experimental)	Age mean (SD)	N (Control)	Age mean (SD)	Time since injury	Analytical method	Selected results
	Smits	2011	19 (1F, 18 M)	26.4 (r 18–50)	12 (4F, 8 M)	28 (10)	30.6d (r 18-40d)	VBA	↓FA in IFOF; no group differences in MD
	Lange	2012	60 (17F, 43 M)	30.8 (9.9)	TC – 34 (9F, 25 M)	37.1 (11.8)	47d (6.5d)	ROI	No FA or MD differences
	Grossman	2013	T1: 20 (4F, 16 M) T2: 10 (2F, 8 M)	34.8 (10.7	16 (3F, 13 M)	35.1 (11.9)	T1: <1 m (r 5-54d) T2: >9 m from T1 (r 238-584d)	ROI	T1: ↓FA and ↑MD in the thalamus, IC, CC, cingulum, OR, centrum semiovale, deep GM, and total WM compared to controls T2: no FA differences; ↑MD in thalamus and total WM compared to controls T2 vs. T1: ↓MD and ↑FA in thalamus, ↑MD in CC and total WM
	Xiong	2014	25 (9F, 16F)	32.5 (10.4)	25 (10F, 15 M)	31.5 (9.5)	32.1d (3.6d)	VBA, TBSS	↓FA and ↑MD in UF, SLF, IC
	Waljäs	2015	48 (30F, 18 M)	36.4 (12.4)	24 (16F, 8 M)	36.6 (10.1)	27.4d (8.9d)	ROI	mTBI more likely to have areas of ↓FA and ↑ADC
	Panenka	2015	Complicated vs. Uncomplicated 62 (?F,? M)	30.6 (8.7)	TC – 34 (?F,? M)	Age-matched	Uncomplicated: 46.0d (5.5d) Complicated: 48.1d (5.6d)	ROI, TBSS	no group differences across 48 ROIs
	Lange	2015	PCS+ vs. PCS- 72 (20F, 52 M)	34.1 (11)	TC – 36 (10F, 26 M)	31.6 (10.2)	46.6d (6.0d)	TBSS	No differences in PCS- vs. TC; ↑RD in PCS+; DTI did not distinguish PCS- and PCS+
Remote history	Kraus	2007	20 (12F, 8 M)	35.8 (SEM = 2.1)	18 (11F, 7 M)	Age-matched	>6 m (mean 107 m)	ROI	↓FA and ↑AD in OR, SLF
	Lipton	2008	17 (9F, 8 M)	r 26–70	10 (sex-matched)	Age-matched	r 8 m-3y	WB, VBA	Whole-brain ↓FA
	Lo	2009	10 (5F, 5 M)	38.2 (r 20–51)	10 (5F, 5 M)	44 (10.9)	r 2.6–10.8y	ROI	↓FA and ↑MD in gCC
	Sugiyama	2009	11 (1F, 10 M)	35.4 (15.1)	16 (4F, 12 M)	31.7 (13.4)	1-20y	VBA, tractography	↓FA in CC, fornix, cingulum, all lobes
	Geary	2010	40 (23F, 17 M)	34.5 (10.2)	35 (19F, 16 M)	32.5 (10.7)	5.3y (1y)	ROI	↓FA in SLF, UF
	Kasahara	2012	10 (3F, 7 M)	39.1 (11.4)	12 (2F, 10 M)	23.0 (4.7)	R 2-12y	ROI	↑AD in CST, ICP, IC, ACR, SFOF; no FA differences
	Wada	2012	51 (23F, 28 M)	37.1 (10.2)	30 (20F, 30 M)	35.8 (13.4)	35.1 m (3.7 m)	TBSS	↓FA in SLF, insula, fornix
	Bouix	2013	11 (2F, 9 M)	33.3 (8.4)	11 (1F, 10 M)	32.1 (8.5)	Mean 62.1 m (r 2.6–138.0 m)	ROI with subject-specific profile analysis	No group differences in FA, MD, AD, or RD for any ROI; heterogeneous subject-specific differences
	Dean	2015	16(9F, 7 M)	26.9 (r 19–39)	9 (5F, 4 M)	21.9 (18–32)	>1y	VBA	↓FA in ACR, ALIC
	Astafiev	2015	42 (14F, 28 M)	35.6 (r 19–60)	25(?F,? M)	Age-matched	r 3 m-5.5y	ROI, TBSS	No group differences in FA, MD, RD, or AD
	Maruta	2016	32 (17F, 15 M)	r 18–55	126 (?F,? M)	r 18–55	90d-5y	WB, ROI	No FA differences

F Female, *M* Male, *r* Range, *med.* Median, *T* Time, *h* Hours, *d* Days, *m* Months, *y* Years, *VBA* Voxelwise analysis, *WB* Whole brain, *TBSS* Tract-based spatial statistics, *ROI* Region of interest, *FA* Fractional anisotropy, *MD* Mean diffusivity, *AD* Axial diffusivity, *RD* Radial diffusivity, *ADC* Apparent diffusion coefficient; see "Glossary of terms" for anatomical abbreviations

Table 2 Summary of DTI literature review findings in adult military mTBI

Injury phase	First author	Year	N (Experimental)	Age	N (Control)	Age	Time since injury / last exposure	Analytical method	PTSD measure	Blast injuries	Selected results
Acute	MacDonald	2011	63 (0F, 63 M)	med. 24 (r 19–58)	Uninjured/blast exposed military: 21 (0F, 21 M)	med. 31 (r 19–49)	med. 14d (r 1-90d)	ROI	Not indicated	Yes	↓FA in cingulum, UF, ALIC; 18/63 mTBI subjects with 2+ ↓FA ROIs
	Adam	2015	95 (2F, 93 M)	med. 26 (r 19–41)	Uninjured military: 101 (22F, 79 M)	med. 28 (r 19–48)	med. 4d (r 1-8d)	WB, ROI	PCL-M – covariate	Yes	↓FA in SLF in 7/95 mTBI subjects
	Li	2016	43 (22F, 21 M)	30.6 (8.6)	22 (14F, 8 M)	36.1 (7.1)	T1: ≤3d T2: 10-20d T3: 1-6 m	TBSS	Yes; 21/43 mTBI + PTSD	n/a	T1: mTBI + PTSD ↑FA in SLF, CC, IFOF, ATR, CST, UF T2: no FA differences T3: same as T1
Subacute / Chronic	Warden	2009	1 (1F, 0 M)	50	n/a	n/a	7 m	ROI	Not indicated	Yes – primary blast	FA histogram for cerebellum shifted left; ADC histogram shifted right
	Costanzo	2014	11 (3F, 8 M)	26.2 (5.5)	11 (4F, 7 M)	Age-matched	Unknown; evaluated <2 m following return from deployment	Diffusion-Oriented Tract Segmentation (DOTS)	PCL-M and CAPS	Not indicated	No statistical differences between groups when multiple comparison corrected
Remote history	Matthews	2011	mTBI + MDD: 11 (0F, 11 M0	26.8 (r 22–45)	mTBI w/o MDD: 11 (0F, 11 M)	30.3 (r 22–47)	mTBI+: 2.8y (1.0y) mTBI-: 3.3y (1.1y)	VBA	CAPS	Yes (all subjects)	mTBI+ ↓FA in ACR, CC, SLF
	Matthews	2012	mTBI + LOC: 22 (0F, 22 M)	29.13 (6.07)	mTBI w/o LOC: 24 (0F, 24 M)	26.59 (4.92)	mTBI+: 3.52y (1.46y) mTBI-: 3.61y (1.43y)	TBSS	Yes; 17/22 in mTBI+, 11/24 in mTBI-	Yes (all subjects)	mTBI+ ↓FA in CC, cingulate, ILF, SLF, IFOF, ALIC, ATR, ACR
	Jorge	2012	72 (0F, 72 M)	~29 (~6)	C1- Uninjured/blast unexposed: 21 (0F, 21 M) C2- civilian mTBI: 14 (?F,? M)	C1: 33.7 (10.6) C2: 38.9 (12.0)	~4y (~1.6y) C2: 1.7 m (1.3 m)	TBSS, VBA, Pothole analysis	CAPS, M.I.N.I.	Yes (all military mTBI)	No group differences in FA, MD; military mTBI more "potholes" than C1; civilian mTBI more "potholes" than military mTBI and C1
	Davenport	2012	25 (1F, 24 M)	36.0 (8.9)	Uninjured/blast unexposed military: 33 (5F, 28 M)	32.5 (8.6)	2-5y	ROI, VBA	CAPS	Yes	mTBI with ↓FA voxels in fMaj, fMin, ATR, CST, IFOF, ILF, SLF; no ROI FA differences
	Morey	2013	30 (1F, 29 M)	39.6 (10.8)	C1-relaxed inclusion: 42 (10F, 32 M) C2- stricter matching criteria: 28 (2F, 26 M)	C1: 36.8 (9.9) C2: 37.5 (11.3)	9.7y (10.8y)	TBSS, TBSS-X w/ partial volume fractions, WB-VBA w/ permutation testing	CAPS	Combined blast and non-blast	↓FA and ↓primary partial volume fraction in CC, fMin, CR, SLF, tapetum, IC
	MacDonald	2013	4 (1F, 3 M)	med. 30 (r 23–36)	18 (0F, 18 M)	med. 30, (r 19–49)	2-4y	ROI	CAPS; ¼ mTBI subjects	Yes	↓FA in MCP in 3/4 subjects; no differences in other 11 ROIs
	Sorg	2014	30 (4F, 26 M)	30.7 (9.3)	Uninjured military: 15 (4F, 11 M)	32.9 (8.2)	36.92 m (20.68 m)	ROI	PCL-M	Combined blast and non-blast	No group differences in FA, RD, or AD for any ROI
	Isaac	2014	Comorbid mTBI + PTSD+ MDD: 25 (2F, 23 M)	46.0 (4.6)	Comorbid mTBI + PTSD w/o MDD: 20 (2F, 18 M)	44.0 (3.3)	Not indicated	ROI	Yes – all subjects	Not indicated	mTBI + PTSD + MDD ↓FA in UF, cingulum
	Petrie	2014	34 (0F, 34 M)	31.6 (9.2), r 23–60	Blast unexposed: 18 (1F, 17 M)	32.8 (7.3), r 22–46	3.8y (1.5y)	WB voxelwise analysis	PCL-M, CAPS	Yes	↓FA in right gCC for mTBI veterans
	Hayes	2015	E1 - mTBI + LOC: 28 (0F, 28 M) E2 – mTBI w/o LOC: 31 (1F, 30 M)	E1–27.9 (4.2) E2–29.6 (7.7)	Uninjured/blast exposed and unexposed: 55 (6F, 49 M)	30.5 (6.7)	E1: 56.3 m (23.2 m) E2: 43.8 m (27.2 m) C: 49.8 m (36.3 m)	ROI, TBSS	CAPS – covariate	Yes	No main effect of group on mean FA in any ROI; mTBI + LOC more likely to have 1+ abnormal ROI
	Davenport	2015	E1 – mTBI + PTSD: 45 (0F, 45 M) E2 – mTBI w/o PTSD: 19 (1F, 18 M)	E1: 30.2 (6.2) E2: 36.6 (9.4)	Uninjured military w/o PTSD: 38 (6F, 32 M)	33.9 (8.8)	2-5y	ROI, VBA	Yes – variable of interest	Yes	No main effect of group on FA or MD in any ROI; no global mTBI effects for FA
	Miller	2016	53 (1F, 52 M);	~28.5 (~6)		30.2 (6.3)	E1: 58.2 m (24.4 m)	TBSS	CAPS – covariate	Yes	

Table 2 (continued)

Injury phase	First author	Year	N (Experimental)	Age	N (Control)	Age	Time since injury / last exposure	Analytical method	PTSD measure	Blast injuries	Selected results
			E1 – mTBI + LOC E2 – mTBI w/o LOC		C1 – Uninjured/blast exposed military: 37 (2F, 35 M) C2 – Uninjured/blast unexposed military: 14 (4F, 10 M)		E2: 44.7 m (27.9 m)				mTBI + LOC more voxel clusters with ↓FA; no difference between uninjured and mTBI w/o LOC; no effect of PTSD sx
	Meabon	2016	19 (0F, 19 M)	33.2 (7.7)	n/a	n/a	5.7y (2.2y)	ROI	CAPS - covariate	Yes	Negative correlation between blast-related mTBI number and MD in cerebellum; no correlation with FA, AD, or RD
Repetitive brain trauma (Blast exposure)	Bazarian	2013	E1 – mTBI + PTSD: 9 E2 – PTSD only: 6 E3 – mTBI only: 21 E4 – blast exposure only: 16 (3F, 49 M)	30.8 (7.1)	Not defined	n/a	48.3 m (22.6 m)	WB, ROI	PCL-M; variable of interest	Yes – blast exposure quantified with CES	Blast exposure associated with 1st %ile of WB FA; no ROI associations with PTSD, mTBI, or blast exposure
	Trotter	2015	Blast exposed: 190 (15F, 175 M)	31.7 (8.0)	Blast unexposed: 59 (18F, 41 M)	32.4 (9.7)	n/a	TBSS, ROI	CAPS	Yes – blast exposure quantified with BAT-L	Age x blast exposure interaction
	Taber	2015	6 (0F, 6 M)	35.8 (8.7)	C1 – Uninjured/blast exposed military: 23 (5F, 18 M) C2 – Uninjured/blast unexposed: 16 (4F, 12 M)	C1: 35.8 (7.4) C2: 37.3 (11.5)	n/a	WB, VBA	SCID-I	Yes	Blast exposed ↓FA in fMaj, SLF, ILF, ATR, IFOF, CST; no effect of mTBI

F Female, *M* Male, *E* Experimental group, *C* Control group, *LOC* Loss of consciousness, *PTSD* Posttraumatic stress disorder, *MDD* Major depressive disorder, R range, *med.* median, *T* Time, *h* hours, *d* days, *m* months, *y* years, *VBA* Voxelwise analysis, *WB* Whole brain, *TBSS* Tract-based spatial statistics, *ROI* Region of interest, *PCL-M* Posttraumatic Stress Disorder Checklist-Military, *CAPS* Clinician-Administered PTSD Scale, *SCID* Structured Clinical Interview for DSM-IV Axis I Disorders, *M.I.N.I.* Mini International Neuropsychiatric Inventory, *CES* Combat Exposure Screening, *BAT-L* Boston Assessment of TBI-Lifetime, *FA* Fractional anisotropy, *MD* Mean diffusivity, *AD* Axial diffusivity, *RD* Radial diffusivity, *ADC* Apparent diffusion coefficient; see "Glossary of terms" for anatomical abbreviations

Table 3 Summary of DTI literature review findings in adult sport-related mTBI

Injury phase	First author	Year	N (Experimental)	Age mean (SD)	N (Control)	Age mean (SD)	Time since injury / last exposure	Analytical method	Selected structural findings
Acute	Henry	2011	College football: 16 (0F, 16 M)	22.1 (1.7)	Uninjured/no cx hx, college football: 8 (0F, 8 M)	22.8 (1.5)	T1: 81.9 h (46.7 h) T2: 6.4 m (0.4 m)	VBA	↑FA in CC, CST at T1 and T2; no main effect of time, no group x time interaction
	Murugavel	2014	College contact sports: 21 (0F, 21 M; *n* = 7 imaged at all 3 time points)	20.2 (1.0)	Uninjured/noncontact college: 14 (0F, 14 M)	19.9 (1.7)	T1: ~2d T2: ~2w T3: ~2 m	WB, VBA, TBSS	↑RD T1- > T2 for concussed group; no FA, RD, AD differences T2- > T3 or T1- > T3
	Jing	2015	College football: 3 (0F, 3 M)	R 19–23	Uninjured college football: 8 (0F, 8 M)	r 19–23	T1: <24 h T2: ~1w T3: ~2w	ROI	↑FA for white matter skeleton at T1 and T2 for concussed group compared to controls; no significant changes over time
	Meier	2016	College sports: 40 (10F, 30 M; *n* = 17 imaged at all 3 time points)	20.1 (1.4)	Uninjured/contact college: 46 (16F, 30 M)	20.3 (1.5)	T1: 1.6d (0.8d) T2: 8.3d (2.2d) T3: 32.1d (4.8d)	WB, VBA, ROI	↑FA clusters in sagittal stratum, SCP, IC, SLF, fMin, IFOF, PCR at T1, T2, and T3; no change over time for either group
Subacute/ Chronic	Zhang	2010	College rugby, hockey, soccer: 15 (experimental + control: 30%F, 70%M)	20.8 (1.7)	Uninjured college: 15 (experimental + control: 30%F, 70%M)	21.3 (1.5)	~30d (~2d)	WB, VBA, TBSS	No group differences
	Cubon	2011	College sports: 10 (5F, 5 M)	19.7 (r 17–22)	Uninjured/ contact and noncontact college: 10 (5F, 5 M)	20.4 (r 18–23)	115d (104d)	TBSS	↑MD in ILF, IFOF, IC, PTR, acoustic rads., SLF; no FA differences
	Chamard	2014	College sports: 10 (10F, 0 M)	21.7 (2.1)	College sports: 10 (10F, 0 M)	21.0 (1.3)	19.5 m (15.0 m)	ROI, VBA, TBSS	↑MD in fMin, IFOF, cingulum, UF, ILF, ATR, SLF, CST; No voxel cluster FA differences
	Sasaki	2014	College hockey: 16 (6F, 10 M)	21.7 (1.5)	Uninjured/no cx hx, college hockey: 18 (8F, 10 M)	21.3 (1.8)	r 42d-6 m	WB, VBA, TBSS	↑FA in CR, PLIC, cortical WM; ↓RD in gCC, CR, IC, EC, cortical WM
	List	2015	Club sport athletes: 20 (2F, 18 M); minimum hx of 2 mTBI	25.5 (5.3)	Club sport athletes w/o hx: 21 (2F, 19 M)	25.7 (5.2)	r 6-44 m	Frontotemporal and hippocampal ROIs	No FA or MD differences in ROIs
	Chamard	2015	Soccer, hockey, water polo: 10 (10F, 0 M)	21.4 (1.7)	Uninjured soccer, hockey: 8 (8F, 0 M)	21.4 (1.0)	>6 m	WB tractography, CC ROIs	↓RD and ↓AD in various CC segments; no FA differences
	Meier	2016	College Football: 49 (0F, 49 M); *n* = 25 with concussion history	20.6 (1.4)	Non-collision sport/non-athlete: 27 (0F, 27 M)	21.9 (2.2)	10.0 m (12.0 m)	ROI	No group differences in FA in any ROIs
Remote History (Retired collision sport athletes)	Strain	2013	Retired NFL: 26 (0F, 26 M); *n* = 5 with MDD	57.8 (11.3)	Non-athlete: 22 (?F,? M)	59.4 (11.8)	Variable (time since retirement)	TBSS, ROI	Higher depression scores associated with ↓FA in fMin, SLF, UF; no FA differences between controls and non-MDD retired NFL
	Casson	2014	Retired NFL: 45 (0F, 45 M)	45.6 (8.9)	n/a	n/a	Variable (time since retirement)	WB global WM	FA negatively associated with NFL concussion hx; peak FA associated with alcohol use, employment status, pre-high school football
	Tremblay	2014	Former college hockey and football: 15 (0F, 15 M)	60.7 (7.5)	Former college hockey and football w/o hx: 15 (0F, 15 M)	58.1 (5.3)	37.1y (7.1y)	VBA, TBSS	↓FA and ↑MD in CC, fMin, SLF, IFOF

Table 3 (continued)

Injury phase	First author	Year	N (Experimental)	Age mean (SD)	N (Control)	Age mean (SD)	Time since injury / last exposure	Analytical method	Selected structural findings
	Hart	2014	Retired NFL: 34 (0F, 34 M)	61.8 (r 41–79)	Non-athlete with no known cx hx	60.1 (r 41.79)	Variable (time since retirement)	TBSS	Symptomatic retired NFL showed ↓FA in frontal, parietal, and temporal lobe and CC compared to controls and asymptomatic retired NFL
	Multani	2016	Retired CFL: 18 (0F, 18 M)	49.6 (12)	Non-athlete: 17 (0F, 17 M)	46.7 (10)	16.2y (13y)	TBSS, tractography	↑AD in SLF, CST, ATR; no FA, RD, MD differences
Repetitive Brain Trauma (subclinical impacts)	Chappell	2006	Boxers: 81 (0F, 81 M)	med. 28 (r 20–42)	Non-boxers: 12 (0F, 12 M)	r 22–31	Current boxers	WB, VBA	↓FA in IC, cortical WM, IFOF, ILF, CST
	Chappell	2008	Boxers: 59 (0F, 59 M)	r 22–31	Non-boxers: 12 (0F, 12 M)	r 22–31	Current boxers	VBA with multivariate and linear discriminant function	Variable FA and MD differences throughout the brain
	Koerte	2012	Elite soccer: 12 (0F, 12 M)	19.7 (1.6)	Swimmers: 11 (0F, 11 M)	21.4 (2.8)	Current athletes	WB, TBSS	Widespread ↑RD; no associations with age or years playing sport
	Koerte	2012	Ice hockey: 17 (0F, 17 M)	22.2 (1.6)	n/a	n/a	Pre and postseason assessment	WB, VBA, TBSS	↑AD postseason in CR, ALIC, PLIC; no FA differences pre to postseason
	Lipton	2013	Amateur soccer players: 37 (9F, 28 M)	~30 (~6)	n/a	n/a	Current athletes	WB, VBA, ROI	More heading exposure associated with ↓FA in temporo-occipital WM
	Shin	2014	Boxers and mixed martial artists (MMA): 155 (0F, 155 M); boxing n = 74, MMA n = 81	~28 (~5)	n/a	n/a	Current boxers and MMA fighters	ROI	Number of knockouts predicted ↓FA in CC; widespread AD and RD changes for boxers in cortical WM
	Bazarian	2014	College football: 10 (0F, 10 M)	20.4 (1.1)	Non-athletes: 5 (0F, 5 M)	20.6 (1.1)	T1: preseason T2: postseason T3: 6 m after season	WB, VBA	Voxel clusters with ↓FA, ↑↓MD from T1- > T2 in CC; diffusion metric changes correlated to head impact biomechanics
	Gajawelli	2014	Contact sport athletes: 11 (0F, 11 M); n = 8 imaged at both time points	20.4 (1.4)	Uninjured/noncontact athletes: 13 (0F, 13 M)	19.5 (1.0)	Pre and postseason assessments	WB, VBA	FA and MD differences in CC, IFOF, CR (direction not indicated)
	McAllister	2014	College football and hockey: 80 (16F, 64 M)	19.0 (1.1)	Uninjured/noncontact college athletes: 79 (23F, 56 M)	19.5 (1.3)	Pre and postseason assessments	ROI	No pre to postseason changes in FA or MD

F Female, *M* Male, *cx hx* Concussion history, *r* Range, *med.* median, *T* Time, *h* Hours, *d* Days, *m* Months, *y* Years, *VBA* Voxelwise analysis, *WB* Whole brain, *TBSS* Tract-based spatial statistics, *ROI* Region of interest, *NFL* National Football League, *CFL* Canadian Football League, *FA* Fractional anisotropy, *MD* Mean diffusivity, *AD* Axial diffusivity, *RD* Radial diffusivity, see "Glossary of terms" for anatomical abbreviations

whom had abnormal CT and/or structural MRI. Specifically, they found no white matter differences when comparing the CT/MRI negative group to controls. The CT/MRI positive group had lower FA in the IC, external capsule (EC), gCC, uncinate fasciculus (UF), and anterior CR (ACR). Other studies of acute mTBI effects note widespread diffusivity changes within white matter deep to the frontal lobes (Lipton et al. 2009). See Table 1 for more detailed descriptions of civilian DTI/mTBI studies.

The above studies with control groups utilized non-injured subjects, and evidence suggests acute DTI findings may vary based on characteristics of the control group. For example, civilians imaged less than four hours after their injury exhibited no FA differences when compared to orthopedic injured controls (Bazarian et al. 2007). In a larger study, Ilvesmäki et al. (2014) reported a similar lack of difference in FA, MD, RD, or AD between acutely injured civilians (within one week of injury) and orthopedic controls, and this held true for both younger (18–30 years) and older aged (41–60 years) controls despite findings of overall lower FA in the older versus younger control groups. Hasan et al. also utilized orthopedic controls when comparing mTBI patients (over half with loss of consciousness) measured at two time points – within 24 h and approximately three months post-mTBI. They found no between or within group FA or MD differences in the CC or hippocampus, though mTBI patients had higher MD in the anterior corona radiata (ACR) within 24 h of injury (Hasan et al. 2014). Wilde and colleagues implemented a similar design with comparable control group, time points, age, gender breakdown, and proportion of patients with LOC. Importantly, they specifically examined LOC duration and found it correlated positively with MD in the UF and inferior fronto-occipital fasciculus (IFOF). Their overall mTBI group (both with and without LOC) showed higher MD in the UF, IFOF, and gCC at time one (within 48 h) but no differences at time two (approximately three months post-TBI) compared to orthopedic injured controls. Once again, no FA differences between mTBI patients and orthopedic controls were noted at either time point (Wilde et al. 2016). Taken together, these data suggest a potential role of general trauma, within both central and peripheral nervous system, on acute white matter diffusivity measures in the brain, particularly FA, though support of this interpretation requires comparison to healthy controls or pre-injury baseline imaging.

Reports of the direction of acute FA differences are somewhat inconsistent. For example, Mayer et al. (2010) show *higher* FA and lower RD values in the genu of the CC (gCC), corona radiata (CR), and UF when measured between two and 20 days post-mTBI, and these authors later report replication of their finding of higher FA in the gCC, though not in the CR and UF. Additionally, they found no multivariate group effect on FA in their ROIs in the subsequent study, though follow-up univariate analyses were still performed on individual ROIs which elicited the significant finding (Ling et al. 2012). Wilde et al. (2012) similarly describe acute FA *increases* in a small longitudinal study, most notably within the cingulum, and highly variable findings for AD, RD, and MD measures throughout the first week after injury. Of note, all patients in this study sustained loss of consciousness at time of injury and may represent a more serious mTBI sample. Higher FA in the acute stage is also reported within cerebellar-specific structures such as the middle cerebellar peduncle (MCP) and pontine crossing tract (Wang et al. 2016). Many researchers have interpreted increased FA in the acute stage to reflect increased anisotropy due to cerebral edema.

Subacute/chronic (DTI between approximately one month and one year post-mTBI)

Diffusion outcomes appear variable in more chronic injury stages as well. Niogi et al. (2008) reported multiple regions where mTBI patients had lower FA when imaged between one and 65 months post-injury, including the ACR, UF, gCC, cingulum, and ILF. Niogi also reported significant inter-individual variability; less than half of these patients had significantly lower FA in the most commonly reduced region (41% in the ACR) and few showed lower FA in the least commonly reduced region (18% in the ILF). These findings highlight the hazards of relying only on group mean comparisons. All subjects in this analysis were symptomatic at the time of assessment (range 1 to 65 months post-mTBI): 32% showed evidence of microhemorrhage, and an additional 35% had white matter hyperintensities or evidence of chronic contusion, potentially limiting generalizability to more typical mTBI cases. Inter-individual variability was also evident in the findings of Waljas et al. (2015), who reported that mTBI subjects, as a group, were more likely to exhibit two or more and three or more areas of low FA scores out of 16 ROIs, and more likely to exhibit two or more or three or more areas of high ADC out of 10 ROIs compared to controls. The raw statistics indicate that, within the mTBI group, 30% and 60% of patients showed less than two and less than three areas of low FA, respectively. Similar patterns were observed for raw statistics underlying the group associations for areas of high MD. Findings from an investigation with a wide range of time since injury (0.1 to 109.3 months, median 5.5 months) indicated that mTBI patients, on average, had 9.1 voxel clusters with lower FA, typically involving white matter underlying the cerebral cortex, and white matter projection and association fibers (Rutgers et al. 2008). Xiong et al. (2014) describe overlapping regions of lower FA and higher MD one month post-mTBI compared to controls in the UF, SLF, and IC, and Smitts et al. reported lower FA in the IFOF one month post-injury (Smits et al. 2011). However, as seen with contradictory findings in the acute setting, a comparable study utilizing orthopedic injured controls found no FA or MD

differences compared to those with mTBI sustained six to eight weeks prior (Lange et al. 2012). Panenka et al. (2015) also found no differences for any diffusion metrics across 48 ROIs when comparing both uncomplicated (no abnormality on CT or MRI) and complicated (evidence of injury on CT and/or MRI) concussions to trauma controls; FA differences between complicated and uncomplicated mTBI did not survive adjustment for multiple comparisons.

Two studies directly examined differential outcomes based on the presence or absence of symptomatology in the subacute/chronic phase. Messé et al. (2011) categorized mTBI patients as "good outcome" and "poor outcome" at 3 months based on the presence or absence of symptoms in three domains: behavioral/emotional, cognitive, and somatic complaints. Patients with poor outcomes had higher MD in the forceps major (fMaj), forceps minor (fMin), IFOF, and ILF than did good outcome patients and controls, and also higher MD in the SLF, corticospinal tract (CST), and anterior thalamic radiations (ATR) than controls only. Good outcome patients did not differ from controls. Lange et al. (2015) defined persistent symptomatology using the International Classification of Diseases, 10th edition, definition of "postconcussional syndrome" (PCS) and required moderate or greater symptom reporting in at least three of six domains: physical, emotional, cognitive, poor sleep, sensitivity to alcohol, and being overly focused on and concerned about their symptoms. Similar to Messe et al.'s findings, mTBI subjects not meeting PCS criteria did not differ from trauma controls, but also did not differ from mTBI subjects with persistent symptoms, on FA, MD, AD, or RD. Additionally, mTBI subjects with persistent symptoms had higher MD in the gCC, bCC, CR, ALIC, and PLIC compared to trauma controls, and this appeared driven by differences in RD. No reviewed studies indicated higher FA or lower MD in adult civilian mTBI patients during the subacute/chronic period after injury.

Remote history (DTI more than one year post-mTBI)

To a greater degree than acute or subacute/chronic time points, diffusivity differences noted more than a year after sustaining an mTBI in a civilian population likely indicate either an inability to repair acute microstructural changes, ongoing or progressive microstructural changes, or preinjury variability in white matter microstructure misattributed to an injury-based etiology. Researchers describe overlapping regions of lower FA and increased AD in the SLF and OR when measured, on average, almost nine years after mTBI (Kraus et al. 2007). Other noted areas of lower FA compared to controls include the bCC, gCC, sCC, fornix, cingulum, SLF, sagittal stratum, UF, IC, centrum semiovale, deep cerebellar white matter, insula, thalamus, and CR (Lipton et al. 2008; Lo et al. 2009; Sugiyama et al. 2009; Geary et al. 2010; Wada et al. 2012; Dean et al. 2015). In contrast, Maruta et al. (2016) found no FA differences when investigating the CR, cerebral peduncles, fornix, posterior thalamic radiation (PTR), IC, sagittal stratum, or SLF. Kasahara and colleagues reported areas of higher AD, but no FA differences compared to controls (Kasahara et al. 2012). Both Bouix et al. (2013) and Astafiev et al. (2015) failed to note differences between remote mTBI patients and controls. Overall, the range of times between mTBI and imaging in these studies is three months to 20 years, with mean and median elapsed time typically being many years after mTBI. This obviously reduces the extent to which generalizations can be made about white matter changes in the chronic period after mTBI. Table 1 shows individual studies have relaxed inclusion criteria in terms of time from injury, which complicates interpretations of results, especially in the context of normal age-related white matter changes across the lifespan and the majority of these studies being cross-sectional.

DTI following history of repetitive brain trauma

To our knowledge, no studies have examined directly the effects of repetitive subclinical brain trauma in an adult, civilian population. It is certainly possible that subjects in the above-reviewed studies participated in activities, such as collision sports, which would have exposed them to repetitive brain trauma; there was no guarantee that some participants in these studies did not, in fact, suffer subconcussive injury in the past. While a history of brain injury is often an exclusion criterion, simply playing collision sports is not. Many studies provide at least some description of injury mechanisms included in their investigations. Most civilian mTBIs result from motor vehicle accidents (MVAs), falls, or assault. Only a small number of the reviewed civilian mTBI studies indicated the inclusion of sport-related brain injury in their total mTBI sample (e.g., 9% (3/16) in Dean et al. (2015), 6% (3/47) in Wang et al. (2016), and 13% (6/48) in Waljas et al. (2015)). Conceivably, if these resulted from collision sports, these studies may have included individuals with a history of repetitive brain trauma, though they comprise a minor subset of the civilian mTBI population relative to athlete-specific investigations. Results from ongoing prospective studies in athletes suggest the need to control for collision sport or other repetitive subclinical brain trauma exposure history in civilian mTBI studies, in addition to prior history of clinically diagnosed mTBI.

Synopsis of DTI in civilian mTBI

Abnormal findings, as indicated by white matter diffusion metrics, have been identified during the acute, subacute/chronic, and long-term period after diagnosed mTBI. There is little consistency in both the presence and regional localization of these findings, and many individuals exhibit no abnormalities at all. Such inconsistency likely reflects the

heterogeneity of mTBI in terms of both physiological and clinical dysfunction. It may also reflect the wide range of analytical techniques, sample sizes, age groups, injury severities (e.g. presence of radiologic abnormalities), and/or sex distribution. Researchers utilizing whole-brain approaches may evaluate areas not investigated by those employing stricter ROI-based analyses. The degree to which studies control for multiple comparisons across analyses is also variable. The most common abnormal diffusion findings are lower FA and higher MD values (and higher MD subcomponents, such as AD and RD) in long white matter projection and association fibers. However, some studies in the acute stage identified mTBI patient groups with higher FA, a discrepancy hypothesized to reflect edema associated with axonal injury. The consistent absence of group differences, particularly in FA, when comparing mTBI groups to orthopedic injured controls is intriguing and warrants further investigation. This underscores the importance of appropriate control groups for comparison, as well as the need for more systematic longitudinal studies.

DTI findings in military mTBI

The presence of blast-related mTBI and comorbid posttraumatic stress disorder (PTSD) are unique components of military TBI. PTSD and mTBI have significant symptom overlap, and mTBI in a military setting is not only traumatic but conducive to the development of PTSD (e.g. unanticipated encounter with improvised explosive devices; witnessing death or injury in others). Clinicians working in a military setting may more readily consider PTSD as a source of persistent symptomatology (compared to civilian and athletic populations where "post-concussion syndrome" is commonly diagnosed). The majority of military-based mTBI studies report whether subjects experienced blast or non-blast injuries, and most include an independent measure of PTSD severity such as the Clinician Administered PTSD Scale (CAPS) or the Posttraumatic Stress Disorder Checklist (PCL). Blast injuries are also often further specified as primary, secondary, or tertiary based on whether the injury was caused, for example, directly by a blast wave (fluid percussion-like mechanism) versus the individual or an object being thrown by the blast wave with resulting blunt force trauma to the head or body resulting in an mTBI. Table 2 describes the manner in which the reviewed studies indicated involvement of blast mechanisms and PTSD symptoms as best as could be determined from published articles.

Acute (DTI within approximately 2–3 weeks of injury)

Not surprisingly, few studies have examined the acute effects of military mTBI using DTI, most likely due to logistical limitations. For many researchers, early access to service members after an mTBI is not feasible, so they must rely on investigating those returning from overseas deployment, which is frequently far removed in time from the event causing the mTBI. Adam et al. (2015) investigated 95 servicemen and servicewomen within eight days of a blast-related mTBI and found lower FA in the SLF compared to non-injured veteran controls**.** While over half of the subjects sustained LOC, subject-specific examination revealed that a small subset of mTBI subjects (7 of 95, 7.4%) with significantly lower FA (two standard deviations below control group mean) likely drove this group difference. Mac Donald et al. (2011) also described blast-related mTBI subjects with areas of lower FA compared to blast-exposed veterans without mTBI, including the cingulum, UF, and ALIC. Subject-specific analyses revealed 29% (18/63) had two or more ROIs with significantly low FA, while 40% had no abnormal ROIs relative to control group means. Despite a median time from injury within the acute phase (14 days post-mTBI), subjects in this analysis ranged from one to 90 days post-mTBI, potentially complicating interpretation of results. A recent longitudinal study found that individuals with mTBI who were later diagnosed with PTSD had *higher* FA in the SLF, sCC, gCC, IFOF, ATR, CST, and UF compared to controls within three days of injury. Those with mTBI that did not develop PTSD had higher FA than controls in the SLF, sCC, ILF, and ATR; mTBI groups did not differ on FA and no MD differences were observed between either mTBI group and controls. However, two to three weeks post-mTBI, MD was higher in the mTBI + PTSD group than in both mTBI only and controls in the SLF, IFOF, ILF, gCC, sCC, ATR, CST, and UF; group differences in FA were no longer present (Li et al. 2016). Sample characteristics for this study were unclear and likely included both civilians and military service members.

Subacute/chronic (DTI between approximately one month and one year post-mTBI)

Few studies of military mTBI have examined subacute/chronic effects with DTI. The previously described investigation (Li et al. 2016) imaged subjects between one and six months post-mTBI and they indicated the combined mTBI group (those with and without PTSD) were not different from each other on DTI measures. The mTBI + PTSD group showed higher FA than both mTBI only and controls in the SLF, IFOF, ILF, gCC, sCC, ATR, and CST. This was one of the few studies of any population showing significantly higher FA values in a later stage post-mTBI. However, the authors did not report any within-group analyses across assessment points, so it is difficult to determine whether between-group differences are driven by within-group changes in diffusion metrics over time after mTBI, or by preexisting group differences not directly related to mTBI or PTSD. Findings at the

wide chronic time point in this study (one to six months post-mTBI) resembled the differences noted acutely (within three days of injury), but were in contrast to the absence of differences in diffusion metrics at the intermediate (two to three weeks post-mTBI) time point. Costanzo and colleagues also found no statistical difference in diffusion metrics between veterans with mTBI evaluated within two months of returning from deployment and controls (Costanzo et al. 2014). The only other reviewed subacute/chronic study was a case study of a 50-year old servicewoman who sustained a primary blast injury (i.e. no head contact, blast wave only) and then experienced concussion-like symptoms. Findings of FA and ADC deviations in the cerebellum provided some of the earliest evidence supporting the notion of primary blast as an mTBI mechanism (Warden et al. 2009).

Remote history (DTI more than one year post-mTBI)

Military mTBI/DTI studies typically examine effects of injury and blast-exposure years after the incident. We included studies here that did not specify explicitly the time between mTBI and imaging. Residual mTBI effects may be present years later, and blast-related mTBI subjects assessed two to five years after injury have a greater number of significantly low FA voxels within the gCC, fMaj, fMin, ATR, CST, IFOF, ILF, and SLF than uninjured veteran controls (Davenport et al. 2012; Petrie et al. 2014). When considering the mean FA across the entire white matter tracts, these group differences disappeared, which raises methodological questions about whether proportions of abnormal voxels within an ROI are more meaningful than consideration of average diffusion indices for the entire ROI, or the possibility that specific regions within a given tract are more selectively affected (Davenport et al. 2012). Mac Donald et al. (2013) describe four veterans still symptomatic two to four years following mTBI with LOC that had lower FA in the MCP (three of four subjects), but no other diffusion abnormalities in the CC, cingulum, ALIC, orbitofrontal white matter, or cerebral peduncles compared to controls. Morey et al. (2013) employed a unique statistical approach referred to as TBSS-X with partial volume fractions, purported to characterize voxels with crossing fibers more accurately. They reported lower primary fiber partial volume fraction and FA in the mTBI group in the bCC, gCC, sCC, fMin, SCR, PCR, PLIC, PTR, SLF, tapetum (terminal branches of the CC), and IC compared to controls, and correlated these findings with duration of LOC despite being, on average, almost ten years removed from injury. One study design utilized a unique comparison of veterans post-mTBI with 1) uninjured/blast unexposed veterans, as well as 2) a civilian mTBI control group. No FA or MD differences were observed across the three groups. "Pothole" analysis (identifying voxel clusters with FA z-scores more than three standard deviations below the uninjured controls' mean) revealed that veterans with mTBI had significantly more potholes than uninjured/blast unexposed veterans, but the civilian mTBI group had more potholes than both injured and uninjured veterans (Jorge et al. 2012).

Analyses of interactions of mTBI, PTSD, and LOC appear particularly warranted in military populations. Miller and colleagues recently compared veterans with mTBI and LOC to those with mTBI but no LOC as well as veteran controls, both with and without blast exposure. The mTBI + LOC group had a greater number of clusters with low FA throughout the brain than both the mTBI without LOC and control groups, and there were no differences between the two latter groups. Additionally, the number of reduced FA clusters was related to physical symptoms in the mTBI + LOC group, though examination of descriptive data revealed that physical symptom reporting was negligible for all groups despite statistically significant differences (Miller et al. 2016). Hayes et al. investigated effects of mTBI + LOC and found no group differences (mTBI + LOC, mTBI without LOC, veteran controls) in FA for any ROI, but those with mTBI + LOC were over three times more likely to have had abnormally low FA in one or more ROIs than controls or those without LOC (Hayes et al. 2015). Matthews and colleagues also found veterans with mTBI + LOC had lower FA in the brainstem, CC, cingulate, ILF, SLF, IFOF, ALIC, ATR, and ACR than those with alteration of consciousness only. Although these results suggest the possibility that LOC is associated with greater DTI abnormalities after mTBI, the mTBI + LOC group reported a significantly higher number of lifetime concussions (mean 14.4 vs. 5.3 in the non-LOC group), and had higher self-reported rates of depression (73%) and PTSD (77%) than did the non-LOC group (29% and 46%, respectively) (Matthews et al. 2012).

Attempts at isolating the effects of PTSD with mTBI have yielded more inconsistent findings. One study showed no effect of mTBI on FA or MD in any of the examined ROIs, nor any effect of mTBI + PTSD compared to uninjured veteran controls. The previously described Hayes et al. (2015) study also found PTSD symptom severity was not associated with FA in any ROI. Counterintuitively, mTBI was associated with *fewer* regions of high MD globally (Davenport et al. 2015). Subjects in all groups of this study reported high rates of previous mTBI, lifetime depression, and lifetime alcohol dependence.

Other clinical outcomes, such as cognitive dysfunction and depression, may modify or further differentiate the effects of mTBI on diffusion metrics. Sorg et al. (2014) evaluated veterans an average of 3 years after mTBI and compared them to an uninjured veteran control group. They found no differences in FA, RD, or AD for any ROI. However, they further categorized mTBI subjects into those with and without executive dysfunction and reported significantly lower FA in the mTBI + executive dysfunction group compared to other mTBI subjects and controls. Affected regions included dorsal

prefrontal white matter, ventral prefrontal white matter, gCC, bCC, sCC, and posterior cingulum (higher RD also noted here). Individuals with executive dysfunction were also more likely to have suffered LOC after sustaining their mTBI**.** Isaac et al. (2015) provided further evidence of the association between persistent symptoms and white matter changes by specifically examining the interaction of mTBI, PTSD, and depression. They compared 25 veterans with co-occurring mTBI, PTSD, and major depressive disorder to 20 veterans with mTBI and PTSD but without depression. Those with comorbid depression exhibited lower FA in the UF and cingulum**.** These findings corroborate an earlier study demonstrating lower FA in the ACR, CC, and SLF in veterans with mTBI + depression compared to those with mTBI only, though 82% of the mTBI + depression group also had LOC compared to just 18% of the mTBI only group (Matthews et al. 2011).

DTI following repetitive brain trauma/blast exposure history

Some studies examined the effects of blast exposure in the absence of any clinically diagnosed mTBI. Bazarian et al. (2013) quantified blast exposure using the Combat Experience Survey and a clinical interview for all study subjects grouped as mTBI only, PTSD only, and mTBI + PTSD. Findings indicated blast exposure alone was associated with being in the first percentile of FA on whole-brain analysis, but ROI-based analysis showed no association of PTSD, mTBI, or blast exposure with diffusion metrics after correcting for multiple comparisons**.** Taber et al. (2015) utilized a three-group design with blast-related mTBI veterans, uninjured veterans with blast exposure, and uninjured/blast-unexposed veterans. They found no main effect of group on diffusion metrics but combining the blast-exposed groups (with and without mTBI) yielded results of lower FA in the fMaj, SLF, ILF, ATR, IFOF, and CST. No differences were found when isolating the blast-related mTBI group, indicating unique effects of blast-exposure alone. The two blast-exposed groups did not differ in number of low-FA voxel clusters, but both had significantly more low-FA voxel clusters than healthy controls (defined based on individual z-scores ≤ -2.0 relative to the sample-specific distribution of FA values from the healthy controls). Uninjured/unexposed veterans also exhibited significantly fewer low FA voxel clusters compared to the two blast-exposed groups, which did not differ from each other. Trotter and colleagues then examined the interaction between blast exposure and age in producing diffusion metric outcomes in veterans with (n = 190) and without (n = 59) blast exposure history. An age x blast exposure history interaction was found, which the authors interpreted to suggest that those exposed to blast forces exhibited accelerated age-related white matter degeneration compared to those without blast exposure. The medial orbitofrontal region appeared particularly susceptible in dose-response fashion (Trotter et al. 2015). However, the suggestion of a more rapid trajectory may be premature since this study used a cross-sectional design.

Synopsis of DTI in military mTBI

Many white matter tracts and regions exhibit changes in diffusivity following mTBI in military servicemen and servicewomen, though no region or cohesive set of regions are implicated consistently. Variability in analytical techniques and control group designs may contribute to these inconsistencies. None of the reviewed studies used orthopedic injured controls, the inclusion of which seemed to mitigate some of the group differences observed in the civilian mTBI literature. In general, the average age of veterans was consistent across studies (typically late 20's to late 30's), as was the predominant inclusion of males – many studies exclusively studied servicemen. As a result, caution should be exercised when attempting to generalize findings to servicewomen, and more research is necessary to examine military mTBI in females. Military DTI literature is somewhat uniquely complicated by the presence of PTSD and other comorbid conditions. Current research in this area does not consistently implicate PTSD as being associated with a replicable pattern of white matter abnormalities, while firmer support exists for the significant negative effects of LOC at time of injury on white matter integrity. Military mTBI studies encompass broad and variable intervals between injury and assessment, and most studies include veterans over two years out from their mTBI. This potentially introduces important confounds into the mix, including the high incidence of comorbid mood and substance use disorders observed in these samples. Recent findings indicate that blast exposure alone (with or without concomitant mTBI diagnosis) may have negative effects on white matter integrity and further research should attempt to track and quantify blast exposure more precisely and accurately, to the extent possible. Accounting for the overlap in PTSD and mTBI symptoms, major depressive disorder, substance use, adjustment disorders post-deployment, effects of blast exposure, and the general logistical considerations associated with systematically, and longitudinally, studying servicemen and women poses great challenges for researchers in this field.

DTI findings in sports-related mTBI

Many of the logistical challenges seen with civilian and military mTBI research are less problematic in studies of sport-related mTBI. Athletes, particularly within organized sports, undergo relatively consistent medical supervision and, in the event of sustaining a concussion, formal concussion

management protocols prescribe systematic assessments across multiple time points. This creates a favorable environment for clinical research particularly at collegiate and professional levels of participation. A great deal can be, and has been, learned from studying athletes and applying results to other populations. However, there are athlete-specific considerations that may not generalize to other populations. Table 3 summarizes findings from reviewed studies on concussion in athletes using DTI.

Acute (DTI within approximately 2–3 weeks from injury)

The reviewed athlete studies with acute assessments utilized longitudinal designs extending beyond the acute time frame. Studies with multiple assessment points and imaging during the acute window are included here. Henry et al. (2011) examined collegiate football players within five days of injury and again six months later compared to a group of football players with no concussion history. Concussed football players had higher FA in the CC and CST, higher AD in the CST, and lower MD in the bCC and CST. These changes were seen both acutely and at six-month follow up. Importantly, there was no main effect of time or group by time interaction, indicating that these changes remained stable over time for both groups. Diffusion metrics did not correlate with symptom scores**.** Jing et al. similarly found higher FA in the white matter skeleton of concussed college football players (n = 3) within 24 h, one week post-injury, and two weeks post-injury compared to controls, but no within-group changes over time (Jing et al. 2015). Murugavel et al. (2014) reported inconsistent DTI findings of concussed contact sport collegiate athletes and non-concussed noncontact collegiate athlete controls at three time points (two days, two weeks, and two months after injury). Within-group analysis of concussed athletes indicated they had higher radial diffusivity (RD) – thought to signify compromised myelin integrity – in the IC, IFL, IFOF, and ATR two days after injury than they did two weeks after injury. However, no longitudinal differences were noted for FA, RD, or AD between two days and two months after injury, or between the two week and two month time point. Compared with controls, concussed athletes exhibited lower whole-brain FA at two days and two months, but not at the two week assessment point. Longitudinal change was absent in an analysis comparing concussed contact athletes to non-concussed contact athlete controls. Between-group comparisons indicated that concussed athletes had *higher* FA in the SLF at time one (within approximately 2 days), time two (mean 8 days from injury), and time three (approximately one month from injury). Voxel clusters of higher FA were also noted in the sagittal stratum, superior cerebellar peduncle (SCP), IC, SLF, fMin, IFOF, and PCR at each time point. As with other longitudinal analyses, FA did not change within groups over time within any ROIs (Meier et al. 2016a). The lack of baseline (preinjury) neuroimaging complicates interpretation of findings from the reviewed longitudinal studies because within- and between-group changes from baseline cannot be examined.

Subacute/chronic (DTI between approximately one month and one year post-mTBI)

The neuroimaging literature on subacute/chronic sports-related mTBI contains conflicting findings. Zhang et al. (2010) found that one month after sustaining a concussion, injured athletes did not differ from non-concussed athlete controls on whole-brain FA or ADC, or within selected ROIs. Although group differences were not significant, wider variability in FA and ADC was seen in the concussed group**.** Other studies have reported no differences between concussed athletes and controls assessed more than six months after injury. List and colleagues specifically examined frontotemporal and hippocampal ROIs and reported no FA or MD differences (List et al. 2015); similarly, Meier et al. (2016b) found no FA differences in any ROI for their collegiate athlete sample an average of 10 months post-concussion (Meier et al. 2016b)**.** Chamard et al. investigated whole brain and CC-specific ROIs and showed concussed athletes exhibited no FA differences compared to controls, though lower MD, RD, and AD were noted in different regions of the CC (Chamard et al. 2015). These differences were relatively weak and likely would not have survived adjustments for multiple comparisons, had they been performed. In a separate study of athletes who had sustained concussion an average of 19.5 months earlier, FA differences were again largely absent between concussed athletes and non-concussed controls except for lower FA seen in the motor segment projection fibers of the CC. Additionally, voxel clusters of higher MD were found in the fMin, IFOF, cingulum, UF, ILF, ATR, SLF, and CST (Chamard et al. 2014)**.** Authors apparently matched concussed athletes with controls from the same sport, but use of contact versus non-contact sports is unmentioned. Cubon et al. found higher MD, but no differences in FA, in a group of concussed athletes with symptoms persisting greater than one month post-injury (mean time 115 days). Regional MD elevations compared to a mix of noncontact and contact control athletes included the ILF, IFOF, IC, PTR, acoustic radiations, and SLF (Cubon et al. 2011). A study of concussed collegiate male and female hockey players compared diffusion metrics to non-concussed collegiate male and female hockey athlete controls and found higher FA for the concussed group in the CR, PLIC, and multiple areas of cortical white matter. Lower RD was noted in the gCC, CR, PLIC, ALIC, cerebral peduncles, and both frontal and temporal white matter. As in previous studies, no diffusivity measure correlated with symptom scores or cognitive performance (Sasaki et al. 2014)**.**

DTI in retired athlete studies

Concern over the potential long-term effects of concussion/mTBI, as well as exposure risk of repetitive brain trauma, has heightened interest in studying the brains of retired athletes, particularly following careers in football or other collision sports. The studies reviewed in this section reflect an overlap of the effects of exposure to repetitive brain trauma and remote concussion history, since all studies were performed years after subjects retired from collision sports and do not isolate single or most recent concussion-events. In one of the first DTI studies of retired National Football League (NFL) players, Strain et al. (2013) compared 26 retirees (mean age 58 years) to 22 non-athlete controls and specifically examined differences in white matter integrity in depressed versus non-depressed athletes. Within the retiree group, they found no differences between depressed and non-depressed participants in terms of NFL experience or concussion history, contrary to previously described correlations between concussion and development of depression (Guskiewicz et al. 2007). Additionally, depression symptoms correlated negatively with FA in the fMin, SLF, and UF. No FA differences were observed between healthy non-athlete controls and non-depressed retired NFL athletes, suggesting that depression, in particular, may influence FA independent of mTBI history (Strain et al. 2013). Hart et al. also reported a potential effect of symptom presence, noting symptomatic retired NFL athletes had lower FA in regions of their frontal, parietal, and temporal lobe, as well as the CC, compared to asymptomatic retired NFL athletes and non-athlete controls (Hart et al. 2013). Casson et al. described a slightly younger cohort of retired NFL players (mean age 46 years) and assessed the relationships between white matter integrity and multiple risk factors. They found that whole-brain peak FA correlated negatively with the number of concussions sustained while playing in the NFL (i.e. those with more concussions had lower peak FA), but it was not associated with current depressive symptoms or cognitive abilities. In addition to concussion effects, FA was associated with inappropriate alcohol consumption, employment status, and pre-high school football exposure (the latter likely an indicator of lifelong exposure to repetitive brain trauma). These results suggested that, in addition to concussion and repetitive brain trauma, other lifestyle and psychosocial factors influence white matter microstructure (Casson et al. 2014). Tremblay and colleagues described more widespread differences in their analysis of previous collegiate football and hockey players with no professional experience. Compared to a control group of former collegiate football and hockey athletes with no history of concussion (mean age 58 years), those with a history of concussion (mean age 60 years) had both lower FA and higher MD in the bCC, gCC, fMin, SLF, IFOF, ALIC, and CR. All former collegiate athletes with a history of concussion were considered cognitively normal at enrollment (Tremblay et al. 2014). The most recent reviewed DTI study of retired collision sport athletes found fewer regional and diffusion differences than Tremblay et al. when investigating retired Canadian Football League (CFL) athletes. Retired CFL athletes had higher AD in the SLF, CST, and ATR, but no differences for FA, RD, or MD (Multani et al. 2016).

DTI following repetitive brain trauma in current athletes

Multiple studies have investigated the effects of repetitive subclinical head impacts in athletes (i.e. a period of time with no reported diagnosed concussion). Results are mixed. Early studies by Chappell et al. examined current male boxers and found lower FA in the IC, IFOF, ILF, and CST compared to non-boxer controls (Chappell et al. 2006; Chappell et al. 2008). Shin et al. (2014) also studied boxers, as well as mixed martial artists (MMA), and determined the number of times a fighter was knocked out predicted decreased FA in the CC. Soccer players have received attention due to the relatively frequent occurrence of head-to-ball contact in the sport, albeit less often and of less magnitude than many of the impacts associated with football, hockey, or boxing. Quantification of soccer heading is difficult and often relies on athlete self-report. Koerte et al. (2012a) compared a group of current elite soccer players (mean age 19.7 years) to a control athlete group of swimmers and found soccer players had higher RD in orbitofrontal white matter, the gCC, IFOF, OR, cingulum, CR, ALIC, EC, and white matter subserving the superior frontal gyrus (SFG). Athlete groups did not differ in FA or MD. This study did not attempt to quantify head impact exposure, and neither age nor years playing soccer were associated with observed differences; therefore, attributing higher RD in this sample to heading in soccer may be premature (Koerte et al. 2012a). However, Lipton et al. (2013) did quantify heading exposure, and reported lower FA within temporo-occipital white matter associated with greater heading exposure, which was associated with poorer memory performance.

The remaining reviewed studies in this area employed a pre- and post-season testing design assessing the effects of a season of collision sport participation on DTI outcomes. Gajawelli et al. (2013) compared a group of contact and non-contact sport athletes before and after one season and reported main effects of group on both MD and FA in the IFOF, CR, and CC (direction of differences not reported). They found no changes from pre- to post-season for either athlete group. In another study, collegiate football players studied over the course of one season experienced a significant increase in percentage of voxels throughout the brain with low FA and both low and high MD, localized to the CC, compared to non-athlete controls. These changes persisted six months after the end of the season (Bazarian et al. 2014).

A larger study of both football and male and female collegiate hockey athletes found no effect of one season of contact exposure on FA or MD in any of the examined ROIs. That study used the Head Impact Telemetry System (HITS) to track impacts during the season and, despite no statistical change in diffusion metrics from pre- to post-season, head impact exposure during the season quantified with HITS correlated with diffusion metrics in the CC, amygdala, cerebellar white matter, and hippocampus (McAllister et al. 2014). Koerte et al. reported higher post-season AD and RD in the CR and IC for a group of male hockey athletes compared to their own preseason values; no FA differences were found and three of the 17 athletes in the sample (18%) sustained a concussion during the season without subsequent exclusion from postseason analysis (Koerte et al. 2012b).

Synopsis of DTI in adult athlete mTBI

In these studies, acute mTBI-related changes in diffusion metrics were inconsistent in regions affected and directions of differences. Although many studies have used DTI to uncover abnormalities in specific white matter tracts after mTBI, no consistent pattern of tract or system damage has emerged. The reviewed studies of acute changes were all longitudinal design investigations, though none found within-group changes over time with the exception of one finding that RD increased from two days to two weeks after injury in various white matter tracts. These studies differed in terms of their control group comparisons. The two studies with contact sport athlete controls showed that concussed contact athletes had *higher* FA than controls, while the one study with noncontact athlete controls revealed *lower* FA in concussed athletes. Given that repetitive brain trauma in the absence of diagnosed concussion can have deleterious effects on white matter integrity, it is conceivable that contact sport athletes serving as controls (even while excluding based on previous history of concussion) may have sustained sufficient subclinical trauma to eliminate group differences when they are compared to athletes with single-event clinically defined concussion. In other words, the cumulative effects of subclinical impacts in a contact athlete control group may mimic changes associated with a concussion in an experimental group. Further supporting this, we have also observed a trend of higher FA in concussed athletes compared to contact athlete control groups in the subacute/chronic stage.

Regarding retired athletes, research in retired athletes faces many of the same challenges as military mTBI research, in that numerous comorbidities and confounding factors interfere with the ability to attribute group differences in white matter integrity to a mTBI per se. For example, the five depressed retired NFL subjects described in the Strain et al. study reported depression onset either immediately after retiring (4/5) or following a career-ending concussion (1/5). With or without a history of concussion or repetitive brain trauma, such major lifestyle adjustments and, for many, loss of personal identity, are independent risk factors for depression, and depression alone has been associated with white matter differences (further described below). Proper control comparisons are integral for this research, in particular. Few studies of retired athletes utilize retired athlete controls, and those that do often have poorly matched control groups in terms of racial/ethnic makeup, age differences, and/or developmental history factors. In this population, age- and education-matching is likely not sufficient given the discrepancy between years of education and intellectual capacity of some retired athletes (Ganim 2014). A great deal more research is needed to better understand the long-term implications of concussion or mTBI, as well as repetitive subclinical brain trauma, on both structural and functional outcomes later in life. The use of comparison/control groups that allow researchers to rule out reasonable alternative explanations of white matter abnormalities in the mTBI group is especially critical.

Summary of DTI in mTBI

DTI is regarded widely as holding promise in furthering our understanding of the microstructural effects of mTBI based on its purported ability to detect group differences in various diffusion metrics interpreted as clinically meaningful. Most authors conclude DTI can provide incremental knowledge to the mTBI research-base and is uniquely suited for studying these injuries. The above review supports the general conclusion that that DTI can sensitively detect differences in mTBI patients, but that evidence for the specificity of these findings is currently low. Many studies do not find differences between mTBI and control groups in diffusion metrics, and the few longitudinal studies undertaken have not shown consistent changes in FA, MD, or other metrics. Significant between-study variability exists in the specific white matter tract(s) or regions that are damaged. Additionally, while beyond the scope of this review, there also appear to be inconsistent relationships between DTI outcomes and symptoms or cognitive profiles. The degree of variability in study design, analytic techniques, and DTI scanning parameters likely contribute to the variable results. Clinicians and researchers alike would benefit substantially from a more standardized approach to DTI-based studies in mTBI.

We found no obvious, consistent group differences in presence or location of DTI-related white matter abnormalities, primarily because most white matter fibers and tracts within the brain exhibited statistical differences in one study or another and the direction of the diffusion metric differences also varied. This is certainly consistent with the heterogeneous nature of mTBI and the previously described diffuse susceptibility of axons to shearing injury. Gardner et al. reached a

similar conclusion in their systematic review of sport-related concussion and DTI, noting inconsistent regional differences, though with an apparent trend towards findings in the longitudinal fasciculi, corpus callosum, and internal capsules.

Despite an inability to identify data consistency or specific anatomical markers of mTBI from DTI studies, important sample differences were apparent. We found the characteristics of injury severity to be quite different between populations and samples despite all being categorized as "mild traumatic brain injury" or "concussion." The civilian literature contained a substantial number of subjects with abnormalities on conventional imaging techniques such as CT or structural MRI. For both civilian and military studies, concomitant loss of consciousness at the time of injury was commonplace. Within the sports concussion literature, presence of abnormality on conventional neuroimaging was often exclusionary, and incidence of LOC was frequently negligible or completely absent. Similarly, military subjects with mTBI presented with significant PTSD and depression symptoms more often than not, and at a comparatively much higher rate than civilians or athletes. Significant variability existed in the age of the subjects, with civilian and military studies typically using inclusion criteria of 18–65 years old and average participant age in the mid- to late- 30's (with wide ranges and high standard deviations). Adult athlete studies, on the other hand, were largely either limited to collegiate athletes with narrow age (between 18 and 25 years old), or older retired athletes with much wider age ranges (anywhere from 30 to 79 years old). Finally, the civilian literature offered a relatively good balance of male and female subjects, while male participants dominate military and athlete studies.

One important conclusion from this review is that the nature of the control group appears to be critical in determining results. In the civilian mTBI literature, comparisons of mTBI subjects to orthopedic injured controls resulted consistently in an absence of FA group differences, and only sporadic findings of differences in other diffusivity measures. Diffusion differences in military studies appeared somewhat attenuated when using veteran controls with blast exposure versus blast-unexposed. In similar fashion, the only instances where we observed the counterintuitive findings of higher FA in concussed athletes were when studies used contact sport athletes as controls. Taken together, these findings highlight the need for appropriate, consistent control group comparisons and the need to incorporate more than one control group, in order to more precisely attribute causality to any white matter abnormalities that may be found.

A small number of studies examined groups of subjects with persistent symptomatology and attempted to correlate their self-reported complaints with underlying changes in white matter structure. Postconcussion syndrome (PCS), major depressive disorder (MDD), and posttraumatic stress disorder (PTSD) have significant symptom overlap, and DTI outcomes in adult mTBI studies were inconsistently associated with these disorders. Athlete and military studies both implicated a unique effect of depression on diffusion metrics above and beyond mTBI. PCS in the civilian literature tended to result in more significant group differences compared to controls and those with mTBI but no PCS, but diffusion outcomes showed poor ability to differentiate those with or without PCS. In military studies, PTSD did not uniquely correlate with diffusion outcomes and generally did not demonstrate an additive effect to mTBI-attributed changes.

DTI findings from other medical and demographic influences

In the mTBI population, demographic factors and medical comorbidities affected both brain structure and function independent of the effects unique to the TBI itself. Conceivably, these factors may account for many of the changes seen after injury. Here we briefly describe DTI studies investigating the effects of socioeconomic status (SES), depression (MDD), and attention-deficit hyperactivity disorder (ADHD). A more comprehensive review of how biopsychosocial factors may interact with history of brain trauma (either independently or in combination) to produce long-term cognitive, mood, and behavioral changes, is found in Asken et al. (2016c).

Developmental environment plays a critical role in early white matter growth, and poor initial development (from malnutrition or abuse) can manifest throughout the lifespan both structurally and functionally. Low SES families face more adversity and exposure to stress, which has been shown to correlate with lower FA in the gCC in a non-clinical sample (Paul et al. 2008). Childhood adversity predicted FA differences in the cingulum, UF, and IFOF in a group of adults with MDD where diffusion metrics did not differ based on depression status alone (Ugwu et al. 2015). DeRosse and colleagues indicated parental SES and a previous history of trauma predicted lower FA in the SLF in adulthood (DeRosse et al. 2014). Taken together, these results suggest adaptive responses to early life adversity may be associated with differential development of white matter microstructure. SES also influences later-life white matter integrity. Findings in older adults indicate correlations between SES, whole brain mean FA (Gianaros et al. 2012), and lower age-related white matter decline in the ACR and frontal white matter regions (Johnson et al. 2013a). Genetic factors interact with SES, consistent with gene-environment conceptualizations of development. Chiang et al. studied 705 twins and their siblings and found FA increases of up to 10% from adolescence to adulthood in most white matter regions. There was an age by heritability interaction whereby FA variance was more attributable to genetic factors during adolescence than adulthood in frontal white matter, the sCC, and ILF/IFOF region, indicating

environmental influences increase with age. They also reported that genetics interacted with SES such that higher SES was associated with higher heritability of FA in the thalamus, temporal white matter, and sCC (Chiang et al. 2011). Lastly, a common proxy for SES is years of education, which Natalie et al. found was positively associated with FA in the SLF and ACR (Natalie and Noble 2014). However, as we previously noted, years of education may misrepresent certain groups of adult athletes. Thus, estimates of IQ or educational achievement (e.g., grade-equivalent literacy) may be helpful in establishing appropriate cognitive expectations or defining control groups.

Mood disorders are among the most common psychiatric syndromes within the population as a whole, and depression is a common neuropsychiatric symptom of mTBI/concussion. MDD in the absence of brain injury can exert independent influences on diffusion metrics. The uncinate fasciculus (UF), in particular, may be related to depression as it connects emotional and memory circuitry in the brain. Bessette et al. (2014) showed adolescents with MDD had widespread regions of lower FA, including the UF, thalamic radiations, EC, CST, MCP, CR, bCC, gCC, cingulum, ILF, and IFOF. De Kwaasteniet et al. (2013) and Zhang et al. (2012) also reported lower FA in the UF for adults with MDD. Aghajani and colleagues (2014) reported findings in the opposite direction for the UF, indicating higher FA, higher AD, and lower RD, but with no correlation to symptom severity. High incidence of comorbid anxiety, ADHD, and behavior disorders within this sample may have contributed to discrepant directional findings. Other white matter tracts implicated in adults with MDD include the IC, gCC, and CR (Guo et al. 2012). Illness duration and severity (indicated by treatment resistance) may unduly influence group differences in diffusion metrics, suggested by findings of lower FA in the IFOF, SLF, fMaj, fMin, bCC, cingulum, and subregions of the UF in treatment resistant/chronic MDD patients compared to both healthy controls and patients with first episode MDD (de Diego-Adeliño et al. 2014). Further complicating matters, microstructural abnormalities may be present due to genetic predisposition even without manifest phenotypic MDD. Compared to controls, "high risk" adolescent and young adult subjects with a biological parent diagnosed with unipolar depression had lower FA in the cingulum, SLF, UF/IFOF region, and sCC (Huang et al. 2011). Frodl et al. (2010) replicated these findings in an older sample, but found high risk subjects had *higher* FA in the bCC, IFOF, SLF, EC, thalamus, and ATR. Childhood stress moderated this relationship such that those at high risk with childhood stress had higher FA in these regions than those at high risk without childhood stress. Interestingly, childhood stress effects were in the opposite direction for healthy controls who exhibited a negative correlation between stress and FA in each of these white matter regions (i.e. higher childhood stress associated with lower FA), indicating a complex interaction between childhood stress (environmental influence) and heritable depression risk (genetic influence).

ADHD affects upwards of 10% of American children (Putukian et al. 2011). ADHD impairs cognitive and behavioral functioning across the lifespan and is often one of the earlier developmental disorders. Diffusion studies in children and adolescents reported lower FA in the UF, ILF, CR, inferior cerebellar peduncle (ICP), and SLF (Nagel et al. 2011) with some evidence suggesting FA in the SLF was specifically associated with symptoms of inattention (Chiang et al. 2015). Hamilton et al. (2008) also found lower FA in the CST and SLF, but no differences in the cingulum, CC, fornix, UF, or IFOF/SFOF region. Other studies reporting diffusion metric differences showed findings in the opposite direction, such as higher FA in the cingulum, CR, UF, IFOF, ATR, and anterior forceps (Tamm et al. 2012; Chen et al. 2015). Two of the ADHD studies reviewed specifically described the cortical areas (grey matter) associated with the white matter regional differences in adolescents with ADHD. Silk et al. (2009) described higher FA in the white matter underlying occipito-parietal cortex (cingulum region), inferior frontal cortex (UF region), and inferior temporal cortex (ILF region). Du Lei et al. (2014) differentiated between ADHD subtypes (inattentive vs. combined inattentive/hyperactive) and reported that, compared to healthy controls, children with the inattentive subtype had higher RD in the occipital lobe and superior temporal gyrus (STG) and lower AD in the middle temporal gyrus (MTG). Combined-type subjects had more widespread differences including the middle frontal gyrus (MFG), supplementary motor area (SMA), precuneus, parahippocampal gyrus (PHG), and STG. When comparing between ADHD subtypes, the combined-type subjects had widespread areas of higher FA, RD, and AD. Sex-specific differences also were apparent, as King et al. (2015) showed adolescent males tended to have higher FA than females, except within ADHD subjects, where females had higher FA in the CST, ILF, and SLF. Conversely, Rossi et al. (2015) and Wolfers et al. (2015) investigated adolescents and adults, respectively, and reported no FA differences between ADHD subjects and healthy controls.

A few studies described the microstructural manifestation of ADHD diagnosis in adulthood. Shaw et al. (2015) compared adults with persistent ADHD from childhood, remitted ADHD from childhood, and adults without lifetime diagnosis, finding those with persistent ADHD had lower FA in the UF and IFOF than never-affected adults, and that those with remitted ADHD did not differ from the never-affected group, suggesting a negative influence of prolonged functional disturbance. However, a 33-year follow-up of adults with ADHD diagnosed in childhood revealed lower FA in the CR, SLF, PTR, IC, and sagittal stratum, irrespective of current ADHD symptoms or diagnosis (Cortese et al. 2013). Chaim et al.

(2014) investigated adults with ADHD and described differences based on cortical white matter projection areas, finding higher FA in the white matter underlying the SFG, MFG, cingulate gyrus, MTG, and postcentral gyrus.

Heritability studies suggested that white matter structure may not only be related to expression of ADHD symptoms, but also may be reflective of ADHD risk. Lawrence et al. (2013) compared children and adolescents diagnosed with ADHD to their unaffected siblings and a group of unaffected controls with no diagnosed siblings. They found no FA differences between groups, but both those with ADHD and their unaffected siblings had higher MD than controls in the ATR, fMin, and SLF. Unaffected siblings did not differ from their ADHD-diagnosed siblings for any white matter tract, again suggesting genetic heritability of microstructural differences in the absence of phenotypic expression.

It was interesting some ADHD researchers described white matter changes relative to their cortical associations in light of our previous observation that reporting whole-tract versus voxel cluster-specific diffusion metrics may result in different outcomes (see the *Remote History* section of the military mTBI review). Study-to-study variability in referencing diffusion metric differences at the grey-white matter cortical junction (possible in voxel-based analyses) versus, for example, mean diffusion metrics of the entire white matter tract, may contribute to the discrepant findings of higher and lower diffusion metric values within the same tract across studies.

Summary of DTI findings from other medical and demographic influences

Research of SES, MDD, and ADHD indicates overlap with many of the reported DTI findings in mTBI. Regional differences were generally widespread but inconsistent, though the uncinate fasciculus may be more specific to depression. Direction of differences in diffusion metrics was also similarly variable. Reporting styles in some ADHD studies (white matter underlying specific cortical regions) may provide insight into the inconsistent findings of higher versus lower diffusion metrics within the same white matter tract between studies. SES, MDD, and ADHD diffusion studies indicate early-life influences often continue to be expressed in adulthood, either structurally, functionally, or both. Civilian, military, and athlete populations represent different demographics; thus, consideration of racial/ethnic makeup (as a potential proxy for SES) is warranted, especially when choosing appropriate control group comparisons. Additionally, studies indicated that subjects with genetic predisposition to MDD or ADHD, even in the absence of clinical expression, still exhibited microstructural differences similar to those with a diagnosed condition. This may provide the impetus for adjusting inclusion and exclusion criteria in mTBI studies to either 1) include and control for individuals either diagnosed with the condition or with a genetic predisposition, or 2) exclude subjects not only with the condition diagnosed but also with predisposition (i.e. immediate family member with disorder). Importantly, the microstructural abnormalities described in studies of SES, MDD, and ADHD did not appear to result from mechanical deformation of axons. In other words, while DTI is considered particularly applicable to studying mTBI because of its purported ability to detect the microscopic damage in axons, non-traumatic factors also clearly influence diffusion metrics. It is important to note that the review of these non-mTBI factors was not systematic in nature and is limited by potential article sampling bias.

Conclusions

We reviewed DTI studies of mTBI in adult civilian, military, and athletic populations. We anticipated these distinct groups would require separate consideration, and various aspects of the study characteristics supported this hypothesis. Inspection of study designs and results also revealed potential explanations for discrepant DTI findings, such as control group variability (e.g. healthy vs. orthopedic injured controls, contact versus noncontact athletes, etc.), analytic techniques and manner of reporting regional differences (e.g., entire tract mean diffusion metrics vs. voxel clusters at certain points along the tract), and the presence or absence of persistent functional disturbances at enrollment. DTI studies reviewed within the SES, MDD, and ADHD literature indicated significant overlap with mTBI studies in terms of the white matter tracts and fibers that differ between experimental and control groups. While mTBI studies often excluded subjects based on certain medical history factors, criteria were inconsistent and data suggested that the absence of a clinical diagnosis did not ensure absence of disorder-related features. Researchers may derive greater benefit from *including* rather than *excluding* due to common medical conditions. If sample size is sufficient to include necessary covariates (i.e. SES indices, mood scales, etc.), this will improve generalizability and confidence in assigning causality or attribution to results. We conclude DTI is sensitive to a wide range of group differences in diffusion metrics, but currently lacks the necessary specificity for meaningful clinical application. DTI research would benefit from more standardized imaging and analytic approaches. Properly controlled longitudinal studies with more consistent correlation to functional outcomes are needed before determining the ultimate utility of DTI in the clinical management of mTBI and concussion.

Glossary of terms

Abbreviation	Term
Anatomical Regions	
IC	Internal capsule
ALIC	Anterior limb of the internal capsule
PLIC	Posterior limb of the internal capsule
CC	Corpus callosum
gCC	Genu of the corpus callosum
bCC	Body of the corpus callosum
sCC	Splenium of the corpus callosum
SLF	Superior longitudinal fasciculus
ILF	Inferior longitudinal fasciculus
IFOF	Inferior fronto-occipital fasciculus
SFOF	Superior fronto-occipital fasciculus
EC	External capsule
UF	Uncinate fasciculus
CR	Corona radiata
ACR	Anterior corona radiata
PCR	Posterior corona radiata
ICP	Inferior cerebellar peduncle
MCP	Middle cerebellar peduncle
SCP	Superior cerebellar peduncle
CST	Corticospinal tract
OR	Optic radiations
ATR	Anterior thalamic radiations
PTR	Posterior thalamic radiations
fMin	Forceps minor
fMaj	Forceps major
SFG	Superior frontal gyrus
MFG	Middle frontal gyrus
IFG	Inferior frontal gyrus
STG	Superior temporal gyrus
MTG	Middle temporal gyrus
PHG	Parahippocampal gyrus
SMA	Supplementary motor area
Other Terms	
mTBI	Mild traumatic brain injury
DTI	Diffusion tensor imaging
WM	White matter
ROI	Region of interest
FA	Fractional anisotropy
MD	Mean diffusivity
AD	Axial diffusivity
RD	Radial diffusivity
ADC	Apparent diffusion coefficient
ADHD	Attention-deficit hyperactivity disorder
MDD	Major depressive disorder
SES	Socioeconomic status
PTSD	Posttraumatic stress disorder

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