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Diffusion MRI in pediatric brain injury

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Abstract

Traumatic brain injury (TBI) is a major public health issue around the world and can be especially devastating in children as TBI can derail cognitive and social development. White matter (WM) is particularly vulnerable to disruption post-TBI, as myelination is ongoing during this period. Diffusion magnetic resonance imaging (dMRI) is a versatile modality for identifying and quantifying WM disruption and can detect diffuse axonal injury (DAI or TAI (traumatic axonal injury)). This review covers dMRI studies of pediatric TBI, including mild to severe injuries, and covering all periods post-injury. While there have been considerable advances in our understanding of pediatric TBI through the use of dMRI, there are still large gaps in our knowledge, which will be filled in by larger studies and more longitudinal studies. Heterogeneity post-injury is an obstacle in all TBI studies, but we expect that larger better-characterized samples will aid in identifying clinically meaningful subgroups within the pediatric TBI patient population.

Keywords

Traumatic brain injury; Diffusion MRI; Diffuse axonal injury; Pediatric; Concussion

Compliance with ethical standards

Conflicts of interest Dr. Giza reports consultant fees from NFL-Neurological Care Program, NHLPA, Pearson PLC, Alcobra, Neural Analytics, serves on the advisory panel for the Major League Soccer, NCAA, US Soccer Federation, California State Athletic Commission, and has received speaker fees from Medical Education Speakers Network.

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children and can cause significant white matter (WM) disruption. These disruptions are associated with cognitive dysfunction and can persist for years post-injury. Disruptions to the *corpus callosum* (CC) are common and are associated with difficulties in cognitive tasks and motor coordination [1–4]. With diffusion MRI (dMRI), researchers can model the WM tracts and quantify the level of organization. dMRI assesses the diffusion of water in the brain by measuring the Brownian motion of water at thousands of points across the brain. Diffuse axonal injury (DAI) is common in TBI, especially in more severe injuries. DAI results from the shearing forces experienced during injury, when neurons are stretched, disrupting ion balance and action potential propagation. DAI can only be definitively diagnosed postmortem, but dMRI is more sensitive to DAI than other imaging modalities such as CT (computed tomography) and conventional MRI. Outcome post-injury is heterogeneous and is only partly explained by indices of acute injury severity. Advanced brain imaging, such as dMRI, holds the potential to reveal biomarkers of injury and recovery that can improve our understanding of this process and facilitate the assessment of new treatments.

Diffusion MRI models the diffusion of water in the brain, by collecting data across multiple directions (at least 6) equally distributed around a sphere. Higher angular resolution sequences are generally better at resolving of crossing fibers, as more detailed diffusion data is collected, but this is only to a point [5]. In each voxel of the brain image, diffusion is represented as an ellipsoid, modeling the diffusion in various directions. Diffusion along the primary eigenvector (primary axis of diffusion—along the fiber bundle) is known as axial diffusivity (AxD); radial diffusivity (RD) is the average of diffusion in the two non-primary directions, perpendicular to the fiber bundle, and mean diffusivity (MD, also called ADC (apparent diffusion coefficient)) is the average of diffusion in all three directions. The most commonly used measure of white matter organization is fractional anisotropy (FA). FA is a ratio of diffusion in all directions, calculated using Eq. 1:

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{\left(\lambda_1 - \hat{\lambda}\right)^2 + \left(\lambda_2 - \hat{\lambda}\right)^2 + \left(\lambda_3 - \hat{\lambda}\right)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (1)$$

It has a scale of 0–1, with 0 meaning perfectly isotropic diffusion (in all directions equally), and 1 meaning perfectly anisotropic diffusion (in only 1 direction). Low FA indicates that the WM organization has been compromised, indicating potential demyelination, inflammation, Wallerian degeneration, or other disruptions to the WM microstructure.

Methods to analyze dMRI data generally fall into five categories, described here in order from basic to more involved. The first is the ROI (region of interest) approach, where microstructural information is averaged across a particular region. The ROI approach is the simplest and requires a prior hypothesis to drive the selection of the ROI, but can be well-powered as averaging the signal over a region can reduce the impact of noise or signal variation. The second approach is the whole-brain voxel-based analysis (VBA), in which

measures are assessed voxel-by-voxel, across the whole WM. VBA does not require a prior hypothesis, but with thousands of voxels to correct across for multiple comparisons, it may not be as well-powered as the ROI approach, although it can be better powered to detect diffuse effects that may not coincide with any one ROI. The third approach is TBSS (tract-based spatial statistics), part of the FSL package [6]. In TBSS, microstructural measures are projected onto a skeleton of the WM. In this way, TBSS limits data dimensionality relative to VBA, improving power, while not requiring prior hypotheses. The fourth category is tractography, in which the vector information in each voxel is used to reconstruct the WM fiber tracts, and microstructural measures can be sampled along a tract. The benefit of tractography is that disrupted areas can be localized to tracts, whereas in voxel-based approaches, this depends on using an atlas, and areas where multiple tracts cross cannot usually be further identified. By identifying affected tracts, ties to neurobehavioral dysfunction can more definitively be made, based on literature in healthy individuals identifying which tracts underlie particular functional domains. Combining the fiber tracts with a cortical parcellation, one can create connectivity matrices, where the nodes are cortical regions, and edges are the density of fibers connecting those regions, the basis of the fifth approach. Graph theory is a branch of mathematics that is concerned with network topology, and there are a number of local and global measures that can be calculated on a given matrix.

Moderate-severe TBI (msTBI), which is marked by a Glasgow Coma Scale (GCS) score of 3–12 [7], can lead to chronic disability, including motor, cognitive, academic, and emotional disturbances [8–12]. There is considerable heterogeneity in the neuropathology caused by TBI, which can be an obstacle to group-level analyses. Mild TBI (mTBI) or concussion makes up the majority of TBI cases, approximately three quarters of all TBI cases. Loss of consciousness either does not occur or is very brief, and the varied and often non-specific symptoms that do occur acutely make it difficult to diagnose at times. Most people recover within a few weeks of the injury, but some patients experience persistent disruptions to cognitive function, sleep, and mood, along with headaches. This has been termed post-concussion syndrome (PCS) and occurs in approximately 10–20% of children in the months to years post-injury [13, 14]. The heterogeneity of mild TBI often results in small effect sizes, making group-level analyses even more difficult than those including more severe brain injuries.

This review covers dMRI studies of closed head injury of all severities across patients under 18 years old. We included studies covering the range of post-injury periods, from 1 day to many years post-injury, but do not include cross-sectional studies with an excessively wide post-injury range (e.g., 1 day to 9 months), as the acute period is highly dynamic and can yield effects in the opposite direction to those from later periods. Some studies include pediatric patients along with adults, but these have not been included here, as ongoing brain development limits the conclusions that can be made from such studies. We are also not including studies of intentional brain injury, as the pathophysiology differs and the sociological factors surrounding child abuse require us to consider it a separate issue. We start with mTBI, from the acute to chronic periods. The review then moves to moderate and severe TBI (msTBI), from the acute to chronic periods, and ends with studies including the whole range of severity. As there are multiple dMRI methods, we have included these

processing details in the text, and in Tables 1 and 2. An important factor to consider is the use of overlapping samples across publications—these can give an impression of a larger body of pediatric TBI work, when it is in fact still a small field. In Tables 1 and 2, we attempted to identify overlapping samples, but we may have missed some due to differences in reporting details on sample ascertainment. Both sections end with special attention paid to longitudinal studies. Especially in children undergoing rapid brain and cognitive development, longitudinal studies are critical to delineate the post-injury trajectory. With the heterogeneity of TBI, more longitudinal studies are necessary to better understand the factors that impact recovery.

Mild brain injury

There are mixed results in studies of dMRI after mild, with both increases and decreases in FA being reported. The time post-injury is critical to consider, as different aspects of the recovery process will differentially affect dMRI measures (e.g., edema can lead to increases in FA). A recent review and meta-analysis of this issue in adults found FA increases in the acute phase, but decreases in symptomatic patients in the chronic phase [52]. The post-acute phase is marked by more heterogeneity, likely in part due to variability in the patient group and differences in the time course of recovery across patients. Adding development to this question complicates it further, as we expect FA to increase as myelination continues until around age 30.

Acute

Immediately following mTBI (or concussion), FA tends to be higher in patients, and MD/ADC and RD are both lower, relative to controls. Analyzing dMRI measures voxel-wise, researchers have shown these effects in the CC, *corona radiata*, along with frontal, temporal, and parietal WM [20, 24], and this correlates with symptoms [20]. Using tractography to focus on the CC reveals similar effects, with higher FA and lower MD in mTBI participants [17, 19], again correlated with symptom severity and cognitive difficulties. Focusing on the fornix, Yallampalli et al. found higher FA in TBI, along with poorer cognitive performance, suggesting that disruptions to the fornix underlie memory and processing speed deficits often seen post-injury [21]. Yuan et al. [26] used graph theory to investigate network topology post-injury, finding higher small-worldness, clustering, path length, and modularity. Longer path length indicates a less efficient network, as information has to traverse more connections to reach a given point. Higher clustering indicates greater segregation between different parts of the brain, as does higher modularity. This redundancy on a local level could be interpreted as adaptive, as local connections are supported to counteract disruptions to long-distance connections. Small-worldness reflects the balance between integration and segregation, and the increases seen here appear to be due to increased clustering, relative to changes in path length [26].

Post-acute

In the post-acute phase, studies again show higher FA and lower MD in concussed patients compared to healthy controls. The two studies included here study patients 2 weeks– 2 months post-injury. This has been shown in FA and MD averaged across the whole brain [23] (see Fig. 1), and specifically in the corpus callosum, anterior *corona radiata*, inferior

fronto-occipital fasciculus, inferior longitudinal fasciculus, anterior thalamic radiation, and uncinate [22] using TBSS. FA and MD were correlated with symptom severity as well. These results come from overlapping samples, however, so dMRI in the post-acute phase remains an understudied question. Publication bias may play a role here, as null findings are rarely reported. Also, the heterogeneity of the recovery period likely makes group analyses of mTBI at this point even more difficult.

Chronic

There are few cross-sectional studies of dMRI in the chronic post-concussion phase, likely because most disruptions have resolved in mild injury, and remaining disruptions are likely nominal and vary among patients. In adults, most studies of the chronic period are focused on individuals still reporting symptoms [52]. While not a study of chronic mTBI in children, Stamm et al. [53] showed that retired NFL players who had started playing tackle football before age 12 had lower FA and higher RD in the corpus callosum using tractography, suggesting that early exposure to repetitive head impacts might impact WM development [53]. While it is unlikely that such a binary variable truly represents risk, there may be a sensitive period of development during which head impacts cause more disruption. Larger studies are needed to truly understand this possibility.

Longitudinal studies

There have been several longitudinal studies of mTBI using dMRI. Mayer et al. (2012) examined patients 1–3 weeks post-injury, and again 3–5 months post-injury, using an ROI approach. They found higher FA and lower RD than healthy controls in the superior and anterior corona radiata, and the cerebellar peduncle at the first time point, which increased over time. Van Beek et al. [25] similarly found higher FA in mTBI patients 1 month post-injury, using tractography. Longitudinal effects were mixed over the next 5–7 months, with the splenium showing increases in FA in both groups, while the genu showed FA increases only in healthy controls [25]. While the mathematical performance of these patients improved over time, working memory performance did not. Two longitudinal studies on the same cohort examined change in adolescent athletes both pre- and post-season. Davenport et al. [16] and Bahrami et al. [18] found that a higher level of exposure to subconcussive impacts, as measured with helmet-based sensors, was associated with lower FA in the IFOF and SLF, and more voxels showing abnormal FA (2 SD above or below healthy controls) [16, 18]. These studies are small and thus more likely to be swayed by outliers. Additionally, impact sensors are an evolving technology, so results must be interpreted with caution.

Moderate-severe brain injury

Acute

There are few imaging studies of the acute time period in msTBI, likely because patients with more severe injuries may be in the hospital for an extended period, unable to complete a research study. The two studies that do include imaging during this time period include patients across the severity spectrum (mild to severe). These studies include partially overlapping datasets, with participants between 1 and 18 years old, and involved a scan in the first 2 weeks post-injury, followed by an assessment either 6–12 months post-injury [47]

or 1–3 years post-injury [45]. Using an ROI approach, researchers found that ADC (apparent diffusion coefficient) from the peripheral gray and white matter explained the level of disability [47] and later neurocognitive function [45].

Post-acute

The post-acute period, here clustering patients between 2 and 5 months post-injury, is largely marked by decreases in FA and increases in MD/ADC and RD. These differences are present in the frontal lobes [34, 36, 38, 42], temporal lobes [34, 42], cingulum bundle [28, 37, 38], uncinate [27, 38], and corpus callosum [34]. Focusing on the amygdala, Juranek et al. found higher MD in the amygdala and hippocampus [40]. Using tractography in overlapping samples, Levin et al. and Oni et al. found that higher frontal FA and lower RD were associated with higher scores on the GCS and GOS and faster reaction time, while McCauley et al. found that the WM integrity of the frontal WM and cingulum were related to a memory task [34, 36, 38]. Wilde et al. found that the WM integrity of a cingulum ROI was also correlated with reaction time [37]. Dividing patients into two groups based on interhemispheric transfer time, Dennis et al. found that one group had widespread deficits in WM integrity, while the other group showed minimal disruptions [43].

Chronic

Here, we consider the chronic phase to include studies at least 6 months post-injury, but often “chronic” is considered anything after the first year post-injury. Across the brain, researchers find lower FA in TBI, relative to healthy controls and those with milder injuries [32, 42, 50] (see Figs. 2 and 3). The corpus callosum in particular shows lower FA in TBI, which is associated with cognitive deficits [2, 41]. Expanding the set of ROIs examined, Yuan et al. and Kurowski et al. used the Johns Hopkins University (JHU) WM Atlas and found significantly lower FA in TBI, which was correlated with injury severity [33] and executive function [48]. These deficits also extend to the ventral striatum, which includes the nucleus accumbens, caudate, and olfactory tubercle. This may partially underlie difficulties in controlling inhibition, and other executive functions [44]. Tracts that support visuomotor function and posture are also disrupted, with lower FA in the corticospinal tract, posterior thalamic radiation, optic radiation, and cerebellum. These are associated with balance issues and poorer eye tracking performance [8, 35]. Using graph theory, Caeyenberghs et al. [39]also found longer path length in TBI and lower global efficiency, along with alterations to the network hubs. These alterations were correlated with deficits in executive function [39]. Adamson et al. found increased AD in TBI in the corpus callosum, *corona radiata*, internal capsule, and cerebellar peduncle, and when focusing on those voxels showing abnormal AD, also found significantly higher MD in TBI [49] (Fig. 4). The inclusion of patients classified as complicated mild may have obscured effects in this study however.

Longitudinal studies

Longitudinal studies of msTBI tell a mixed story—with some evidence of recovery paired with evidence of continued disruption. In two longitudinal studies of overlapping samples, Wu et al. and Wilde et al. found evidence of recovery, in FA increases and MD/ADC decreases, along with continuing disruption, in FA decreases and MD/ADC increases [1, 51] (see Fig. 3). Clinical and demographic factors may influence recovery as well: Ewing-Cobbs

et al. found signs of recovery in younger children but not in adolescents [29], and Genc et al. found greater recovery in patients with milder injuries [46]. Dennis et al. did not find a significant effect of age or severity, but found two subgroups of patients based on post-acute interhemispheric transfer time (IHTT). Those patients with significantly slower IHTT than healthy controls showed progressive decline in WM organization over time, while those with IHTTs within the healthy control range showed evidence of recovery [30]. Several studies have examined how dMRI measures in the acute or post-acute phase can predict chronic outcome. Higher FA and lower MD/ADC predict improved scores on tests of reading [28], executive function [27], and a global measure spanning nine cognitive domains [45]. Using a graph theory approach, Yuan et al. found higher small-worldness in the TBI group at time 1, which decreased over time [31]. Small-worldness is a ratio of clustering to path length, factors that individually show non-significant effects at time 1, but decreases in clustering appear to underlie the longitudinal changes in small-worldness. Unlike dMRI metrics, the direction of these results appears to be consistent across mTBI and msTBI, as Yuan et al. found similar effects after concussion [26].

Conclusions

Diffusion MRI is a useful and popular tool for examining WM disruptions after TBI, as evidenced by the increasing number of publications each year [54]. Here, we review recent work using dMRI to examine WM disruption in pediatric TBI. Mild TBI is typically marked by initial increases in FA relative to healthy controls that may continue over the next few months. While initial increases in FA may reflect edema and other acute neuropathology, higher FA after this period in mild injury is less likely to indicate such neuropathology, as cerebral edema following moderate-severe TBI generally resolves within the first 10 days [55]. There are many possible explanations behind the increased FA seen after mild TBI—axonal edema/swelling could lead to increased FA through the restriction of free water diffusion. Additionally, diffusivity measures are very likely impacted by interactions with nonneuronal cells, such as microglia. One study cited here included patients across the severity spectrum in the first several months post-injury [46]. They showed non-significantly higher FA in mild TBI, while severe TBI patients had significantly lower FA relative to healthy controls. The discrepancy between the acute effects seen in mild TBI and those seen in more severe injuries is likely due to differences in neuropathology—macroscopic injuries seen in more severe cases may be a larger factor than those at play in mild cases. We speculate that the higher FA that may be seen in mild TBI after the first 2 weeks may indicate recovery processes. Animal studies have shown that FA increases in areas of fiber reorganization and remyelination after injury [56, 57]. Repeated mild head impacts, however, are associated with decreased FA. Similarly, more severe head injury leads to decreased WM organization (decreased FA), which may recover in some patients or in some tracts, but can also become a continuing and progressing problem. The works cited here report disruptions to the WM organization in nearly every WM tract, but the corpus callosum is still the most commonly cited area of disruption.

The heterogeneity of TBI raises the question of why the field considers TBI patients as a singular group, when the data suggests this is not the case. It seems likely that identifying subgroups within the patient population based on clinical, demographic, and/or imaging

variables might advance our understanding of mechanisms of injury and recovery, as other fields have done [58]. However, the vast number of possible clinical and demographic variables makes identifying groups difficult. There are few studies that have reported age effects. Myelination continues through early adulthood, so we could hypothesize that younger children would show disruption in different tracts than older adolescents, or that those tracts that mature later are more likely to show disruptions, but this has not been thoroughly examined in the literature. Of the papers covered here, only Ewing-Cobbs et al. [29] reported a significant age effect, with adolescent patients not showing the same signs of recovery as younger patients. Beyond age, pubertal status might reveal some effects, as other studies have shown that hormones play a role in injury and recovery [59]. Through larger collaborative studies, such as the ENIGMA model [60–62], the CARE consortium [63], and TRACK-TBI study [64], this task will hopefully become easier. With a greater understanding of the factors that affect recovery from TBI, and especially those unique to developing children and adolescents, we will be able to reduce the morbidity of TBI.

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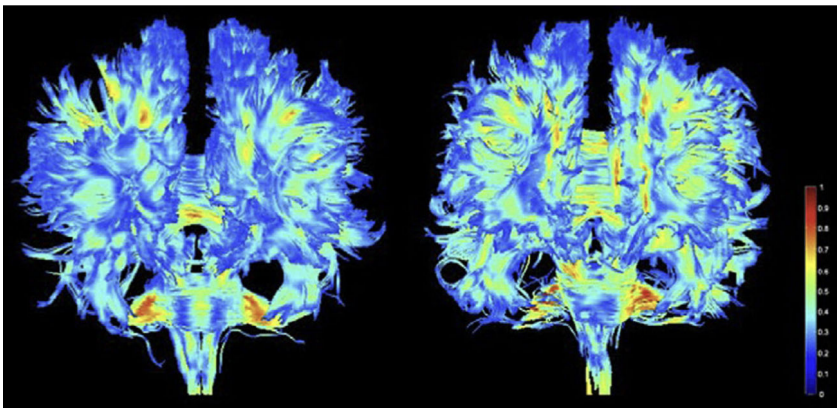

Fig. 1.

Whole-brain diffusion tensor imaging tractography for one healthy adolescent (*left*) and one adolescent after concussion (*right*). *Warmer colors* indicate higher fractional anisotropy, whereas *cooler colors* indicate lower fractional anisotropy values. Diffuse increases in white matter tract fractional anisotropy are present after injury compared with an uninjured brain, likely reflecting subtle tissue damage associated with concussion. Reprinted with permission from Virji-Babul et al. [23]

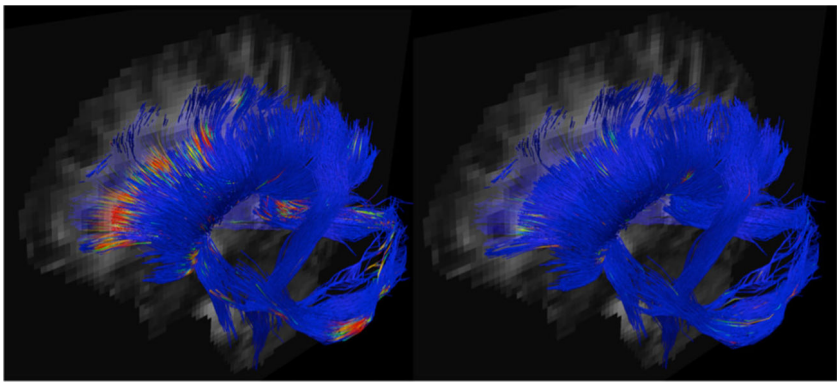

Fig. 2.

Differences between IHTT-slow and control groups (*left panel*), and between IHTT-normal and control (*right panel*) in FA of the frontal corpus callosum. The *p* values are shown corresponding to the color bar, and results are FDR corrected across all points on all tracts tested ($q < 0.05$)—*blue areas* are those at or above the FDR threshold (not significantly different). Adapted with permission from Dennis et al. [43]

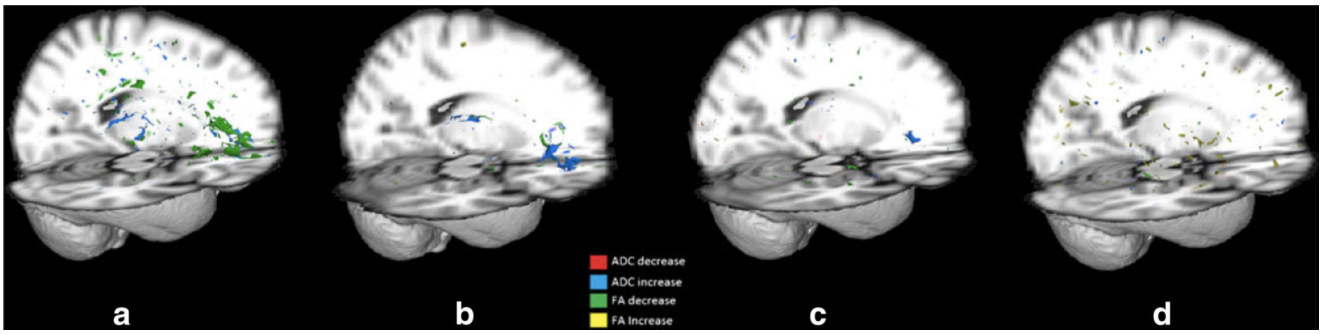

Fig. 3.

Part a illustrates group differences at 3 months post-injury in TBI versus OI participants derived from TBSS and rendered upon a series of three-dimensional T1-weighted images from a template image as this allows a more global perspective of changes occurring throughout the brain. Part b illustrates group TBI versus OI group differences at 18 months post-injury. Part c reflects changes within the TBI group (18–3 months), and part d reflects changes within the OI group over time. The following is applied to the TBI group in all comparisons (a–d): areas denoted in *red* represent areas of lower ADC, areas in *blue* indicate areas of higher ADC, areas in *green* represent areas of lower FA, and areas in *yellow* represent areas of higher FA. Reprinted with permission from Wilde et al. [51]

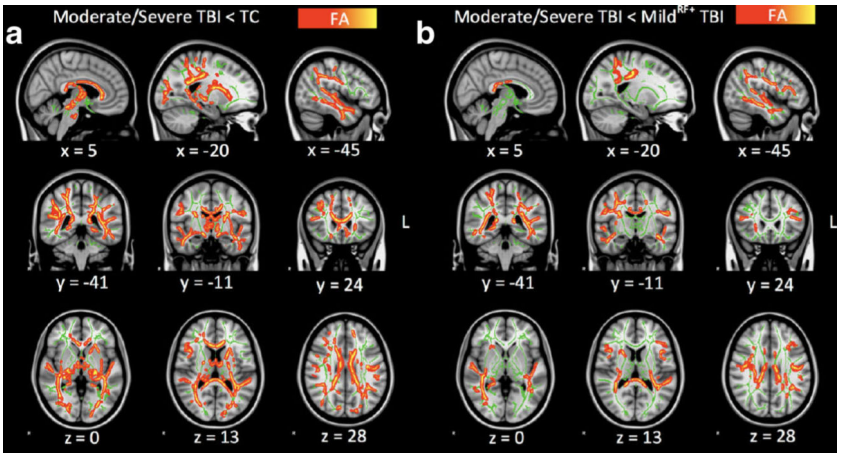

Fig. 4.

Voxel-wise comparison of FA maps using threshold-free cluster enhanced correction in TBSS. Note. Results of voxel-wise group comparisons showing the parts of the whole brain skeleton (at FA > 0.2, in *green*) with differences in terms of FA between the moderate/severe TBI group as compared to the TC group (a) and mild RF + TBI group (b). Lower values in the moderate/severe TBI group as compared to other groups are displayed in *red-yellow*. The results are overlaid on a MNI152 1 mm T1 brain in radiological convention (*right = left*), and for visualization purposes, regions in the whole brain skeleton with significant group differences were "thickened" towards the full width of the white matter tract. *TC* trauma control group, *TBI* traumatic brain injury, *FA* fractional anisotropy. Adapted with permission from Königs et al. [50]

Table 1

Characteristics of mTBI studies

Paper	Number	Age	Long/CSx	TSI	Method	Dataset
				Mild		
[15]	15 TBI/15 HC	10–17 years	Long	1–3 weeks, then 3–5 months	ROI	–
[16]	24 athletes	8–13 years	Long	Pre- and post-season	VBA	1
[17]	20 TBI/20 HC	7–13 years	Long	1 month, then 6–8 months	Tractography	2
[18]	25 athletes	8–13 years	Long	Pre- and post-season	Tractography	1
[19]	10 TBI/10 HC	14–19 years	CSx	1–6 days	Tractography	3
[20]	10 TBI/10 HC	14–17 years	CSx	1–6 days	VBA	3
[21]	11 TBI/11 HC	14–19 years	CSx	1–6 days	ROI	3
[22]	12 TBI/10 HC	13–17 years	CSx	Subacute (month or 2)	TBSS and tractography	4
[23]	12 TBI/10 HC	14–17 years	CSx	2 weeks–2 months	ROI	4
[24]	23 TBI/20 OI	11–16 years	CSx	Acute (days post-injury)	VBA	5
[25]	18 TBI/18 HC	7–13 years	CSx	6–30 days	Tractography	2
[26]	23 TBI/20 OI	11–16 years	CSx	Acute (days post-injury)	Graph theory	5

For each study included, we list the number of TBI subjects and orthopedic injury (OI) or healthy controls (HC), the age range of the subjects, whether the study was cross-sectional (CSx) or longitudinal, the time since injury (TSI) in months or years, the method used (described in “Introduction”), and a code to designate overlapping cohorts. Figure 1 is taken from the study highlighted in gray

Table 2

Characteristics of msTBI studies

Paper	Number	Age	Long/CSx	TSI	Method	Dataset
Moderate-severe (or complicated mild)						
[1]	23 TBI/25 OI	7–17 years	Long	3 and 18 months post-injury	ROI	6
[27]	15 TBI/15 OI	6–15 years	Long	Scan at 3 months, cog at 12 months	TBSS	7
[51]	20 TBI/21 OI	7–17 years	Long	3 and 18 months post-injury	TBSS	6
[28]	29 TBI/27 OI	6–16 years	Long	Scan at 3 months, cog at 12 months	TBSS	7
[29]	16 TBI/18 OI	6–15 years	Long	3 and 24 months post-injury	TBSS	7
[30]	21 TBI/20 HC	8–18 years	Long	2–6 and 13–19 months post-injury	Tractography	8
[31]	17 TBI/11 HC	9–19 years	Long	12 months+ and then 3 months later	Graph theory	
[2]	16 TBI/16 HC	8–17 years	CSx	1–10 years post-injury		
[32]	14 TBI/14 HC	10–18 years	CSx	6–12 months post-injury	ROI	
[33]	9 TBI/12 OI	6–9 years	CSx	>12 months post-injury	ROI	9
[34]	32 TBI/36 OI	7–17 years	CSx	3 months post-injury	Tractography	6
[35]	12 TBI/14 HC	8–20 years	CSx	9 months–years post-injury	Tractography	10
[8]	17 TBI/14 HC	8–20 years	CSx	9 months–years post-injury	Tractography	10
[36]	46 TBI/47 OI	8–16 years	CSx	3 months post-injury	Tractography	6
[37]	46 TBI/43 OI	7–17 years	CSx	3 months post-injury	ROI	6
[38]	40 TBI/37 OI	7–16 years	CSx	3 months	Tractography	6
[39]	12 TBI/17 HC	8–20 years	CSx	6 months–years post-injury	Graph theory	10
[40]	21 TBI/20 OI	6–16 years	CSx	Scan at 3 months	ROI	7
[41]	74 TBI/23 OI/23 HC	6–18 years	CSx	5 months–12 years post-injury	Tractography	7
[42]	28 TBI/28 HC	8–18 years	CSx	2–6 and 13–19 months post-injury	Tractography	8
[43]	28 TBI/28 HC	8–18 years	CSx	2–5 months post-injury	Tractography	8
[44]	21 TBI/18 HC	10–18 years	CSx 5–15 years post-injury		ROI	–
[45]	17 TBI	2–18 years	Long	Scan days post-injury, cog year(s)	ROI	–
Mild-severe						
[46]	15 TBI (larger CSx sample)	5–14 years	Long	Month or 2, then 2 years	TBSS	–
[47]	37 TBI/10 HC	1.5–18 years	Long	First 2 weeks post-injury	ROI	–
[48]	9 TBI/12 OI	3–7 years	CSx	1–3 years post-injury	ROI	9

Paper	Number	Age	Long/CSx	TSI	Method	Dataset
[49]	17 TBI/13 HC	12–17 years	CSx	1–3 years post-injury	TBSS	–
[50]	37 TBI/27 OI	8–14 years	CSx	Chronic (average 3 years)	TBSS	–

For each study included, we list the number of TBI subjects and orthopedic injury (OI) or healthy controls (HC), the age range of the subjects, whether the study was cross-sectional (CSx) or longitudinal, the time since injury (TSI) in months or years, the method used (described in “Introduction”), and a code to designate overlapping cohorts. Figures 2, 3, and 4 are taken from the study highlighted in gray