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Characteristic patterns of white matter tract injury in sport-related concussion: An image based meta-analysis

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ABSTRACT

Sports-related concussion (SRC) is sustained by millions of people per year, yet the spatiotemporal patterns of white matter (WM) injury remain poorly understood. Several SRC studies have implemented the standardised approach Tract-Based Spatial Statistics (TBSS). The aim of this image-based meta-analysis was to identify consensus patterns of SRC-related WM injury across TBSS studies. We included studies comparing the diffusion MRI measurement fractional anisotropy (FA) in SRC or subconcussive injury vs. controls using TBSS, as FA is the most frequently examined diffusion tensor imaging metric. Authors of eligible studies were contacted to request unthresholded statistical map outputs from TBSS, and image-based meta-analyses were performed using Seed-Based D-Mapping. Eight studies contributed to our meta-analyses, comprising 174 SRC or subconcussive injury participants and 160 controls. Our primary meta-analysis (n = 8), encompassing subjects with acute SRC (n = 2), chronic SRC (n = 4) and subconcussive injuries (n = 2) revealed dominant bilateral increased FA in the superior longitudinal fasciculus (SLF) and internal capsule. Subconcussive injury was associated with small clusters of increased and decreased FA in the arcuate fasciculus compared to control. In acute SRC, we found diffuse foci of raised FA at WM/grey matter border-zone associated with the bilateral SLF and right inferior fronto-occipital fasciculus. In contrast, chronic SRC had a pattern of deep WM alteration, asymmetrically located in the right optic radiations and arcuate fasciculus. Our findings represent the most powerful analysis of TBSS data in SRC, supporting the use of this approach to analyse diffusion data. TBSS is sensitive to WM abnormalities resulting from SRC or subconcussive injury over a range of temporal and clinical scenarios. Our data show spatially concordant patterns of WM injury unique to subconcussive, acute and chronic phases, highlighting the future utility of diffusion MRI for concussion diagnosis.

1. Introduction

Sports-related concussion (SRC) is a form of mild traumatic brain injury (mTBI) sustained by up to 3.8 million people per year (Langlois et al., 2006). SRC is induced by biomechanical forces occurring as a result of collisions sustained during contact sports (McCrory et al., 2017), with neurological, cognitive and vestibular consequences typically resolving over days and weeks, while neuropathology may persist for years (Churchill et al., 2019). The underlying pathobiology of SRC is complex and centred around diffuse alterations in axonal neuromechanics which are difficult to detect in vivo (Smith 2016), hence despite extensive research into sports concussion the spatial extent and patterns of white matter (WM) injury remain poorly understood. A major barrier is lack of objective tools to assess WM pathology in injured athletes, although advances in diffusion imaging and analysis highlight this as an increasingly sensitive technique for both detection and monitoring of WM pathology after concussion.

There is now substantial evidence for axonal injury acutely in response to primary injury and as a long-term perpetuation of secondary injury (McKee and Daneshvar 2015), however more recent attention has been paid to the effects of subconcussive injury and their long-term implications, including chronic traumatic encephalopathy (CTE) (McKee and Daneshvar 2015). Using accelerometer-instrumented helmets, athletes playing NFL football and ice hockey have been found to experience hundreds (if not thousands) of non-concussive head impacts

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in a single season (Bailes et al., 2013; Bazarian et al., 2014; Wright et al., 2018). Several studies have now found that these head impacts not eliciting concussive sequelae are still capable of causing WM alteration (Bazarian et al., 2014; Hirad et al., 2019), which may underlie neurophysiological changes (Bailes et al., 2013; Hirad et al., 2019).

Clinical assessment of SRC frequently includes neuroimaging via computerized tomography (CT) and conventional magnetic resonance imaging (MRI), however these methods lack specificity and are sensitive only to overt structural alterations. CT and conventional MRI are therefore primarily used to rule out skull fracture and haemorrhage rather than quantify white or grey matter pathology. Recent advances in neuroimaging – particularly diffusion MRI (dMRI) – now provide superior resolution, allowing for detection of microscale alterations in WM. dMRI techniques are a sensitive biophysical proxy for axonal pathology, since the motion of water relative to axons is extremely sensitive to changes in microstructure (Pierpaoli and Basser 1996). The most frequently assessed metric derived from dMRI (and specifically, diffusion tensor imaging, DTI) is fractional anisotropy (FA), which quantifies water diffusion relative to white matter tracts and is considered to reflect axonal density, diameter and tract complexity (Beaulieu 2002). A considerable drawback of dMRI is the difficulty in comparing WM changes across variable anatomy due to differences in head size, anatomy, and geometry (Yeh et al., 2009). These issues have made interpretation of FA data from multiple participants difficult, limiting clinical application. The tract-based spatial statistics (TBSS) analysis technique circumvents these issues via non-linear registration and projection of individual FA onto a mean FA 'skeleton', allowing direct comparison between participants and improving sensitivity and objectivity (Smith et al., 2006). TBSS has now been successfully applied to a wide range of neuropathology, with more recent uptake in the field of SRC. TBSS also permits combinations of data across studies - enabling image-based meta-analysis, and so improving power to detect unreported sub-threshold findings. This consideration is particularly important in the context of SRC, in which studies are often underpowered.

As reports of TBSS findings in SRC emerge it is important to clarify whether there are consistent findings in areas of altered FA across studies. It is also especially crucial to ascertain whether detected FA increases or decreases are spatiotemporally consistent across the short- and long-term, and whether similar profiles exist across sports and age groups. In order to address this, we performed a series of image-based meta-analyses using original statistical maps gathered from TBSS SRC studies. We aimed to identify 1) whether there was a statistical consensus for regional WM vulnerability across SRC and subconcussive injury regardless of time post-injury; 2) whether a different pattern of WM change was present in subconcussive hits; 3) whether a similar pattern of WM alteration was present in acute ($\leq$48 h) and chronic ($\geq$ 3 m) SRC.

2. Methods

This systematic review and meta-analyses were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. The study protocol was pre-registered on PROSPERO (CRD42019137337).

2.1. Literature search

A literature search was conducted to identify studies using TBSS for analysis of tract FA to evaluate white matter abnormalities in sport-related mTBI. We focused on the most common diffusion metric for inclusion into our primary group comparison of FA in mTBI exposure vs. controls. The search and screening processes was performed independently by two authors (VPBN & RNJ), with any disagreements resolved by consultation with co-authors (SCH & TW). Between November and December of 2018, the terms "white matter", "mTBI OR concussion" and "TBSS" were used to search the following electronic databases: Google Scholar, Web of Science, Pubmed, PsychINFO. Full texts of articles and their citations were downloaded and exported to Endnote (X7, Thompson Reuters, Ontario, Canada). References' titles and abstracts were screened to remove duplicate search results and any papers not addressing sport-related mTBI in humans. The remaining full text articles were screened to select only those using dMRI TBSS analyses. Reference lists of included articles were also searched for relevant studies that were not returned by our database search. Where multiple studies reported on the same participant cohort, data from the earlier of the studies was included.

2.2. Data collection

Corresponding authors of each article were contacted by e-mail to request the unthresholded TBSS 'T-statistic' outputs comparing mTBI participants to controls. T-statistic comprise statistical information from each voxel in the brain regardless of group-based significance, yielding superior information over coordinate-based significance data. We recorded the following study characteristics from each article: number of patients and controls, sport, mean age, gender and imaging parameters.

2.3. Risk of bias, methodological and imaging quality

Risk of bias and methodological quality were assessed using the Newcastle-Ottawa Scale (NOS), a 9-point scale based on participant selection, comparability and assessment (Wells et al., 2012). Imaging quality was assessed using the multiple parameter scale of Kmet (Kmet et al., 2004) adapted by Welton et al. (Welton et al., 2015).

2.4. Image-Based meta-analysis

Meta-analysis of the contributed TBSS *t*-statistic images was performed using Seed-Based D-Mapping (SDM; version 5.14) as described previously (Peters et al., 2012; Radua et al., 2012; Welton et al., 2015). As is standard for SDM analysis, the analytic parameters were set as a voxel threshold of $p < 0.005$, peak height threshold of SDM-$Z > 1.00$, and extent threshold of $\geq$ 10 voxels. A jackknife sensitivity analysis was also conducted to assess the robustness of the main meta-analysis. This was achieved by serially excluding each study and repeating the analysis.

3. Results

3.1. Literature search

224 articles were identified from our literature search (Fig. 1), of which 47 (21%) represented duplicate records. Of the 177 unique search results, 128 (73%) were excluded based on screening of their titles and abstracts because they did not analyse diffusion data from mTBI or subconcussive participants using TBSS. After reviewing full text articles, 45 further studies were excluded because they did not meet the full inclusion criteria (further information available in Supplemental methods). A final 24 articles met the inclusion criteria, and the corresponding authors were contacted to request statistical maps of TBSS FA analysis. Of these, we received eight datasets for inclusion in the meta-analysis. The remaining 16 contacted authors either were unable to share the data due to institutional, ethical or funding body restrictions regarding data sharing, or were unable to be contacted.

3.2. Sample demographics

The combined cohort included 334 participants, with 124 participants exposed to mTBI, 50 to subconcussive injury, and 160 controls (Table 1). The combined subject and control cohorts included in these

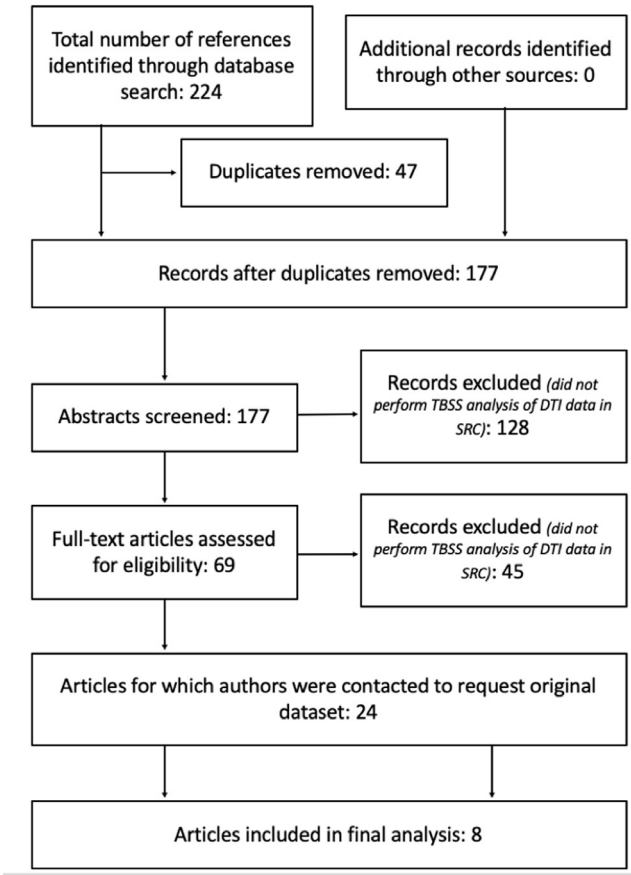

Fig. 1. PRISMA flow chart of the literature search. DTI, diffusion tensor imaging; SRC, sports-related concussion; TBSS, tract-based spatial statistics.

individual studies were of variable size, ranging from 24 to 62 participants, with a mean of 41.8 ± 14.2. There was a wide range of ages across studies with a bias toward younger, active participants: in the mTBI or subconcussive cohorts, mean age ranged from 17.6 to 56.7 years, with sample-size weighted mean of 29.0 ± 5.8 years. There was a predominance of male participants in all cohorts, with no studies exclusively focusing on females. Of the three studies including females with SRC, females comprised 15% (Mayer et al., 2017), 37% (Sasaki et al., 2014) and 50% (Zivadinov et al., 2018), with a sample-size weighted mean of 89.4% in favour of males.

Athletes were recruited across a range of sports: two studies examined collegiate (NCAA) football (American football) players (Mayinger et al., 2018; Mustafi et al., 2018), one combined high school and college American football players (Lancaster et al., 2016), and one recruited professional players in the Canadian football league (CFL) (Multani et al., 2016). Zivadinov and colleagues studied retired professional football (NFL) and ice hockey players recruited from players associations (Zivadinov et al., 2018), while Sasaki focused exclusively on ice hockey players (Sasaki et al., 2014). Two studies examined contact sports, enroling amateur boxers (Herweh et al., 2016) and mixed martial artists (Mayer et al., 2017). Five of the studies were conducted in the US (Lancaster et al., 2016; Mayer et al., 2017; Mayinger et al., 2018; Mustafi et al., 2018; Zivadinov et al., 2018), two in Canada (Sasaki et al., 2014; Multani et al., 2016) and one in Germany (Herweh et al., 2016). Two of the eight studies focused on subconcussive (or majority subconcussive) repetitive head impacts (Herweh et al., 2016; Mayinger et al., 2018), two acquired MRI scans in the acute phase within 48 h of injury (Lancaster et al., 2016; Mustafi et al., 2018), and the remaining four studies were conducted in the chronic post-injury phase (more than 3 months post-injury) (Sasaki et al., 2014; Multani et al., 2016; Mayer et al., 2017; Zivadinov et al., 2018).

3.3. Quality assessment and risk of bias

Supplementary Table 1 summarises the risk of bias and quality across the included studies. The mean NOS was 6.25 (1.75 SD) out of a possible score of 9, with an overall rating of 'fair'. Studies were assessed on criteria of selection, comparability and exposure/outcome, with comparability scores most problematic due to infrequent control of risk factors. For methodological quality of imaging, the average score was 10.1 ± 1.6 out of 13, with no study scoring <8. The most frequent unmet criteria were using b-values >1000 mm/s^2 and using a voxel size ≤2 mm.

3.4. Meta-analysis of FA in concussion-exposed vs. control participants

A total of 21 positive clusters were identified in which FA was increased over controls (Fig. 2 & Table 2), with no negative clusters. These extensive regions of concordance were bilateral (although more pronounced in the right hemisphere) and were found in the superior longitudinal fasciculus (SLF), arcuate fasciculus, retrolenticular part of the internal capsule, inferior fronto-occipital fasciculus and inferior longitudinal fasciculus. Of these, the two dominant clusters were located in the right SLF (178 voxels) and retrolenticular part of the internal capsule (128 voxels), with the remaining small clusters closely regionally associating with the primary clusters.

3.5. Sensitivity analysis

As shown in Supplementary Table 2, jackknife sensitivity analysis demonstrated that clusters of FA increase were highly replicable in the SLF, internal capsule (left and right retrolenticular), and arcuate fasciculus (left and right anterior, left long segment), with findings preserved across all combinations of 8 studies. The clusters of increased FA in the splenium were replicated in 6 of 8 studies, the left inferior occipitofrontal fasciculus and the right posterior corona radiata in 5 of 8 studies, while the least replicable cluster (of the largest 10 clusters) was located in the left corticospinal tract, replicated in 4 of 8 studies. No additional significant clusters were revealed by jackknife analysis.

3.6. Meta-analysis of FA in subconcussive vs. control participants

Subconcussive injury (n = 2 studies) was associated with bidirectional changes in FA. Three key clusters were demonstrated, with 9 further smaller clusters associating with the larger clusters (Fig. 3 & Supplementary Table 3). Two of the 3 dominant clusters were positive (i.e. increased FA) and were located in the posterior segment of the left arcuate fasciculus (12 voxels apiece). The negative cluster (decreased FA compared to control; 13 voxels) was found in the anterior segment of the right arcuate fasciculus. The arcuate fasciculus clusters overlapped with those present in the overall meta-analysis. In contrast, the negative arcuate fasciculus cluster was unique to this meta-analysis.

3.7. Meta-analysis of FA in acutely concussed sportspeople vs. control participants

Eight small positive clusters were found in acute concussion (n = 2 studies) when compared to controls (Fig. 4 & Supplementary Table 4), with no negative clusters identified. These clusters were bilateral and located at the WM/grey matter borders. The largest of these clusters were located in the SLF (right: two clusters of 18 voxels; left: 12 voxels) and the right inferior fronto-occipital fasciculus (16 voxels). Small bilateral cortico-ponto-cerebellar clusters (right: 12 voxels; left: 10 voxels) appeared unique to acute concussion and were not detected in our other meta-analyses. The largest right SLF clusters overlapped with

Table 1
Characteristics of studies included in the image-based meta-analysis.

Author	Sport	FA finding	mTBI Participants			Scan time	Control participants			Control source
			n	Male (%)	Age, mean ± SD (years)		*n*	Male (%)	Age, mean ± SD (years)	
Herweh (Herweh et al., 2016)	Boxing (amateur)	FA ↓ bilateral corticospinal tract, centrum semiovale, posterior limb internal capsule, splenium of corpus callosum, longitudinal fasciculus (inferior & superior), frontal & parietal subcortical association fibres, tegmentum	31	100	27.1 ± 13.6	Subconcussive	31	100	27.6 ± 10.7	Healthy, no history of contact sport, matched on age & intelligence
Lancaster (Lancaster et al., 2016)	Football (high school and collegiate)	No FA differences vs control	26	100	17.6 ± 1.5	14–24 h post-SRC	26	100	18.0 ± 1.5	Non-injured, matched on age, sex, sport, verbal intelligence, GPA
Mayer (Mayer et al., 2017)	Mixed martial arts	FA ↓ bilateral corona radiata, corpus callosum, internal & external capsule, superior longitudinal fasciculus, cingulum	13	85	28.2 ± 4.9	Variable (chronic post-SRC)	14	86	28.1 ± 5.1	Healthy, matched on age, sex & education
Mayinger (Mayinger et al., 2018)	Football (NCAA)	FA ↑ L parietal lobe	19	100	20.0 ± 1.0	Majority subconcussive (80%)	5	100	20.9 ± 1.1	Non-athlete, University source
Multani (Multani et al., 2016)	Football (CFL)	No FA differences vs control	18	100	49.6 ± 12.0	Mean 16.2 years post-SRC	17	100	46.7 ± 10.0	Healthy, no history of mTBI
Mustafi (Mustafi et al., 2018)	Football (NCAA)	No FA differences vs control	30	100	19.2 ± 1.0	24–48 h post-SRC	28	100	19.5 ± 1.4	Active in contact sport, matched on age, sex, education, n previous mTBI, verbal intelligence
Sasaki (Sasaki et al., 2014)	Ice hockey	FA ↑ bilateral corona radiata, posterior limb internal capsule, superior frontal, superior temporal	16	63	21.7 ± 1.5	At least 3 months post-SRC	18	45	21.3 ± 1.8	Teammates with no history of mTBI
Zivadinov (Zivadinov et al., 2018)	Ice hockey, football (NFL)	No FA differences vs control	21	50	56.7 ± 9.5	Variable (post-retirement from professional play)	21	50	55.4 ± 9.3	Master athletes in non-contact sports, matched to age range of SRC participants, no history of mTBI
Total	–	–	174	–	–	–	160	–	–	–
Sample-size weighted mean ± SD	–	–	–	89.4	29.0 ± 5.8	–	–	87.9	29.4 ± 5.5	–

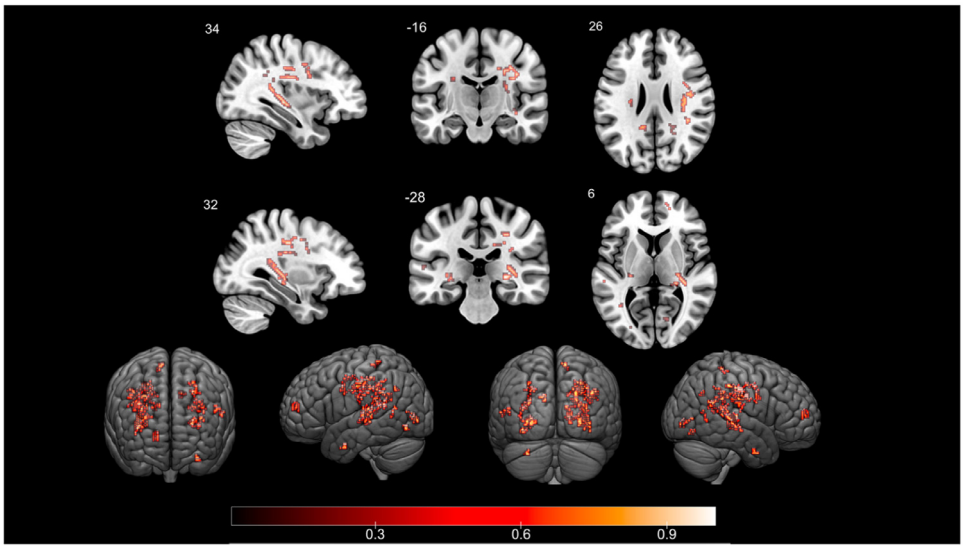

Fig. 2. Significant clusters of white matter pathology in sports concussion. Clusters in which FA values are significantly higher than controls in sports concussion (all studies). 21 clusters were detected, with dominant clusters in the superior longitudinal fasciculus and retrolenticular part of the internal capsule.

those present in the main meta-analysis, while smaller left SLF cluster and lateralised clusters in the inferior occipitofrontal fasciculus and cingulum were unique to acute injury.

3.8. Meta-analysis of FA in chronically concussed participants vs. control participants

Studies reporting imaging findings in the months to years after participants sustained sports concussion ($n = 4$) detected 16 positive clusters, with no negative clusters (Fig. 4 & Supplementary Table 5). These clusters were concentrated predominantly in the deep WM, with dominant clusters in the right optic radiations (126 voxels) and arcuate fasciculus (94 voxels). Both of these clusters overlapped with those present in the main meta-analysis across all SRC data. Several smaller midline clusters were also detected in the corpus callosum, cingulum and internal capsule (20–23 voxels apiece). Of these, the right cingulum and left SLF clusters appeared unique to chronic injury.

4. Discussion

To our knowledge this is the first meta-analysis examining TBSS in SRC. Our findings are timely given the increasing use of TBSS in the SRC (and wider mTBI) literature, with all but one of the included studies published within the last 3 years, and three within the past year.

Overall, our findings support the use of tract-based analysis of diffusion data as a sensitive tool to detect WM alterations and differentiate SRC subjects from controls in appropriately powered cohorts. We further used TBSS to reveal complex spatial patterns of FA change that vary in the subconcussive, acute and chronic settings. Using SDM to combine data from each included study in a voxel-wise meta-analysis, our results showed a high rate of concordance across studies for most of the clusters detected, with 60% of the top 10 clusters replicated in all studies. The most pronounced pattern of WM alteration was bilateral elevation of FA seen across the SLF, internal capsule and arcuate fasciculus.

Comparing acute and chronic post-injury settings, we found that acute concussive injuries were characterised by broadly distributed clusters of superficial WM pathology, while chronic assessment was typified by alteration of the deep WM. One might hypothesise that superficial clusters at the grey and white matter interface reflect particular vulnerability of these short range association fibres to coup-contrecoup injury (Povlishock and Christman 1995; Armstrong et al., 2016; Stojanovski et al., 2019), potentially as these axons are not completely myelinated until at least the third decade of life (Parazzini et al., 2002). In contrast, clusters of deep WM alteration seen in the chronic post-concussive phase may reflect late-stage progressive WM degeneration, and may be a downstream consequence of demyelination, impaired axonal transport, and ultimately, Wallerian degeneration and disconnection (Johnson et al., 2013; Armstrong et al., 2016). mTBI is most frequently observed as a diffuse axonal injury, with rapid axonal swelling and oedema impinging on the interstitial space and increasing anisotropic diffusion causing focal increases in FA (Niogi and Mukherjee 2010; Shultz et al., 2012; Kimura-Ohba et al., 2016). In contrast, tract disruption, progressive Wallerian degeneration and loss of myelin integrity are thought to result in decreased FA values (Shenton et al., 2012; Yin et al., 2019). This has led to the common theory that FA is elevated acutely after mTBI and depressed thereafter (Bazarian et al., 2007). This idea has been supported by a meta-analysis examining dMRI findings in mTBI of any aetiology (Eierud et al., 2014), which found that anisotropy was increased in studies conducted in the first four days post-injury, and from then predominantly decreased compared to controls. Concentrating specifically on SRC in the acute and chronic phases, our data reveal a more complex picture, whereby mTBI participants have regionally specific and quite diffuse increases in FA in both the acute (≤ 48 h) and chronic setting (months to years post-injury). From a mechanistic standpoint, it is important to note that FA does not just reflect axonal structure in isolation, but also incorporates heterogeneous properties of the supporting brain parenchyma. The long-term increases in FA we have observed across these 8 studies could potentially be driven by a prolonged proinflammatory environment, whereby immune mediators may perpetuate a glial response involving active presence of macrophages and promotion of astroglial scarring in the WM (Johnson et al., 2013; Morganti-Kossmann et al., 2019), impeding isotropic diffusion.

The evidence of raised FA acutely was expected, however our finding of FA increases chronically requires further exploration. Review of the literature, however reveals that these reported changes are frequently focal (for example see Table 2 and supplementary Table 2 in: (Eierud et al., 2014)). Our results demonstrate diffuse positive changes which collectively involved quite large areas of WM, and these findings were associated with large effect sizes (Z-scores between 2–3). As a meta-analysis examining cross-sectional data, our study is not a good design to directly address this unexpected observation, however we highlight several factors that may explain our findings:

Table 2
Top 10 clusters in which FA values in sports-related concussion are significantly elevated over control.

Cluster group	Number of voxels	MNI coordinates	SDM Z-score	p Value	Sub-components
R Superior longitudinal fasciculus	178	34, −16, 26	3.2	$P < 0.001$	Superior longitudinal fasciculus, superior corona radiata, posterior corona radiata
R Internal capsule (retrolenticular part)	129	32, −28,6	3.14	$P < 0.001$	Internal capsule (retrolenticular part), stria terminalis, sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)
L Internal capsule (retrolenticular part)	44	−24, −24, 2	2.63	$P < 0.001$	Internal capsule (retrolenticular part), stria terminalis
L Inferior occipitofrontal fasciculus	33	−24, −86, −2	2.64	$P < 0.001$	Inferior occipitofrontal fasciculus, inferior longitudinal fasciculus
R Posterior corona radiata	33	22, −36, 32	2.24	$P < 0.001$	Posterior corona radiata, body of corpus callosum, splenium of corpus callosum
R Arcuate fasciculus (Anterior segment)	30	38, −38, 28	2.73	$P < 0.001$	–
L Arcuate fasciculus (long segment)	29	−34, −42, 14	2.76	$P < 0.001$	Arcuate fasciculus (long segment), optic radiation, corticospinal tract
R Splenium of Corpus Callosum	26	22, −52, 22	2.55	$P < 0.001$	Splenium, internal capsule
L corticospinal tract	27	−30, −26, 34	2.34	$P < 0.001$	Corticospinal tract, internal capsule
L Arcuate fasciculus (Anterior Segment)	19	36, 2, 28	3.60	$P < 0.001$	–
L Superior longitudinal fasciculus	18	−50, −40, 12	2.38	$P < 0.001$	–

First, our study concentrated specifically on SRC, with pooled data from sportspeople who most likely also experienced repetitive head impacts and impacts with a rotational acceleration component. Even if these repetitive impacts do not result in overt concussive symptoms, they may contribute to a fundamentally different pathophysiological state in those currently (or formerly) participating in contact sports compared to those with isolated head injuries (Kulkarni et al., 2019). Second, prior measured decreases in FA have typically been quite focal. For homogenous cohorts with a specific mode of injury this makes sense. In a meta-analysis such as ours, it is natural to potentially "lose" smaller regions change in FA magnitude. Diffusion MRI is a somewhat noisy technique, and larger, more diffuse change may be poorly detected in lower-powered studies. Third, the use of skeleton projection in a TBSS approach may be more selective than other analysis methods due to voxel inclusion based on local maxima within the bounds of the skeleton, whereby voxels further from tract centres are weighted differently to those closer to centre (Zalesky 2011). Because of this, small clusters ("negative" FA change) of white matter external to the centre of a tract may be underestimated relative to diffuse change of a similar magnitude., which may also explain FA differences between studies of different methodologies. Fourth, WM registration is prone to tract misalignment and partial volume effects (Vos et al., 2011), with values potentially contaminated with grey matter or CSF. Misalignment may increase the likelihood of erroneous voxel inclusion of more isotropic tissue compartments, and calculating a lower 'WM' FA value. Region of interest and voxel-based morphometry approaches may be more sensitive to registration errors than TBSS, which can alleviate some of these problems through the process of projecting each individual's WM onto a common FA skeleton using nonlinear registration, hence permitting more accurate group-based comparisons (Smith et al., 2006; Jahanshad et al., 2013). Finally, directional differences may be due to other variables such as imaging protocols, post-processing and analysis strategies, and the ways in which authors choose to report their findings.

In contrast to findings in the acute and chronic settings, subconcussive injuries were the only analysis in which we detected a reduction in FA. While there were only two studies reported in this category, the specific localisation of both positive and negative WM clusters to the arcuate fasciculus is an interesting finding, and one worthy of further exploration. The arcuate fasciculus is an association fibre tract of particular importance for language (Geschwind 1970), injury to which may cause comprehension, speech and paraphasia (Jang et al., 2016). Given that these symptoms are often reported in patients with progressive and/or long-term complications of mTBI such as CTE, the arcuate fasciculus ought to be a focus of research into consequences of subconcussive injury.

Finally, our results suggested greater WM alteration in the posterior rather than anterior structures for which limited clusters of WM change were found. This contrasts with a prior meta-analysis of the wider dMRI mTBI literature, which revealed a particular anterior vulnerability to mTBI, with dissipation along a gradient from anterior to posterior (Eierud et al., 2014). Beyond the underlying methodology differences discussed above, these differences could be due to specific linear and/or rotational head acceleration (Kleiven 2013; Cullen et al., 2016) unique to contact sports, or other unknown factors. Comparison between injuries of different aetiologies will be a crucial next step to understand these differences in pathology.

A particular strength of our study is the use of unthresholded image data in the meta-analysis. Most commonly, reported coordinates of supra-threshold peak activations are used to pool studies without regard to their activation magnitude. In contrast, our study used the full statistical data available across the entire brain, including regions which lacked statistical power in individual studies, but which may become significant when observed consistently across studies. This allowed for the use of hierarchical mixed-effects models which can take into account intra- and inter-study variance and have been shown to be

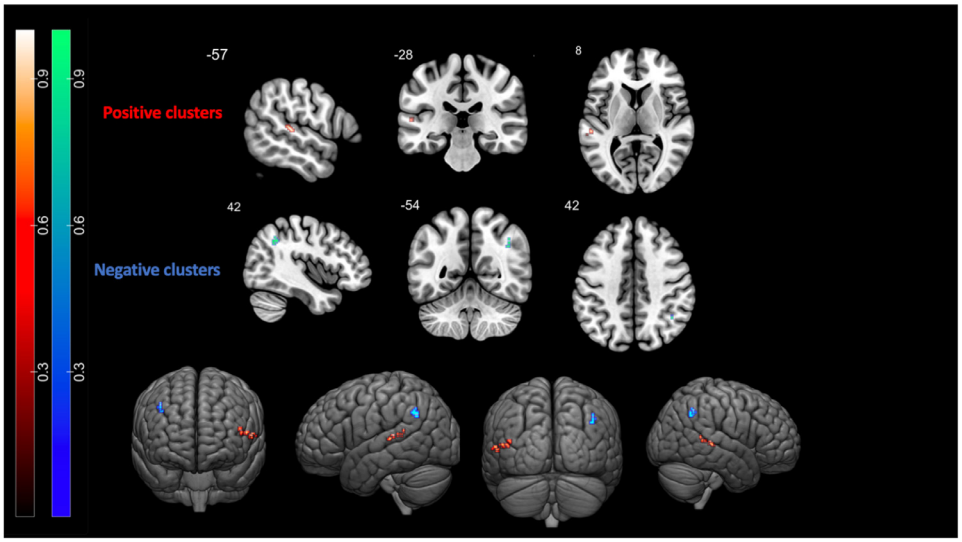

Fig. 3. Significant clusters of white matter pathology in repetitive subconcussive hits. FA values are in the posterior segment of the left arcuate fasciculus were significantly higher compared to control (red clusters), while FA in the anterior segment of the right arcuate fasciculus was significantly lower (blue clusters) after subconcussive hits.

preferable to coordinate-based analyses (Salimi-Khorshidi et al., 2009). The advantage of this technique is evident in this current meta-analysis, for which half the studies reported no significant between-group findings in FA.

While FA is the most frequently reported DTI metric, a criticism of the DTI model in general is the necessary assumption of a Gaussian distribution, which might overlook the complexities of fibre orientation. Alternative analysis approaches have been suggested, including diffusion kurtosis imaging, which is sensitive to the variance (kurtosis) from a Gaussian distribution and is an emerging marker of white matter pathology (Welton et al., 2019). Recent advances in high angular resolution multi-shell imaging have also substantially improved accuracy and sensitivity of fibre tracking (Callaghan et al., 2018), and may present a clinically viable option to assess brain network abnormalities. Emerging dMRI techniques applicable for quantifying WM alteration in mTBI also include track-weighted imaging and curvature, which examine streamlines and their characteristics within a voxel (Wright et al., 2016; Wright et al., 2017), as well as fixel-based analyses, which reflect specific properties of fibres within a voxel (Raffelt et al., 2017; Lyon et al., 2019).

The findings of this study should be considered in the context of several important limitations. A small number of studies were included in our meta-analyses. As TBSS is a relatively new technique to be applied to the field of SRC, this is not unexpected but still represents a very meaningful increase in statistical power. Data were contributed for 8 of the 24 studies identified, with authors of the remaining 16 articles either unable to be contacted or bound by ethical, institutional or funding body restrictions on data sharing. Barriers such as these have been a cultural research norm, with limited desire and/or ability to make raw data available. However, the landscape is now changing to one in which open data and data sharing are favoured. Databases such as NeuroVault (https://neurovault.org) will be a useful tool going forward to store and share unthresholded statistical maps for the benefit of collaborative research. Nonetheless, the 8 studies included in our main meta-analysis represented a range of contact sports and participant ages, and although findings were encouragingly consistent, care should be taken to extrapolate results to the wider SRC literature, particularly when considering the specific settings of subconcussive, acute and chronic pathologies as separate entities. Further research should aim to clarify these areas in a larger data pool, and also to clarify gender-specific WM alterations in these settings.

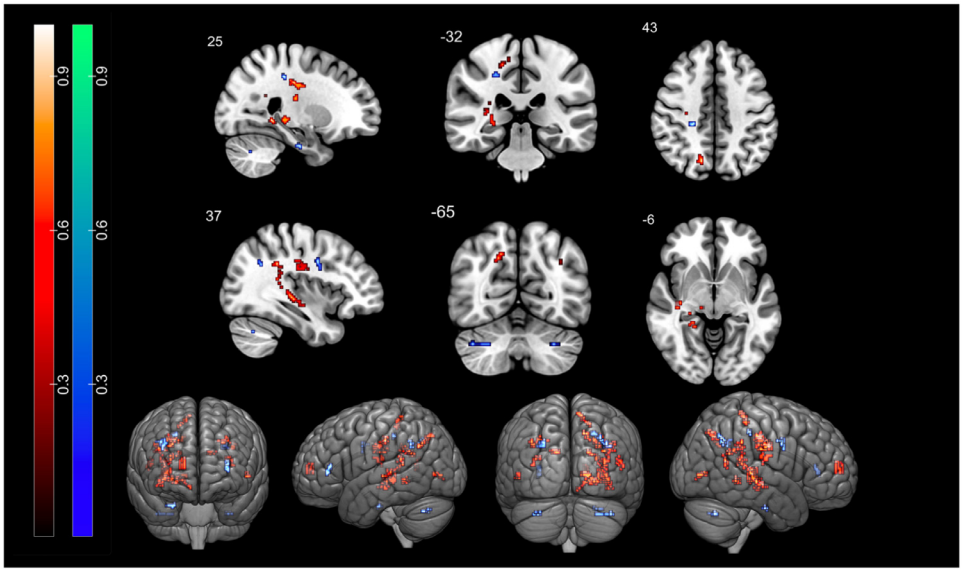

Fig. 4. Clusters of white matter pathology acutely and chronically after sports-related concussion. Significant positive clusters of white matter abnormality were found acutely (blue) and chronically (red) following sports concussion. Small focal clusters detected after acute injury were predominantly located in the superficial white matter, while studies chronically after injury showed alteration of deep white matter, with larger clusters in the optic radiations and arcuate fasciculus.

5. Conclusion

TBSS is sensitive to white matter abnormalities resulting from sports concussion over a range of temporal and clinical scenarios. Our data suggest concordant pathological features unique to subconcussive, acute concussive and chronic post-concussive phases, highlighting the future utility of tract FA for concussion diagnosis.

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Data availability

Combined T Statistical maps from TBSS analyses were uploaded to https://neurovault.org/.

CRediT authorship contribution statement

Sarah C. Hellewell: Conceptualization, Methodology, Data curation, Formal analysis. **Vy P.B. Nguyen:** Methodology, Data curation, Formal analysis. **Ruchira N. Jayasena:** Methodology, Data curation, Formal analysis. **Thomas Welton:** Conceptualization, Methodology, Data curation, Formal analysis. **Stuart M. Grieve:** Conceptualization, Formal analysis.

Declaration of Competing Interest

No conflict of interest is declared by any author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2020.102253.

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