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Brain Structure and Function Associated with a History of Sport Concussion: A Multi-Modal Magnetic Resonance Imaging Study

Nathan Churchill,[1] Michael Hutchison,[2] Doug Richards,[2] General Leung,[1,3] Simon Graham,[4,5] and Tom A. Schweizer[1,6,7]

Abstract

There is growing concern about the potential long-term consequences of sport concussion for young, currently active athletes. However, there remains limited information about brain abnormalities associated with a history of concussion and how they relate to clinical factors. In this study, advanced MRI was used to comprehensively describe abnormalities in brain structure and function associated with a history of sport concussion. Forty-three athletes (21 male, 22 female) were recruited from interuniversity teams at the beginning of the season, including 21 with a history of concussion and 22 without prior concussion; both groups also contained a balanced sample of contact and noncontact sports. Multi-modal MRI was used to evaluate abnormalities in brain structure and function. Athletes with a history of concussion showed frontal decreases in brain volume and blood flow. However, they also demonstrated increased posterior cortical volume and elevated markers of white matter microstructure. A greater number of prior concussions was associated with more extensive decreases in cerebral blood flow and insular volume, whereas recovery time from most recent concussion was correlated with reduced frontotemporal volume. White matter showed limited correlations with clinical factors, predominantly in the anterior corona radiata. This study provides the first evidence of the long-term effects of concussion on gray matter volume, blood flow, and white matter microstructure within a single athlete cohort. This was examined for a mixture of male and female athletes in both contact and noncontact sports, demonstrating the relevance of these findings for the overall sporting community.

Key words: blood flow; concussion; diffusion tensor imaging; MRI; traumatic brain injury

Introduction

Concussion is recognized as a clinical syndrome of biomechanically induced brain alterations, often associated with physical, cognitive, and behavioral dysfunctions.[1] Despite symptom resolution most commonly occurring within 7–10 days post-injury for adults,[2,3] athletes with prior concussions are at elevated risk of future injury[4] and prolonged recovery time.[4] In recent years, there has also been growing concern over the long-term consequences of sport concussion, particularly for young athletes, who may be more vulnerable to the sequelae of concussion because of ongoing brain development.[5] Studies of retired professional athletes have shown that a history of concussion is associated with higher risk for clinically diagnosed depression and mild cognitive impairment, along with self-reported memory problems.[6–8] In addition, there is ongoing debate regarding chronic traumatic encephalopathy (CTE) as a postmortem diagnosis, with some researchers suggesting that repetitive head impact leads to neurodegeneration, including gross cortical atrophy and neurofibrillary tangles.[9] However, the absence of prospective or epidemiological CTE studies makes it difficult to establish a causal link among concussions, pathophysiology, and symptoms.[10]

Following injury, long-term changes in brain structure and function may play a significant role in post-concussion risk factors, as studies have identified abnormalities in cognition[11] and brain activity[12] of concussed athletes beyond medical clearance. Despite the evidence for long-term health risks, conventional clinical neuroimaging using CT or MRI rarely detects gross brain abnormalities after concussion.[13] However, advanced MRI methods have been used to identify more subtle post-injury abnormalities in brain function, metabolism, and cerebral microstructure. Further examination of MRI biomarkers for brain injury is critical

[1]Keenan Research Centre of St. Michael's Hospital, Toronto, Ontario, Canada.
[2]Faculty of Kinesiology and Physical Education, [3]Department of Medical Imaging, [5]Department of Medical Biophysics, [6]Faculty of Medicine (Neurosurgery), [7]Institute of Biomaterals and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada.
[4]Physical Sciences, Sunnybrook Research Institute, Toronto, Ontario, Canada.

to our understanding of concussion pathophysiology and recovery processes.

The majority of MRI studies have been undertaken between 1 week and 1 month post-injury, when athletes are asymptomatic at rest and beginning a graded return to full activity. Following injury, athletes have shown altered brain activity[14–16] and significant metabolic disturbances.[17] In addition, arterial spin labelling (ASL) shows suppressed cerebral blood flow (CBF) among symptomatic athletes.[18] Examinations of white matter microstructure via diffusion tensor imaging (DTI) have been inconsistent for symptomatic athletes, variously reporting altered DTI metrics,[19] limited effects,[16] or no significant differences.[20]

At present, far less is known about the long-term sequelae of concussion on a time scale of months to years. There is evidence that brain activity has largely recovered beyond 6 months post-injury, with no significant abnormalities seen in concussed athletes,[21] although persistent metabolic disturbances have been identified in some cases.[17,22] In addition, CBF abnormalities have shown resolution by 1 month post-injury,[18] although this study focused on brain regions showing significant changes over time in concussed athletes. The approach may be insensitive to areas with persisting, long-term CBF abnormalities, which are potentially associated with impairments in brain function.[23]

There is also evidence for long-term structural alterations of the brain following concussion. The majority of large-scale studies have focused on former athletes with a significant history of concussion and subconcussive impact, including hockey, football, and boxing. For these cohorts, DTI has shown significant markers of white matter damage.[24,25] More recently, studies of young hockey players have shown elevated markers of white matter[26] and associations between concussion history and cortical volume loss,[27] particularly in frontotemporal gray matter, which is vulnerable to impact from bony skull protuberances.[23] Similarly, hippocampal atrophy has been reported among collegiate football players with prior concussion.[28] To date, studies of structural brain changes have primarily focused on male athletes in a subset of high-risk sports, with most structural analyses limited to retired athlete cohorts.[24,25] Hence, there is a need for comprehensive assessment of brain changes within a sample that is representative of the wider athletic community.

Growing evidence supports the utility of advanced MRI for studying concussion. Significant gaps remain, however, particularly in our understanding of long-term alterations in brain structure and CBF, and their correlations with clinical history. The present study examined the long-term effects of concussion based on a multi-modal MRI battery that assesses CBF (ASL), cortical volume (T1 voxel-based morphometry), and white matter microstructure (DTI). This novel multi-modal approach allows for a more complete picture of the sequelae of concussion within a single cohort, as the majority of previous concussion studies have studied a single MRI measure, with few exceptions.[20,22,29,30] These markers are examined in a balanced cohort of male and female athletes, and a mixture of contact and noncontact sports (volleyball, hockey, soccer, football, rugby, basketball, lacrosse), which will significantly extend our understanding of brain injury in the sporting community.

The MRI measures were compared between varsity athletes with a prior history of concussion, relative to a matched cohort without documented injury. Further, among athletes with prior injury, the MRI measures were correlated with two clinical factors related to prior injury: the number of documented concussions, and recovery time from the last concussion.

Methods

Participants

Athletes were recruited from seven interuniversity (''varsity'') sport teams at the University of Toronto (volleyball, hockey, soccer, football, rugby, basketball, and lacrosse) during pre-season concussion evaluations. Demographic data were collected at the time of recruitment using the Sport Concussion Assessment Tool 3 (SCAT3),[31] including number of previously documented concussions, time since last concussion (in months), and recovery time for the last concussion (number of days from reported injury to medical clearance). All concussions were determined based on diagnosis at the time of injury. Forty-three active athletes without recent injury were recruited and scanned: 21 with prior history of concussion and 22 with no documented prior concussions. The University of Toronto and St. Michael's Hospital research ethics boards approved study procedures, and all study participants provided written informed consent prior to neuroimaging.

MRI

Participants were scanned at St. Michael's Hospital using an MRI system operating at 3 T field strength (Magnetom Skyra, Siemens, Erlangen, Germany) and a standard 20 channel head receiver coil. All imaging parameters and preprocessing details are provided in Supplementary Text File 1 (see online supplementary material at http://www.liebertpub.com). Voxel-wise CBF was estimated in mL/100 g/min using a two-dimensional (2D) multi-slice pulsed ASL sequence. Gray matter volume was assessed by acquiring a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence. Subsequently, tissue segmentation and voxel-based morphometry were applied to MPRAGE images to obtain probabilistic maps of gray matter volume fraction. White matter microstructure was evaluated using a DTI sequence (30 gradient directions) followed by the calculation of voxel-wise fractional anisotropy (FA) (characterizing the directionality of water diffusion) and mean diffusivity (MD) (the diffusion coefficient averaged over three orthogonal directions). Thus, a set of four brain maps were generated per participant, for further analysis: CBF, gray matter volume, FA, and MD. All MRI scans were visually inspected for structural abnormalities or significant artifact. Of the 43 participants, one DTI scan and three T1 scans were excluded from analysis, because of either missing data or image artifacts.

Statistical analysis

Demographic and clinical parameters are expressed as mean ± standard deviation (SD) unless otherwise stated. To examine group differences for demographic and clinical features, normality was assessed, and appropriate parametric or nonparametric tests were applied. MRI measures were compared between athletes with and without prior concussion by measuring the mean difference in MRI measures between groups, and computing nonparametric two tailed bootstrapped significance estimates.[32] This approach was chosen to avoid any distributional assumptions about MRI data, as all measures showed evidence of significant non-normality ($p < 0.05$, Kolmogorov–Smirnov test). Participants in each group were resampled with replacement, the mean difference between groups recomputed for each iteration (1000 re-samples), and an empirical p value obtained based on the fraction of re-samples that overlapped with zero effect. For each MRI measure, multiple comparison correction was performed over all voxels using a false discovery rate (FDR) threshold of 0.05. Brain images were displayed as the mean fractional difference in MRI values between athletes with/without prior injury, to demonstrate effect sizes for significant brain regions.

For athletes with prior concussion, additional testing was performed to determine whether differences in MRI measures were associated with clinical factors implicated in brain recovery,[3] specifically 1) number of prior concussions and 2) recovery time for their last concussion, defined as days from diagnosis of concussion to return-to-play clearance. At each brain voxel, nonparametric Spearman correlation was computed between the clinical covariate and MRI measure. As with the mean-difference analysis, bootstrapped voxel p values were obtained for each MRI measure, with multiple comparison correction at an FDR threshold of 0.05. Brain images for each MRI measure were then plotted as the mean bootstrapped Spearman correlation within significant brain regions.

Results

Clinical demographics

The clinical and demographic measures for participants are summarized in Table 1. Both groups were balanced on male and female athletes, along with contact sports (men's hockey and lacrosse, rugby, soccer, football) and noncontact/collision sports (women's hockey, basketball, volleyball). Age ranges for the groups were consistent (18–23 years), although athletes with prior concussion were older (difference, 1.50 [95% CI, 0.5–2.5]; $p=0.01$). Nonetheless, the effects of age on the brain do not significantly overlap with concussion history in this cohort, as shown in a supplemental analysis (Supplementary Text 2 and Figure S1) indicating it is unlikely to be a significant confound (see online supplementary material at http://www.liebertpub.com).

Athletes with prior concussions had a median of two previous injuries, with time to medical clearance occurring an average of 18 days for their last concussion, although a wide range of recovery times were reported. There were no significant differences between male and female athletes with prior concussion, in number of concussions, recovery time, or time since last injury ($p>0.45$, all variables). Athletes reported an average SCAT total score of 3.02 (SD = 3.7), with no significant differences between groups with and without prior concussion (difference, 1.50 [95% CI, –2.22–5.22]; $p=0.42$). The groups showed no significant differences for SCAT symptom severity or cognitive scores, although differences were observed for Balance Error Scoring System (BESS) Total Score, with greater errors for athletes without prior concussion (difference, 1.87 [95% CI, 0.12–3.63]; $p=0.037$).

Table 1. Clinical and Demographic Measures for Participants, Including Test Scores for the Sport Concussion Assessment Tool (SCAT) and Subscales, Including the Balance Error Scoring System (BESS)

	No prior injury (n = 22)	*Previous concussion (n = 21)*
Age (mean ± SD)	19.5 ± 1.5	21.0 ± 1.7
Contact sport	9/22	8/21
Female	11/22	11/21
Time since injury (median)	-	26 months (range: 9, 120)
Number of concussions (median)	-	2 (range: 1, 5)
Recovery time (median)	-	18 days (range: 2, 120)
SCAT (mean ± SD)		
Symptoms	3.45 ± 3.98	2.59 ± 3.50
Symptom severity	5.27 ± 7.05	3.77 ± 5.01
Orientation	4.90 ± 0.29	4.86 ± 0.35
Immediate memory	14.27 ± 1.49	14.55 ± 0.60
Concentration	3.27 ± 1.28	3.86 ± 1.23
Delayed memory	3.48 ± 1.29	4.06 ± 1.05
BESS total errors	3.86 ± 3.37*	1.81 ± 2.23

Comparing athletes with and without prior concussion

In Figure 1, the fractional difference in voxel-wise MRI measures is plotted for athletes with prior concussion, relative to those without. Figure 1A shows greatest volumetric decreases in the left cerebellum (z = –20), temporal lobes (z = 0, +22) right pre-central gyrus (z = +42), supplementary motor area, and superior frontal lobes (z = +60, +68). Significant volumetric increases were also observed, principally in the right hippocampus (z = –20), left caudate (z = 0), and cuneus (z = +22). Figure 1B shows decreased CBF in cortical domains that show reduced gray matter volume, including pre-central gyrus (z = +42), supplementary motor area, and superior frontal lobes (z = +60, +68), although differences in CBF tend to be more spatially extensive than for volumetric measures. CBF increases were also seen in regions of volumetric increase, including right hippocampus (z = –20) and posterior cingulate (z = +22), proximal to the cuneus.

The DTI-based measures also showed consistent differences in athletes with prior injury, albeit with smaller proportionate differences, compared to gray matter volume and CBF. FA had the most spatially extensive differences between groups, as concussed athletes show increased FA primarily in the corona radiata (anterior and posterior; z = 0, +22) and genu of the corpus callosum (z = +22). Conversely, MD was decreased in athletes with prior concussion, primarily in the posterior corona radiata and corpus callosum (z = +22).

Association with clinical factors

Brain regions showing a significant association between MRI measures and clinical factors are plotted in Figure 2 as axial and sagittal maximum intensity projections (MIPs). For all MRI measures and clinical factors, regions of significant correlation were observed, although the spatial extent depended on the MRI modality. For volumetric analysis (Fig. 2A) a higher number of previous concussions was mainly associated with increased volume in the parietal and occipital lobes, and with decreased volume in the insula bilaterally. A longer recovery time was mainly associated with reduced volume in temporal lobes, supplementary motor area, and anterior cingulate, although the parahippocampal gyrus and rolandic operculum showed increased volume. For CBF (Fig. 2B), a higher number of prior concussions was correlated with perfusion decreases in the frontal and temporal lobes. However, a longer recovery time was associated with minimal differences in CBF, mainly focal increases in the cerebellum and middle occipital lobe. Compared with other measures, DTI metrics of white matter FA (Fig. 2C) and MD (Fig. 2D) showed minimal correlations with clinical factors, with the anterior corona radiata showing greatest sensitivity. The most extensive effects were seen for number of prior concussions, with increased FA and decreased MD.

Discussion

This study employed multi-modal MRI to characterize brain abnormalities associated with a history of sport concussion, including alterations in CBF, gray matter volume, and white matter microstructure. These metrics were examined for a group of male and female athletes, with balanced representation of both contact and noncontact sports. This provides a novel perspective on the effects of

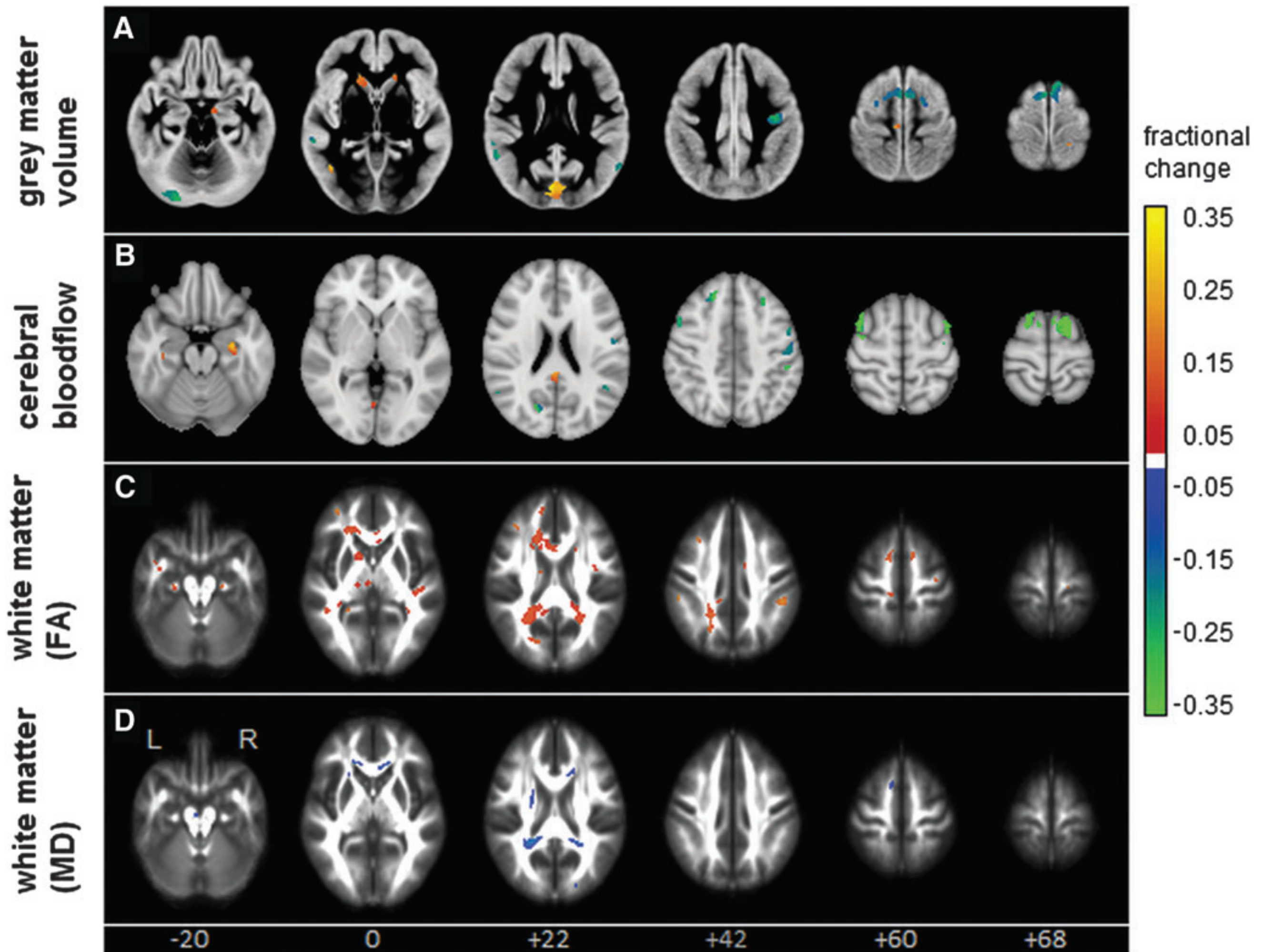

FIG. 1. Voxel-wise differences in MRI measures associated with prior history of concussion. Measures include **(A)** gray matter volume, **(B)** cerebral blood flow (CBF), **(C)** fractional anisotropy (FA), and **(D)** mean diffusivity (MD). The fractional difference in MRI measures is shown in regions significant at false discovery rate threshold of 0.05. Slice numbers correspond to z-axis coordinates of the Montreal Neurological Institute (MNI) template. Color image is available online at www.liebertpub.com/neu

concussion within this broad cohort and extends prior research, which has largely focused on high-risk contact sports and male cohorts. Differences in MRI measures were associated with a prior history of concussion, and showed correlations with the clinical factors, including number of concussions and recovery time. The latter are important measures that are recommended for clinical assessment of concussion risk,[3] but are rarely examined in relation to neuroimaging data.

Athletes with prior concussion had lower cortical volume (Fig. 1A), primarily in regions that are vulnerable to injury in TBI because of bony skull protuberances,[23] including the frontal cortex and cerebellum. This is consistent with prior studies of clinical TBI,[33–35] although the cerebellum has been rarely examined. In addition, decreased volume was identified in regions distal from the expected primary sites of impact, including middle temporal lobes and postcentral gyrus. This has been observed in both animal models and human neuroimaging,[36,37] and may be the result of connectivity loss with the primary site of injury. However, volumetric increases were also observed in internal gray matter, in the limbic (hippocampus and caudate) and visual (cuneus) systems, which may indicate cortical reorganization beyond simple atrophy. Although not, to our knowledge, previously reported in the concussion literature, cortical growth has long been recognized as part of neuroplastic adaptation in brain injury; for example, stroke.[38,39] The regions showing significant differences are of particular interest, as they are implicated in emotion and visual attention, two domains that often show dysfunction after brain injury.[6,10,11] Given that athletes with prior history of concussion had no persistent symptom complaints, volumetric increases may reflect adaptation to preserve these domains following injury.

The differences in cortical volume were also linked to clinical factors (Fig. 2A). A greater number of concussions was mainly associated with focal volumetric decreases in the insula, a component of the limbic system. This suggests a potential neural basis for increased mood disorders in athletes with a greater number of concussions.[6] These alterations may also reflect long-term neuroplastic reorganization secondary to injury, rather than the direct effects of tissue damage, as internal structures are less vulnerable to head impact.[23] A longer recovery time (i.e., more persistent post-concussion symptoms) was associated with widespread decreases in frontal and temporal cortical volume, and may, therefore, more directly reflect the amount of impact-related tissue damage. These

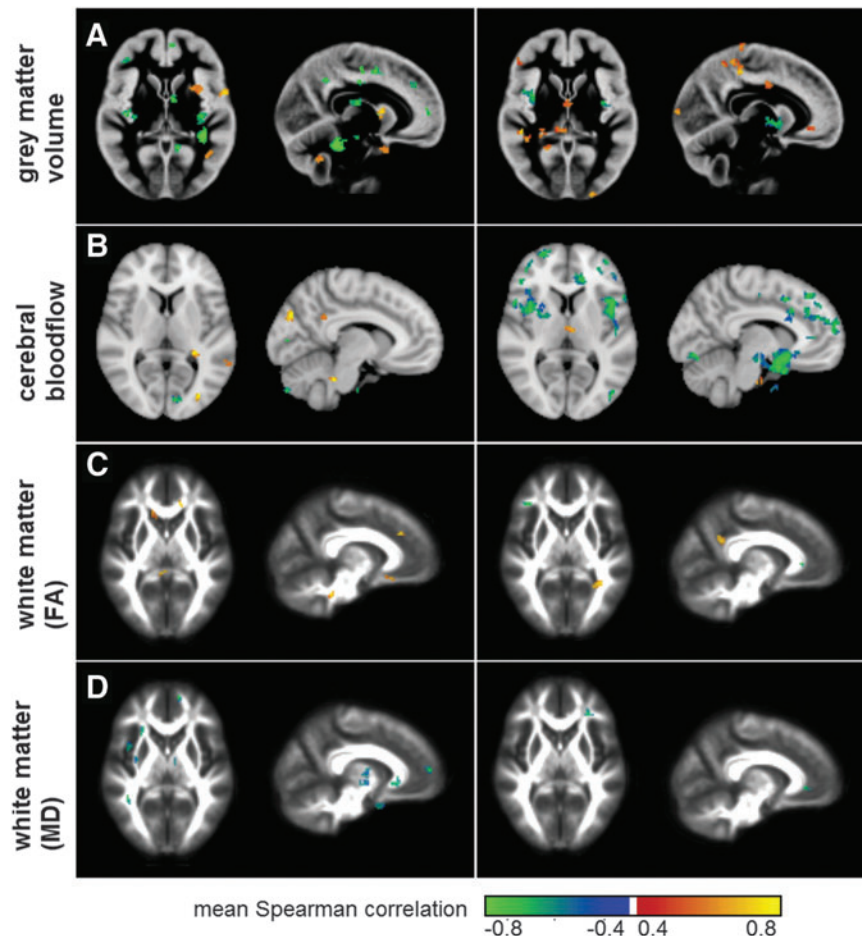

FIG. 2. Voxel-wise correlations between MRI measures and clinical factors for athletes with prior concussion, including number of concussions (left) and recovery time (right). Measures include **(A)** gray matter volume, **(B)** cerebral blood flow (CBF), **(C)** fractional anisotropy (FA), and **(D)** mean diffusivity (MD). The mean bootstrapped correlation is shown in regions significant at false discovery rate threshold 0.05. For visualization, images are displayed as axial and sagittal maximum intensity projections (MIPs), overlaid on anatomical slices after thresholding at minimum cluster size ≥ 10. Color image is available online at www.liebertpub.com/neu

regions are also consistent with previous volumetric studies of more severe TBI, which have shown extensive frontotemporal reductions associated with negative outcomes.[35,40]

The CBF analyses revealed significant differences among athletes with a history of concussion (Fig. 1B), including decreased CBF in the temporal lobes, frontal lobes, and supplementary motor area. These findings align with volumetric analyses (Fig. 1A), indicating that long-term decreases in CBF may be partly associated with cortical volume loss. Critically, this is a different mechanism from acute concussion, which is driven by compromised cerebral autoregulation.[41] Reduced CBF has been previously reported among symptomatic athletes[18] and was found to resolve at 1 month post-injury. However, this prior study examined brain regions showing significant effects of time on CBF (including the insula and temporal lobes).[18] In contrast, the current study tested for regions where CBF abnormalities do not dissipate over time (mainly in the frontal cortex). Taken together, these findings suggest that CBF recovery time may depend upon the examined brain region, with the frontal lobes being more vulnerable to persistent cerebrovascular changes, potentially driven by decreased blood flow demand because of cortical volume loss.

As further evidence of persistent functional changes, CBF was significantly correlated with clinical factors (Fig. 2B). Whereas frontotemporal reductions in volume were correlated with recovery time, frontotemporal CBF reductions were mainly correlated with number of concussions. Therefore, different aspects of concussion history show different relationships with brain structure and function. One potential explanation is that the neurovascular system is more impaired under chronic, repeated injury, although it may not be highly correlated with tissue damage (and, therefore, atrophy). The hypothesis that CBF effects are mediated by impaired cerebrovascular response is supported particularly by lower cortical volume in the insula (Fig. 2A). This region is part of the autonomic control system, and, therefore, atrophy in this region may lead to decreased cerebrovascular function.[42] The decrease in CBF with number of concussions is also consistent with fMRI analyses showing that functional impairments are correlated with the number of prior concussions for symptomatic athletes.[15]

Examining white matter microstructure, DTI also showed differences that reflected both injury and recovery (Fig. 1C,D). For athletes with prior concussion, elevated FA and decreased MD were consistently identified. These results extend prior DTI studies of acute and subacute concussion, in which decreased FA and increased MD were seen at acute injury,[19,22] but returned toward baseline 1 month after injury.[19] The present study indicates that increased FA and decreased MD may extend beyond the 1 month

interval for concussed athletes. These trends are opposite to those seen in more severe TBI and high-risk sports such as boxing,[25] where decreased FA and increased MD are generally observed.[43] However, they agree with long-term studies of mild TBI patients with good recovery[44] and a prior study of concussed hockey players,[26] suggesting a distinct DTI response for athletes with less severe and infrequent trauma. In addition, the changes in FA are consistent with the gray matter volumetric increases discussed. The mechanism for long-term FA increase after mild brain injury is debated, but it may reflect axonal budding and growth in response to injury[44] and/or gliosis.[45] However, DTI measures showed limited sensitivity to clinical correlates (Fig. 2C,D) compared with volumetric and CBF analyses. For both number of concussions and recovery time, increased FA and decreased MD were seen in the anterior corona radiate; however, significant brain regions are small and potentially support multiple brain functions.

Although results indicate a robust relationship between concussion history and multi-modal MRI, there are a few limitations. This study is cross-sectional in nature, and, therefore, brain abnormalities cannot be interpreted in terms of within-subject change. In addition, concussion history was based on patient self-report, which may be subject to errors in reporting. Hence, future longitudinal studies, with documentation beginning at the time of injury, will be critical to validate the current findings. As a second limitation, this study employed basic MRI and analytic techniques, which may have limited sensitivity to concussion pathophysiology. In terms of MRI sequences, current findings for white matter were based on 30 direction DTI, which is recommended for robust clinical imaging.[46] However, high angular resolution diffusion imaging (HARDI) is also routinely used for improved resolution of white matter tracts, along with more advanced multi-shell sequences.[47] Similarly, alternative methods of analyzing gray matter morphology, such as surface-based techniques,[48] may be sensitive to structural changes not detected using volumetric methods used in the current article. Finally, the analysis techniques used in this study were primarily univariate. Multivariate methods may be better able to identify distributed patterns of change in the brain associated with a prior history of concussion. In the future, it will be critical to determine whether the current findings generalize to alternative MRI sequences, brain measures, and analytic techniques.

The results of this article extend our understanding of the sequelae associated with sport concussion, and help to drive further research into long-term consequences of brain injury. One key finding is the evidence for persistent reductions in frontotemporal volume and hypoperfusion. Given the importance of these regions in memory, cognition, and perception, an important next step is to correlate frontotemporal MRI measures with neurocognitive tests in athletes with a history of concussion, to determine the severity of behavioral effects, and utility of MRI as a biomarker of injury. Similarly, significant volumetric and CBF differences were observed in the insula; given its role in emotion regulation, further research should examine whether MRI measures in this region are correlated with tests of mood and depression in young athletes. Finally, further research is needed to determine the underlying cause of differences in FA and MD that are distinct from the effects observed in more severe TBI. A potential approach is to use advanced DTI techniques[47] coupled with the latest generation of MRI hardware to probe the microstructure of the brain in greater detail.

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Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Nathan Churchill, PhD
Keenan Research Centre of the Li Ka Shing Knowledge Institute
at St. Michael's Hospital
209 Victoria Street
Toronto, Ontario M5B 1M8
Canada

E-mail: nchurchill.research@gmail.com