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ARTICLE

Mapping brain recovery after concussion

From acute injury to 1 year after medical clearance

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Abstract

Objective

To test the hypothesis that concussion-related brain alterations seen at symptomatic injury and medical clearance to return to play (RTP) will have dissipated by 1 year after RTP.

Methods

For this observational study, 24 athletes with concussion were scanned longitudinally within 1 week after injury, at RTP, and 1 year after RTP. A large control cohort of 122 athletes were also scanned before the season. Each imaging session assessed global functional connectivity (Gconn) and cerebral blood flow (CBF), along with white matter fractional anisotropy (FA) and mean diffusivity (MD). The main effects of concussion on MRI parameters were evaluated at each postinjury time point. In addition, covariation was assessed between MRI parameters and clinical measures of acute symptom severity and time to RTP.

Results

Different aspects of brain physiology showed different patterns of recovery over time. Both Gconn and FA displayed no significant effects at 1 year after RTP, whereas CBF and MD exhibited persistent long-term effects. The effects of concussion on MRI parameters were also dependent on acute symptom severity and time to RTP for all postinjury time points.

Conclusion

This study provides the first longitudinal evaluation of concussion focused on time of RTP and 1 year after medical clearance, using multiple different MRI measures to assess brain structure and function. These findings significantly enhance our understanding of the natural course of brain recovery after a concussion.

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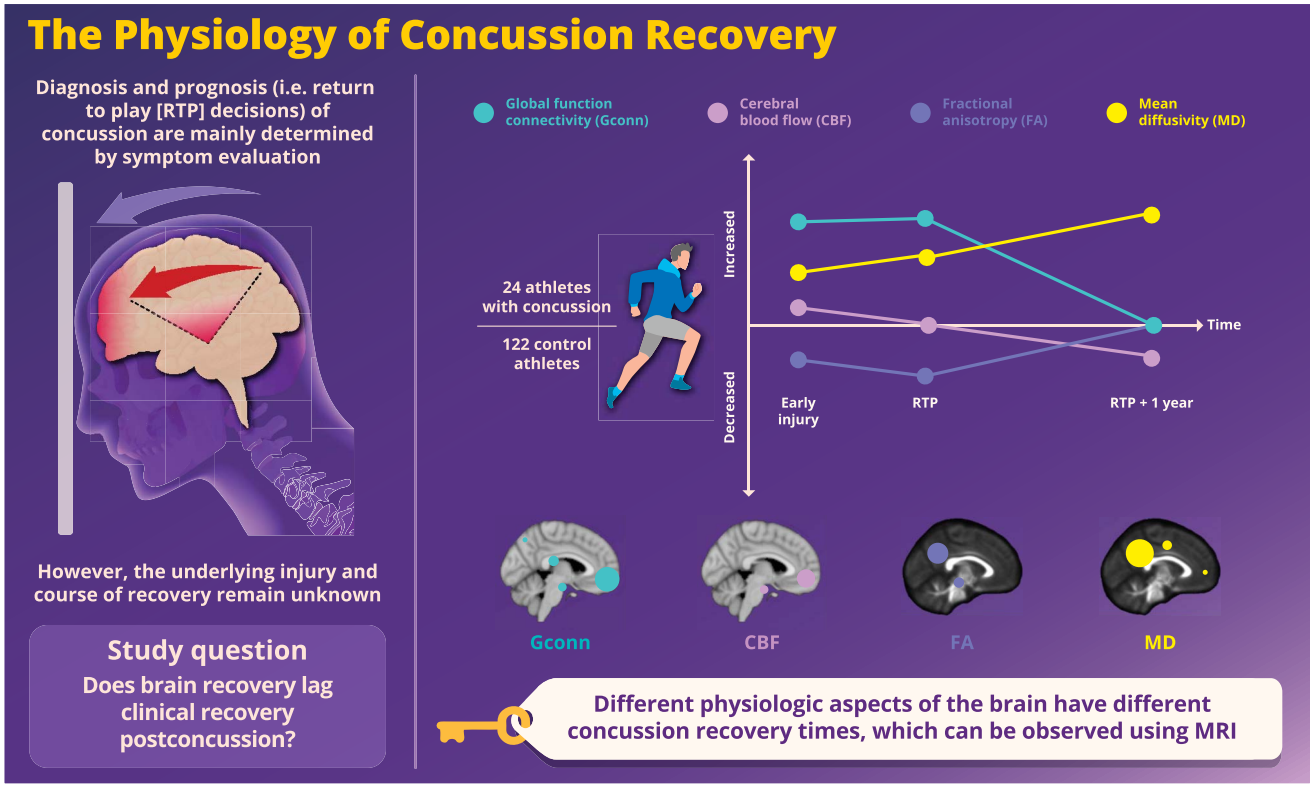
Glossary

AFNI = Analysis of Functional Neuroimages; **BW** = bandwidth; **CBF** = cerebral blood flow; **CI** = confidence interval; **CS** = clinical severity; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FSL** = fMRIB Software Library; **FOV** = field of view; **FWHM** = full width at half-maximum; **Gconn** = global functional connectivity; **MD** = mean diffusivity; **MNI** = Montreal Neurological Institute; **RTP** = return to play; **SCAT3** = Sport Concussion Assessment Tool 3; **SYM** = early symptomatic injury; **TBI** = traumatic brain injury; **TE** = echo time; **TI** = inversion time; **TR** = repetition time; **WM** = white matter.



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The diagnosis of concussion is currently based on symptom status and brief evaluations of cognition and balance. Similarly, return to play (RTP) is determined primarily by symptom resolution on completion of a graded exercise protocol.[1] However, these assessments indirectly reflect the underlying brain injury, and the natural course of physiologic recovery remains to be determined. This is a critical area of investigation, given concerns that subtle yet permanent brain changes may play a role in the neurologic sequelae associated with history of concussion.[2] In this respect, advanced MRI has emerged as a powerful tool for measuring changes in brain function, cerebral blood flow (CBF), and white matter that occur after concussion.

There is growing recognition of the importance of longitudinal MRI when investigating brain recovery after concussion.[3–6] However, there has been minimal examination of longitudinal changes relative to RTP, which is critical to our understanding of whether, and to what degree, brain recovery lags clinical recovery. Moreover, longitudinal imaging studies typically focus on a single modality, making it unclear whether different aspects of brain physiology have different patterns of recovery. The present study acquired multimodal MRI for concussed athletes at the early symptomatic phase of injury (SYM) , RTP, and 1 year after RTP, along with a large normative control group. It was hypothesized that, for all advanced MRI parameters, concussed athletes will show significant alterations at both symptomatic injury and RTP,[7] but the effects will have dissipated by 1 year after RTP.

Methods

Study participants

One hundred forty-six athletes were scanned for this study. Twenty-four concussed athletes were recruited consecutively from university-level sport teams at a single institution (including volleyball, hockey, soccer, football, rugby, basketball, lacrosse, and water polo) through the academic sport

medicine clinic after concussion diagnosis. Diagnosis was determined by a staff physician after a sustained direct or indirect contact to the head with the presence of signs or symptoms as per the Concussion in Sport Group guidelines[8] with standard neurologic assessment conducted, including examination of cranial nerves, gait, balance, and gross motor function. None of the athletes participating in this study were found to have gross neurologic impairments. Scanning was conducted an average of 4 days (range 1–6 days) after injury, after medical clearance to RTP, and 1 year after RTP. As a control group, 122 athletes were also consecutively recruited and imaged at the start of their competitive season. All athletes in the study completed baseline assessments with the Sport Concussion Assessment Tool 3 (SCAT3)[9,10] before the beginning of their respective athletic seasons. Athletes diagnosed with a concussion also completed SCAT3 assessments at acute injury and time of RTP, along with 1 month after RTP to verify the stability of SCAT3 measures after medical clearance.

Standard protocol approvals, registrations, and patient consents

The study was carried out in accordance with the Canadian Tri-Council Policy Statement 2 and with approval of the University of Toronto and St. Michael's Hospital research ethics boards, with all participants giving free and written informed consent.

Magnetic resonance imaging

Athletes were imaged using a 3T MRI system (Magnetom Skyra, Siemens Healthineers USA, Malvern, PA) with a standard multichannel head coil. Structural imaging included 3-dimensional T1-weighted magnetization prepared rapid acquisition gradient echo imaging (magnetization prepared rapid acquisition gradient echo imaging; inversion time [TI]/echo time [TE]/repetition time [TR] 1,090/3.55/2,300 milliseconds, flip angle 8°, 192 sagittal slices with field of view [FOV] 240 × 240 mm, 256 × 256–pixel matrix, 0.9-mm slice thickness, 0.9 × 0.9–mm in-plane resolution, bandwidth [BW] 200 Hertz per pixel), fluid-attenuated inversion recovery imaging (fluid-attenuated inversion recovery imaging; TI/TE/TR 1,800/387/5,000 milliseconds, 160 sagittal slices with FOV 230 × 230 mm, 512 × 512 matrix, 0.9-mm slice thickness, 0.4 × 0.4–mm in-plane resolution, BW 751 Hz/pixel), and susceptibility-weighted imaging (susceptibility-weighted imaging; TE/TR 20/28 milliseconds, flip angle 15°, 112 axial slices with FOV 193 × 220 mm, 336 × 384 matrix, 1.2-mm slice thickness, 0.6 × 0.6–mm in-plane resolution, BW 120 Hz/pixel). The magnetization prepared rapid acquisition gradient echo imaging, fluid-attenuated inversion recovery imaging, and susceptibility-weighted imaging scans were inspected by an MRI technologist during imaging and later reviewed by a neuroradiologist, with clinical reporting if abnormalities were identified. No abnormalities (white matter hyperintensities, contusions, microhemorrhage, or statistical outliers) were found for the concussed athletes and controls in this study.

Functional MRI

Resting-state fMRI was acquired via multislice T2*-weighted echo planar imaging (TE/TR 30/2000 milliseconds, flip angle 70°, 32 oblique-axial slices with FOV 200 × 200 mm, 64 × 64 matrix, 4.0-mm slice thickness with 0.5-mm gap, 3.125 × 3.125–mm in-plane resolution, BW 2,298 Hz/pixel), producing a time series of 195 images. During acquisition, athletes were instructed to lie still with their eyes closed and not to focus on anything. Processing and analysis were performed with Analysis of Functional Neuroimages (AFNI; afni.nimh.nih.gov), fMRIB Software Library (FSL; fsl.fmrib.ox.ac.uk), and customized algorithms developed in the laboratory. After the first 4 volumes were discarded to allow scans to reach equilibrium, this included rigid-body motion correction (AFNI 3dvolreg), removal of outlier scan volumes using (SPIKECOR; nitrc.org/projects/spikecor), slice-timing correction (AFNI 3dTshift), spatial smoothing with a 6-mm full width at half-maximum (FWHM) isotropic 3D gaussian kernel (AFNI 3dmerge), and regression of motion parameters and linear-quadratic trends as nuisance covariates. To control for physiologic noise, PHYCAA+ (nitrc.org/projects/phycaa_plus) was used to spatially down-weight areas of nonneural signal. This was followed by regression of mean white matter (WM) signal, calculated from voxels with probability $p(\mathrm{WM}) \geq p_{95\%}(\mathrm{WM})$, i.e., the distribution 95th percentile, based on the probabilistic tissue maps described below. The fMRI data of each athlete were coregistered to a common template with the use of FSL flirt to compute the rigid-body transform of the mean fMRI volume to the T1 image, along with the affine transformation of the T1 image to the Montreal Neurological Institute (MNI) 152 template. The net transform was then applied to fMRI data, resampled at 3 × 3 × 3–mm^3 resolution. To ensure that only gray matter regions were analyzed, voxels were retained that intersected with the MNI152 brain mask and a gray matter mask. The latter was obtained by applying FSL fast to subject T1 images, producing segmented gray matter, white matter, and CSF maps. The maps were then transformed to the MNI152 template with the FSL fslvbm protocol and smoothed with a 6-mm FWHM isotropic 3D gaussian kernel, followed by group averaging. A gray matter mask was then chosen to include only regions where $p(\mathrm{GM}) > p(\mathrm{WM}) + p(\mathrm{CSF})$, where GM is gray matter and WM is white matter, and remaining voxels that overlapped with ventricles on the MNI152 template image were removed manually. After data processing, global functional connectivity (Gconn) brain maps were calculated as follows. For each gray matter voxel, the set of Pearson correlations were calculated between its blood oxygen level–dependent time series and the blood oxygen level–dependent time series of all other gray matter voxels. The root mean square was then computed over this set of connectivity values, thereby providing a summary measure of total functional connectivity at each voxel.

Arterial spin labeling

Two-dimensional pulsed arterial spin labeling was acquired with the PICORE QUIPSS II sequence (TE/TR 12/2,500 milliseconds, TI1/TI1s/TI2 700/1,600/1,800 milliseconds,

flip angle 90°, 14 oblique-axial slices with FOV 256 × 256 mm, 64 × 64 matrix, 8.0-mm slice thickness with 2.0-mm gap, 4.0 × 4.0–mm in-plane resolution, BW 2,368 Hz/pixel). A single M_0 calibration scan and a series of 45 tag-control image pairs were acquired. Data were processed and analyzed via a combination of AFNI, FSL, and customized algorithms developed in the laboratory. Rigid-body motion correction of tag-control scans was performed with AFNI 3dvolreg, aligning the images to the M_0 scan. Filtering of outlier tag-control pairs was performed with the protocol described previously,[11] followed by spatial smoothing with AFNI 3dmerge, with a 6-mm isotropic 3D gaussian kernel. Voxel-wise estimates of CBF were then calculated in units of milliliters per 100 g per minute on the basis of the mean difference over all tag-control pairs, using the previously applied kinetic modeling parameters.[12] The CBF brain maps were then coregistered to MNI152 template and masked to include only gray matter using the same procedure reported for the resting-state fMRI data above. To further control against including voxels with white matter partial volume effects in the analysis of lower-resolution arterial spin labeling data, an additional mask iteration was performed by retaining only voxels with mean control CBF values >20 mL/100 g/min.

Diffusion tensor imaging

A diffusion-weighted imaging protocol was performed (66 axial slices with FOV 240 × 240 mm, 120 × 120 matrix, 2.0-mm slice thickness, 2.0 × 2.0 in-plane resolution, BW 1,736 Hz/Px) consisting of 30 diffusion-weighting directions (TE/TR 83/7,800 milliseconds, b = 700 s/mm^2, 9 b0 scans). The diffusion tensor imaging (DTI) data were processed with utilities from FSL and customized algorithms developed in the laboratory. The FSL eddy_correct protocol was used to perform simultaneous correction of eddy currents and rigid-body head motion; FSL bet was used to mask out nonbrain voxels; and FSL dtifit was used to calculate voxel-wise measures of fractional anisotropy (FA) and mean diffusivity (MD). Coregistration of brain maps was based on the FSL FDT protocol: masked subject FA maps were eroded by 1 voxel width at brain edges and coregistered affinely to the FMRIB58 template with FSL flirt; a symmetric, study-specific template was computed by averaging transformed FA maps, reaveraged with flipped left/right orientations; the average template was used as a reference, and FA maps were coregistered nonlinearly with FSL fnirt and were used to update the study-specific template; the FA maps were coregistered to the new template via fnirt, and the mean template was updated. During the final registration step, images were resampled to 3 × 3 × 3–mm^3 resolution and convolved with a 6-mm FWHM 3D gaussian smoothing kernel to minimize the effects of local variation in white matter structure. All analyses were performed within a mask of regions with a mean FA >0.25 to restrict analyses to white matter tracts.

Clinical and demographic data

Participant demographics are listed in table 1, including age, sex, and concussion history, along with time to RTP for concussed athletes. SCAT3 symptom scores are included, along with brief cognitive testing and scores for the Modified Balance Error Scoring System. A symptom severity score was obtained by summing across a 22-item symptom scale, with each item receiving a 7-point Likert scale rating. A total symptoms score was also obtained by counting symptoms with nonzero ratings. All scores were tested for significant difference relative to baseline via nonparametric Wilcoxon paired-measures tests. Table 2 lists athlete numbers by sport for both the control and concussed groups.

Neuroimaging data: Main effects of concussion

For each MRI parameter (Gconn, CBF, FA, and MD) and time since injury, the effects of concussion were evaluated with voxel-wise nonparametric analyses to avoid assumptions about the statistical distributions for different parameters. For concussed athletes, the MRI parameter values x_s were first converted into difference scores relative to a subgroup of matched controls, defined as follows: control athletes were selected who matched the concussed athlete on sex and prior concussion; within this pool, controls who had ≤2 years of age difference from the concussed athlete were selected; if the control sample pool had n < 20, the maximum age difference was increased by 1 until this threshold was reached. This produced a median of 22 controls (interquartile range 21–26) as reference for each concussed athlete. From the control subgroup, a robust normative mean $m_{c(s)}$ was then calculated via location M-estimator[13] with tuning parameter k = 1.35; the difference was then calculated relative to the normative mean, $\Delta x_s = x_s - m_{c(s)}$. These difference values robustly quantify how much each concussed athlete deviates from his or her demographically matched cohort.

For each time point after injury (SYM, time of RTP, and 1 year after RTP), the group mean of difference score Δx_s was calculated for concussed athletes at each voxel. In addition, bootstrapped empirical distributions were obtained by resampling on participants with replacement (1,000 iterations). Significant brain regions were identified where the 99.5% confidence interval (CI) did not overlap zero (equivalent to $p < 0.005$, 2-tailed significance). Subsequently, cluster-size thresholding was performed at an adjusted $p = 0.05$ with AFNI 3dFWHMx used to estimate the intrinsic spatial smoothness of maps, followed by AFNI 3dClustSim to obtain minimum cluster size.

Neuroimaging data: Covariate effects

A secondary analysis determined whether the neuroimaging measures of concussed athletes were influenced by clinical factors, specifically SCAT3 total symptom severity score at acute injury and days to RTP, defined as the number of days from the concussion event to symptom resolution, following a graded exertional protocol.[1] Given the high correlation between symptoms and recovery time (see Results: Analysis of Clinical and Demographic Data below), a composite measure was produced by renormalizing via inverse empirical distribution function, mean centering, and then

Table 1 Demographic data for athletes with concussion and controls, along with symptom and cognitive scores, based on the SCAT3

	Control		Concussion		
Age (mean ± SD), y	20.3 ± 2.0		20.0 ± 1.9		
Female, n (%)	60/122 (49)		13/24 (54)		
Prior concussion, n (%)	57/122 (47)		14/24 (58)		
Number of concussions (for athletes with prior concussion)	2 (1, 2)		2 (1, 3)		
Months since last concussion (for athletes with prior concussion)	35 (19, 56)		26 (4, 60)		
Days to RTP	—		27 (15, 54)		
	Baseline	**Baseline**	**SYM**	**RTP**	**Post-RTP**
Total symptoms	3 (0, 5)	2 (0, 5)	10 (5, 15)[a]	0 (0, 2)	1 (0, 2)
Symptom severity	3 (0, 8)	2 (0, 8)	15 (6, 28)[a]	0 (0, 2)	1 (0, 3)
Orientation	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (4, 5)
Immediate memory	15 (15, 15)	14 (14, 15)	15 (14, 15)	15 (14, 15)	15 (14, 15)
Concentration	4 (3, 5)	3 (2, 4)	4 (3, 5)	4 (3, 5)	4 (3, 5)
Delayed memory	5 (4, 5)	4 (2, 5)	4 (3, 5)	5 (4, 5)	5 (4, 5)
M-BESS errors	2 (0, 4)	3 (0, 4)	3 (0, 5)	1 (0, 2)	2 (0, 4)

Abbreviations: M-BESS = Modified Balance Error Scoring System; RTP = return to play; SCAT3 = Sport Concussion Assessment Tool 3; SYM = early symptomatic injury.
All nonbinary variables except age are summarized by the median (quartiles 1, 3). Clinical scores are reported for preseason baseline, SYM, medical clearance to RTP, and 1 month after RTP (post-RTP). Only total symptoms and symptom severity were significantly elevated at SYM relative to baseline.
[a] Significant difference in scores for SYM relative to all other groups.

averaging the 2 variables. The resulting clinical severity (CS) score was then correlated against the neuroimaging difference measures Δx_s for each parameter and time point with nonparametric Spearman correlations. As in the previous section, bootstrap resampling was used to construct empirical distributions, followed by thresholding of the correlation maps at an adjusted $p = 0.05$ significance via cluster-size thresholding.

Data availability

The authors have documented all data, methods, and materials used to conduct this research study, and anonymized data will be shared by request from any qualified investigator.

Results

Clinical and demographic data

Table 1 reports demographic and clinical information for the concussed athletes and controls. Both groups constitute a balanced sample of male and female athletes with and without a history of concussion. For athletes with a history of concussion, no significant differences were seen in the total number of previous concussions or months since their last concussion ($p > 0.26$ for both, 2-sample Wilcoxon test). For concussed athletes, symptoms were significantly elevated at SYM compared to baseline for both total number of symptoms (median [quartiles 1, 3]: 6 [3, 10], $p < 0.001$) and symptom severity (9 [3, 25], $p < 0.001$) but were not significantly elevated at RTP for both total number of symptoms (−1 [−2, 0], $p > 0.99$) and symptom severity (−1 [−6, 0], $p > 0.99$). For the other cognitive and balance tests, no significant

Table 2 Athlete numbers by sport for both male and female groups

Controls (n = 122), n	Concussion (n = 24), n
Water polo (1 M)	Water polo (1 F)
Lacrosse (9 M[a]/2 F)	
Basketball (7 F)	Basketball (1 M/2 F)
Rugby (3 M[a]/9 F[a])	Rugby (3 M[a]/5 F[a])
Football (9 M[a])	Football (2 M[a])
Soccer (10 M/7 F)	
Hockey (17 M[a]/23 F)	Hockey (4 M[a]/3 F)
Volleyball (13 M/12 F)	Volleyball (1 M/2 F)

[a] Collision sports, defined as involving routine, purposeful body-to-body contact.[47]

effect of concussion was seen at either acute injury or RTP ($p \geq 0.31$ for all tests). In addition, no significant changes were seen on any of the clinical measures from RTP to 1 month after RTP ($p > 0.125$, all tests). Among concussed athletes, symptom severity scores were variable across individuals, as was the time to RTP, with both variables having a relatively high Spearman correlation ($\rho = 0.669$, 95% CI 0.410–0.828, $p < 0.001$). None of the concussed athletes had acquired a new concussion between the SYM and 1-year post-RTP scanning time points, and all athletes had returned to normal school/work, social, and sport activities at this time.

Neuroimaging data: Main effects of concussion

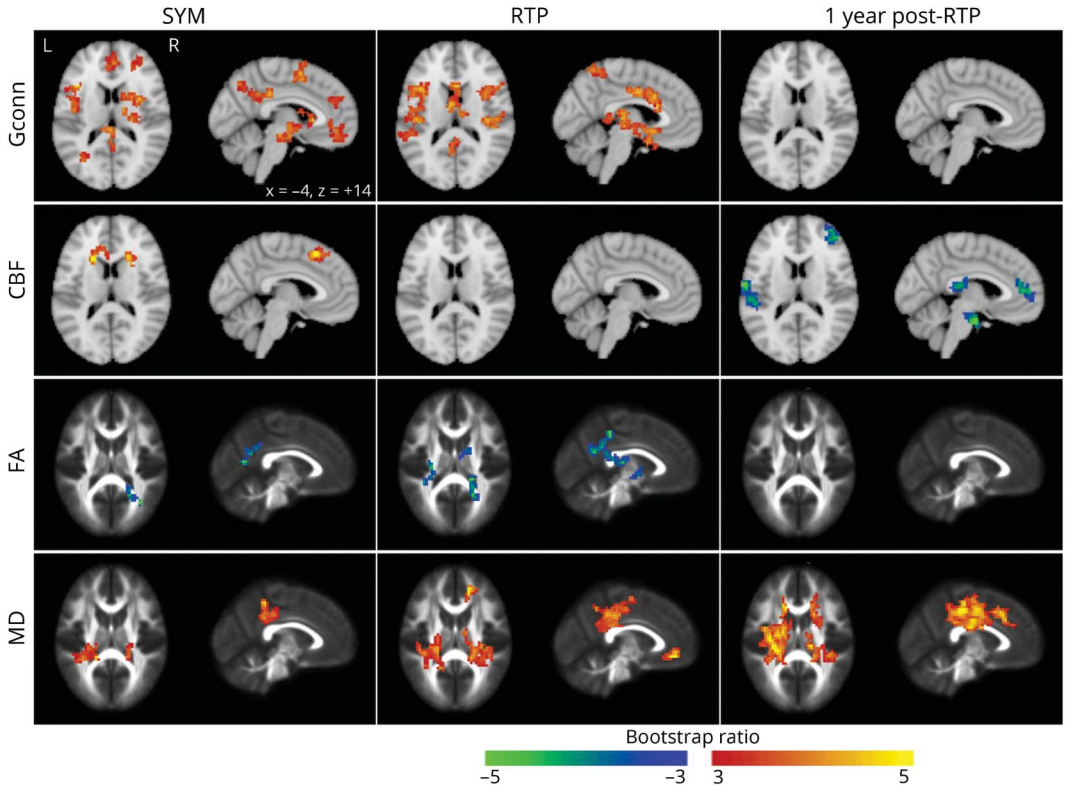
In figure 1 and table 3, the effects of concussion are shown at each postinjury time point for the 4 different MRI parameters. For Gconn (first row), elevated connectivity was observed at SYM (mean effect 0.0275, 95% CI 0.0175–0.0386), with clusters in frontal, temporal, and parietal regions, along with the posterior cingulate. Significant elevations in connectivity were also seen at RTP (0.0291, 95% CI 0.0170–0.0423) in similar brain regions, although frontal effects were reduced and more extensive temporal regions now identified; significant effects were also seen in the insula. By 1 year after RTP, however, there were no significant effects of concussion for Gconn. For CBF (second row), blood flow was also elevated at SYM (10.72 mL/100 g/min, 95% CI 6.05–15.76), with effects that were more spatially limited than Gconn and restricted to the superior frontal gyri. At RTP, no significant effects of concussion were detected for CBF. At 1 year post-RTP, however, significant reductions in CBF were observed (−10.03 mL/100 g/min, 95% CI −13.38 to −7.03) within middle frontal and temporal regions.

The DTI-based white matter measures are also depicted in figure 1. For FA (third row), concussion was associated with reductions mainly in the posterior corona radiata at SYM (mean −0.0194, 95% CI −0.0270 to −0.0121) and at RTP (mean −0.0156, 95% CI −0.0207 to −0.0105), with more spatially extensive effects seen at the later time point. No significant concussion effects were identified at 1 year post-RTP for FA. For MD (bottom row), significant elevations were observed mainly in the posterior and superior corona radiata for SYM (mean 1.62×10^{-5} mm^2/s, 95% CI 0.85–2.37), RTP (mean 1.48×10^{-5} mm^2/s, 95% CI 0.82–2.16), and 1 year after RTP (mean 1.32×10^{-5} mm^2/s, 95% CI 0.86–1.78), with increasingly spatially extensive effects observed at later time points.

Neuroimaging data: Covariate effects

In figure 2 and table 4, correlations between MRI measures and CS score (i.e., symptom severity and time to RTP) are

Figure 1 Brain areas showing significant effects of concussion at SYM, medical clearance to RTP, and 1 year after RTP



Parameters include global functional connectivity (Gconn), cerebral blood flow (CBF), fractional anisotropy (FA), and mean diffusivity (MD). Slices are shown as maximum-intensity projections in axial and sagittal planes (Montreal Neurological Institute coordinates: x = −4, z = +14). RTP = return to play; SYM =early symptomatic injury.

Table 3 Cluster report for main effects of concussion in figure 1

	Cluster	Center of mass			Brain region	Cluster size, mm^3	Peak value, bootstrap ratio
Gconn							
SYM	1	0	48	−12	Superior frontal (medial orbital)	2,079	3.63
	2	27	3	57	Superior frontal R	2,079	4.17
	3	0	−39	33	Cingulate (posterior)	1,863	4.05
	4	−42	−6	−6	Superior temporal L	1,161	3.68
	5	−45	12	6	Inferior frontal (opercular) L	1,134	4.72
	6	−30	−66	42	Inferior parietal L	1,134	3.48
	7	30	45	27	Middle frontal R	1,080	2.99
	8	24	−18	18	Parahippocampal R	945	3.91
RTP	1	−45	12	33	Precentral L	2,592	4.23
	2	0	0	33	Cingulate (mid)	2,565	5.02
	3	45	−21	9	Heschl R	2,187	4.00
	4	−45	−18	6	Superior temporal L	1,836	4.62
	5	−39	3	−9	Insula L	1,674	4.08
	6	36	9	−21	Temporal pole (superior) R	1,296	4.13
	7	45	15	26	Inferior frontal (opercular) R	1,296	3.95
	8	−3	−54	60	Precuneus L	1,242	3.76
	9	−54	−39	6	Middle temporal L	1,080	3.47
1 y post-RTP	—						
CBF							
SYM	1	−15	24	51	Superior frontal L	1,566	5.36
	2	24	21	51	Superior frontal R	1,269	4.56
RTP	—						
1 y post-RTP	1	39	48	9	Middle frontal R	2,349	−4.46
	2	−54	−27	15	Superior temporal L	1,809	−4.13
	3	−60	−15	−24	Inferior temporal L	1,647	−5.69
FA							
SYM	1	24	−54	27	Posterior corona radiata L	1,080	−5.51
RTP	1	21	−45	33	Posterior corona radiata R	1971	−6.23
	2	−30	−30	15	Internal capsule (retrolenticular part) L	1,350	−4.48
	3	15	−9	−3	Internal capsule (posterior limb) R	648	−3.63
1 y post-RTP	—						
MD							
SYM	1	−24	−36	36	Posterior corona radiata L	3,186	4.54
	2	21	−33	39	Posterior corona radiata R	999	3.64
RTP	1	−27	−33	36	Posterior corona radiata L	5,184	4.17
	2	24	−33	36	Posterior corona radiata R	4,860	4.26
	3	18	39	−6	Anterior corona radiata R	1,026	5.83

Continued

Table 3 Cluster report for main effects of concussion in figure 1 *(continued)*

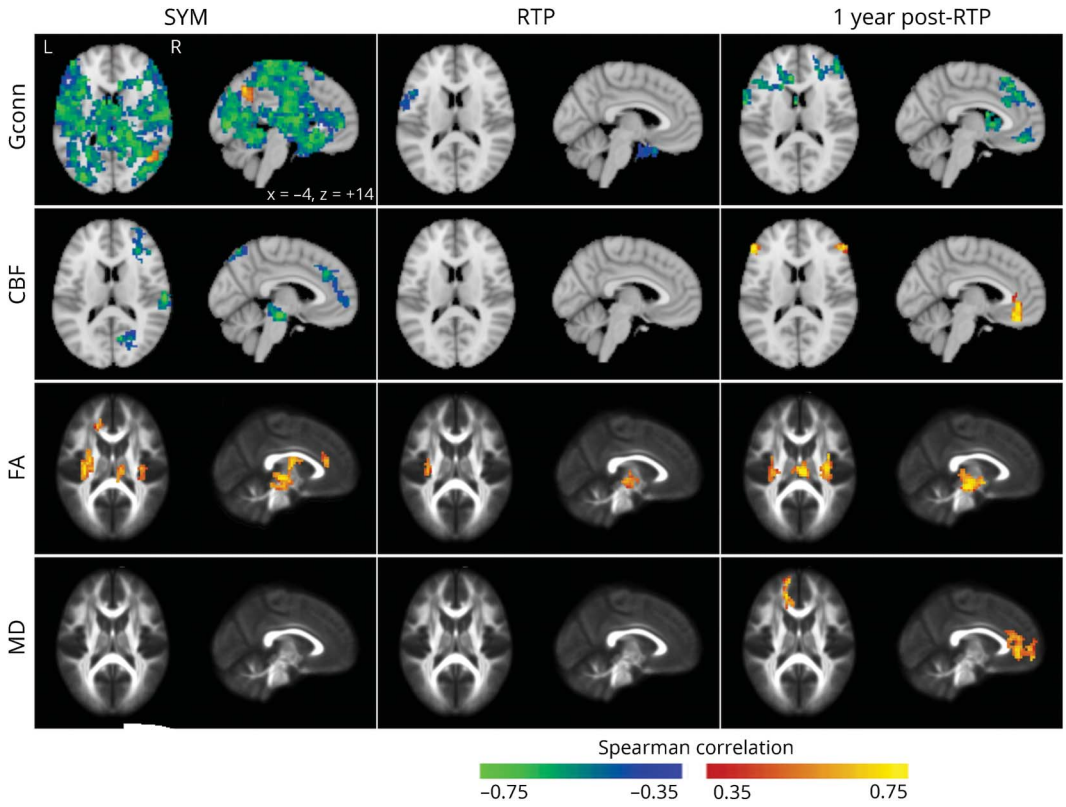
	Cluster	Center of mass			Brain region	Cluster size, mm^3	Peak value, bootstrap ratio
1 y post-RTP	1	−27	−18	39	Posterior corona radiata L	13,392	5.95
	2	21	12	36	Superior corona radiata R	2,457	4.24
	3	18	−27	45	Superior corona radiata R	2,403	4.85
	4	36	−36	33	Superior longitudinal fasciculus R	918	4.08
	5	−18	18	33	Anterior corona radiata L	910	4.72

Abbreviations: CBF = cerebral blood flow; FA = fractional anisotropy; Gconn = global functional connectivity; inf = inferior; MD = mean diffusivity; RTP = return to play; SYM = early symptomatic concussion.
Centers of mass are in Montreal Neurological Institute coordinates and brain region based on nearest labeled gray matter region in the Automated Anatomical Labeling atlas (Gconn and CBF) or nearest labeled white matter tract in the Johns Hopkins University atlas (FA and MD).

shown at each postinjury time point for the 4 different MRI parameters. In general, Gconn was negatively correlated with CS score, with the most spatially extensive effects at SYM, including large clusters in the frontal and occipital lobes. At RTP, effects were greatly reduced and limited to left middle temporal gyrus; however, more extensive, predominantly frontal effects were again observed at 1 year post-RTP. For CBF (second row), a similar but less spatially extensive response was observed as a negative correlation of CBF with CS score at SYM in frontal, temporal and parietal regions. At RTP, no significant effects were observed, whereas at 1 year after RTP, positive correlations were seen between CBF and CS score in frontal areas.

In terms of DTI measures, FA (third row) correlations with CS score included more ventral white matter regions such as the internal capsule, cerebral peduncle, and anterior corona radiata. Similar to Gconn, these effects were present at all

Figure 2 Brain areas where severity of concussion effects is significantly associated with both acute symptom severity and time to RTP, shown for SYM, medical clearance to RTP, and 1 year after RTP



Parameters include global functional connectivity (Gconn), cerebral blood flow (CBF), fractional anisotropy (FA), and mean diffusivity (MD). Slices are shown as maximum-intensity projections in axial and sagittal planes (Montreal Neurological Institute coordinates: x = −4, z = +14). RTP = return to play; SYM = early symptomatic injury.

Table 4 Cluster report for covariate effects of concussion in figure 2

	Cluster	Center of mass			Brain region	Cluster size, mm^3	Peak value, correlation
Gconn							
SYM	1	−42	−3	30	Precentral L	61,128	−0.79
	2	54	−3	15	Rolandic operculum R	25,839	−0.72
	3	39	63	3	Middle occipital R	18,198	−0.71
	4	−27	78	24	Middle occipital L	8,154	−0.78
	5	30	−9	63	Superior frontal R	2,592	−0.64
	6	−27	−57	9	Fusiform L	2,403	−0.66
	7	−3	−15	15	Thalamus L	2,268	−0.78
	8	48	−60	39	Angular R	2025	0.69
	9	33	27	−12	Inferior frontal (orbital) R	1,269	−0.68
	10	51	−42	18	Superior temporal R	1,161	−0.67
	11	18	24	60	Superior frontal R	1,161	−0.7
RTP	1	−54	6	−30	Middle temporal L	1,593	−0.57
1 y post-RTP	1	−18	30	45	Superior frontal L	2,673	−0.77
	2	45	45	−12	Inferior frontal (orbital) R	1809	−0.66
	3	24	42	33	Middle frontal R	1,431	−0.64
	4	−60	9	6	Rolandic operculum L	1,161	−0.71
	5	−42	27	30	Inferior frontal (triangular) L	1,161	−0.62
CBF							
SYM	1	33	42	21	Middle frontal R	3,267	−0.63
	2	63	−24	−12	Middle temporal R	2,268	−0.78
	3	21	−69	57	Superior parietal R	1,701	−0.69
RTP	—						
1 y post-RTP	1	54	39	−9	Inferior frontal (orbital) R	1,566	0.73
	2	−48	36	−15	Inferior frontal (orbital) L	1,242	0.75
FA							
SYM	1	−30	−15	3	Internal capsule (retrolenticular part) L	2,727	0.72
	2	33	−18	6	External capsule R	810	0.63
	3	9	−24	−12	Cerebral peduncle R	702	0.66
	4	−18	33	15	Anterior corona radiata L	702	0.65
RTP	1	−33	−15	−3	External capsule L	864	0.62
1 y post-RTP	1	30	−18	−3	External capsule R	2,295	0.7
	2	6	−15	−12	Cerebral peduncle R	1,566	0.78
	3	−33	−18	−3	External capsule L	1,161	0.61

Continued

Table 4 Cluster report for covariate effects of concussion in figure 2 *(continued)*

	Cluster	Center of mass			Brain region	Cluster size, mm^3	Peak value, correlation
MD							
SYM	—						
RTP	—						
1 y post-RTP	1	−18	42	6	Anterior corona radiata L	2,754	0.69

Abbreviations: CBF = cerebral blood flow; FA = fractional anisotropy; Gconn = global functional connectivity; inf = inferior; MD = mean diffusivity; RTP = return to play; SYM = early symptomatic concussion.
Centers of mass are in Montreal Neurological Institute coordinates and brain region based on nearest labeled gray matter region in the Automated Anatomical Labeling atlas (Gconn and CBF) or nearest labeled white matter tract in the Johns Hopkins University atlas (FA and MD).

imaging time points but were the least spatially extensive at RTP. Finally, for MD (bottom row), no significant correlations with CS score were seen at SYM or at RTP. At 1 year post-RTP, MD was significantly correlated with injury severity within the anterior corona radiata.

Discussion

Despite concussion being conventionally described as a transient disturbance in brain function,[14] there is growing evidence that neurobiological recovery may be incomplete at RTP.[7] It is important to determine whether disturbances in brain physiology seen at this time are permanent or resolve over a longer time interval, so as to better understand the biological mechanisms of neurologic sequelae associated with a history of concussion.[2] It was hypothesized that for all advanced MRI parameters, athletes would show significant concussion effects at both symptomatic injury and RTP, but the effects would no longer be present by 1 year post-RTP. The principal finding of this study was that different aspects of brain physiology have different patterns of long-term recovery, with only a subset of MRI parameters showing nonsignificant concussion effects at 1 year after RTP. For brain function and white matter diffusion anisotropy, no significant concussion effects were seen at 1 year after RTP, whereas for CBF and white matter diffusivity, persistent effects were seen at this time. Secondary analyses showed that the effects of concussion on the brain also vary as a function of clinical measures, including acute symptom severity and time to RTP, for all examined MRI parameters. The design of this study has enabled us to highlight that the effects of an acute concussive event on brain physiology are both complex and long-lasting.

In an examination of resting brain function, Gconn was elevated during the symptomatic phase of concussion. This response has previously been reported in the traumatic brain injury (TBI) literature,[15,16] although studies of sport concussion have also identified both focal increases and decreases in connectivity.[17,18] The elevations in Gconn at symptomatic injury also remained present at RTP, suggesting statistically significant and persistent concussion-related brain changes at medical clearance. The elevated connectivity seen at early injury and RTP is a common biomarker of acquired brain injury[16,19] and has been hypothesized to reflect increased functional redundancy as an adaptive response to disrupted brain function. However, at 1 year after RTP, these effects were no longer observed, providing evidence that postconcussion alterations in functional connectivity have resolved at this time.

CBF was also elevated at symptomatic injury, which is consistent with studies of mild TBI in younger individuals,[20] although reduced CBF at symptomatic injury has also been reported in some cohorts.[6,21] The increased delivery of oxygenated blood to gray matter tissues may serve to compensate for increased metabolic demand after injury,[14] consistent with the higher Gconn observed in this cohort. The effects seen during the symptomatic phase of injury had dissipated by RTP, which is consistent with a prior longitudinal study of concussed athletes in which CBF effects had resolved by 1 month after injury.[6] However, by 1 year post-RTP, significantly reduced CBF was found, suggesting emerging long-term brain changes. These CBF effects are consistent with a prior cross-sectional study of athletes with a history of concussion in which lower frontal CBF was observed.[22] The observed effects may be related to subtle long-term decreases in gray matter volume after injury, which have been observed in prior cross-sectional studies[22,23] and would lead to reduced CBF demand. Alternatively, it may represent a persistent mismatch between CBF and neurometabolic activity, similar to that observed at early injury.[20] The study findings suggest that the effects of concussion on CBF may be more subtle than for Gconn but persist over a longer time scale.

For DTI measures of white matter, concussion was associated with decreased FA and increased MD, which has previously been reported among symptomatic concussed athletes.[3,24] The observed effects also remained present at RTP, suggesting ongoing changes in tissue microstructure at medical clearance. However, these parameters showed distinctive spatial patterns of effect and different responses by 1 year post-RTP. For FA, the effects were nonsignificant at 1 year after RTP, similar to Gconn, whereas MD showed increasing spatial extent of effects at 1 year after RTP. Prior literature has

also reported differences between DTI parameters in the effects of subconcussive impact[25] and concussion after 1 month after injury.[24] Thus, different DTI parameters may be sensitive to different aspects of brain recovery. The results of this study suggest that FA may be more sensitive to processes linked to early injury such as vasogenic or cytotoxic edema.[26] Conversely, MD may be more sensitive to processes showing delayed effects, including neuroinflammation-mediated glial activation,[27] which has been found to be elevated in athletes with a history of concussion.[28,29]

Concussed athletes with greater CS scores (i.e., with greater symptom severity and longer time to RTP) had lower Gconn values primarily at the early phase of injury, which is consistent with prior research in this cohort.[30] The main effect of elevated Gconn may therefore be an adaptive response to injury. Surprisingly, significant effects were also evident at 1 year after RTP, indicating that athletes with higher CS scores may have persistent differences in brain function despite the resolution of symptoms at this time. Although athletes in this study were asymptomatic after RTP, these findings also align with the postconcussive symptom literature, in which the effects of concussion on functional connectivity were found mainly in temporal and insular regions at 1 to 3 weeks after injury but had become increasingly frontal at 6 months after injury.[31]

For CBF, negative correlations with CS scores were also seen frontally, indicating that the main effect of elevated frontal CBF seen at symptomatic injury may constitute a normal brain response to injury. This is consistent with prior research in which greater cognitive symptom burden was correlated with reduced frontal CBF for symptomatic athletes.[32] Interestingly, the effects seen in this study had reversed by 1 year post-RTP; greater frontal CBF correlated with higher CS scores at this time. This further indicates that the CS variable may be an early indicator of long-term effects on functional brain physiology.

In an examination of the DTI measures, elevated FA was associated with greater CS scores at all time points after injury, primarily in ventral white matter regions. These results are contrasted with the main effects of concussion, which included reduced FA in dorsal white matter. Elevated FA in individuals with mild TBI endorsing greater postconcussive symptoms has been previously reported[33] and may reflect spatial heterogeneity in the effects of edema on white matter tissues; i.e., compression of intracellular spaces may lead to the elevations in FA seen in these brain regions. For MD, the covariate effects were far more spatially limited and observed only at 1 year after RTP, with greater CS scores corresponding to greater diffusivity frontally, potentially reflecting enhanced microstructural injury in these brain regions.

This study featured a comprehensive longitudinal examination of multiple different MRI parameters, including Gconn, CBF, FA, and MD within a single concussed athlete cohort. Comparing the results for the different MRI parameters may enable a better understanding of how different aspects of pathophysiology are related and may be used to form novel hypotheses about mechanisms of brain recovery. The significant CBF effects seen at SYM were no longer present at RTP, whereas Gconn effects seen at symptomatic injury had shown relatively little change at RTP. This mismatch suggests that changes in Gconn are not driven by altered CBF and are likely due to other concussion-related processes, which may include neurometabolic dysregulation,[14] reorganization of functional brain networks[16] or disruption of the underlying neural substrate. In addition, FA shows a trajectory similar to that of Gconn, with effects at symptomatic injury and RTP but resolution at 1 year after RTP, further indicating that white matter microstructural changes may contribute to altered brain function. Associations between functional connectivity and microstructure have previously been reported for more severe forms of TBI[34,35] but are less understood in concussion. In contrast to FA, MD shows spatially extensive effects at 1 year after RTP, concurrent with significantly decreased CBF. It may therefore be hypothesized that the emergence of delayed pathophysiologic processes that affect MD such as neuroinflammation may contribute to the observed longitudinal declines in CBF.[36] These intriguing findings provide preliminary evidence of relationships between the different aspects of brain physiology after a concussion that should be investigated in greater detail in future research.

Although this study provided novel information about brain recovery after concussion, a few limitations should be taken into consideration. In particular, gaps remain in the understanding of time-evolving pathophysiology. This includes potential transient brain changes between RTP and 1 year post-RTP that were not observed in the current design. The longitudinal effects of concussion during this time interval may also be influenced by participant-dependent factors such as detraining before RTP and the effects of exertion and subconcussive impacts after RTP. A strength of the present study is that, despite potentially heterogeneous post-RTP activities, significant main effects of concussion were identified within the examined cohort. Nevertheless, future studies may benefit from more detailed monitoring and MRI scanning within the first year after RTP. Moreover, although this study examined recovery over one of longest postconcussion time intervals to date, the observed effects cannot yet be confirmed as permanent in nature. Future longitudinal research is required to link the present findings to long-term sequelae associated with history of concussion, as seen in retired athletic cohorts.[37,38]

In addition, all neuroimaging data of concussed athletes were acquired after concussion, limiting the ability to assess whether concussed brains had returned to normal preinjury physiology. To mitigate this issue, the present study included an extensive control group—to the best of our knowledge, the largest to date—as a robust normative cohort for

evaluating concussion changes. However, preinjury clinical and demographic factors may significantly affect both baseline brain physiology and response to concussion, including sex, concussion history, sport type, and position played. For athletes with a history of concussion, factors such as the number of prior concussions and time since last injury may also affect concussion response.[22] The present study measured concussion effects within a demographically mixed cohort to ensure that the findings are most broadly relevant to sport-related concussion, but future large cohort studies should directly evaluate the influence of demographic factors on concussion-related neuroimaging.

This study focused on sport-related concussion because of the demographic homogeneity, good premorbid health, and well-established clinical assessment protocols for the athletic cohort. To be relevant to other populations, however, more research is required to determine how to integrate the findings with respect to modifiers of brain physiology, including age[39,40] and physical fitness.[41,42] Moreover, for individual patients, it must be emphasized that the present findings reflect the mean response to injury. The present findings therefore define the most consistently affected brain regions, which may be relevant in the development of targeted biomarkers and interventions. However, as shown in the clinical covariate analyses, there is likely significant heterogeneity between individuals,[43,44] which should also be considered in the evaluation of the generalizability of findings.

This study examined recovery of the brain after a concussion relative to the time of RTP using multiple different MRI measures of brain physiology. The findings of this study may serve to refine our clinical understanding of concussion recovery, showing it to be a more complex, long-lasting process than previously thought.[14] Current consensus guidelines for safe RTP are based primarily on the resolution of symptoms[1]; however, the findings in this study indicate that more research is needed within the post-RTP time window to better understand optimal recovery time from a biological standpoint. At RTP, multiple aspects of brain physiology show concussion effects (Gconn, FA, MD), providing evidence of incomplete or ongoing recovery. Moreover, some aspects of brain physiology show resolution by 1 year post-RTP (Gconn and FA), while others show persistent or emerging long-term effects (CBF and MD). These results provide evidence of long-term brain changes in response to concussion and suggest a potential risk for long-term sequelae, given the evidence of worse outcomes if a second concussion occurs before recovery is complete.[45,46] Finally, the MRI measures showed the effects of CS of injury throughout the recovery timeline, reinforcing that neurobiological recovery may be highly variable across individuals and partly dependent on initial clinical presentation. These findings provide novel insights into the response of the brain to concussion and help to better understand how interindividual heterogeneity in long-term brain recovery is related to clinical measures.

Author contributions

N. Churchill: study design, analysis planning and execution, interpretation of results, statistical analysis. M. Hutchison: study design, critical revision of manuscript. Simon Graham: analysis planning, critical revision of manuscript. T. Schweizer: study design, analysis planning, critical revision of manuscript.

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Disclosure

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