J Head Trauma Rehabil

Multimodal Imaging of Retired Professional Contact Sport Athletes Does Not Provide Evidence of Structural and Functional Brain Damage

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Background: Long-term consequences of playing professional football and hockey on brain function and structural neuronal integrity are unknown. **Objectives:** To investigate multimodal metabolic and structural brain magnetic resonance imaging (MRI) differences in retired professional contact sport athletes compared with noncontact sport athletes. **Methods:** Twenty-one male contact sport athletes and 21 age-matched noncontact sport athletes were scanned on a 3 tesla (3T) MRI using a multimodal imaging approach. The MRI outcomes included presence, number, and volume of focal white matter signal abnormalities, volumes of global and regional tissue-specific brain structures, diffusion-tensor imaging tract-based spatial statistics measures of mean diffusivity and fractional anisotropy, quantitative susceptibility mapping of deep gray matter, presence, number, and volume of cerebral microbleeds, MR spectroscopy *N*-acetyl-aspartate, glutamate, and glutamine concentrations relative to creatine and phosphor creatine of the corpus callosum, and perfusion-weighted imaging mean transit time, cerebral blood flow, and cerebral blood volume outcomes. Subjects were also classified as having mild cognitive impairment. **Results:** No significant differences were found for structural or functional MRI measures between contact sport athletes and noncontact sport athletes. **Conclusions:** This multimodal imaging study did not show any microstructural, metabolic brain tissue injury differences in retired contact versus non-contact sport athletes. **Key words:** *brain atrophy*, *cerebral microbleeds*, *concussion*, *diffusion-imaging*, *perfusion imaging*, *spectroscopy*, *sport athletes*, *susceptibility imaging*, *white matter signal abnormalities*

THERE IS ACCUMULATING EVIDENCE suggesting that sports-related repetitive mild traumatic brain injury (mTBI) may lead to transient or permanent functional and structural brain alterations in previously healthy individuals.[1–3] These mTBI events, consisting predominantly of subconcussive head blows without reported symptoms, are occurring particularly frequently in professional players engaging in sports requiring substantial physical head contacts (eg, American football and ice hockey).[1–3]

An increasing number of recent imaging and cognitive studies, conducted in retired contact sport athletes with a history of concussions,[4–17] indicate that

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We wish to thank the following organizations for financial support: The National Institutes of Health (National Center for Advancing Translational Sciences) award number UL1TR001412; the Robert Rich Family Foundation; and the Ralph and Mary Wilson Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or any other funding source. We also want to thank the research team at Boston University, in particular Dr Robert Stern, for their willingness to share their protocol for evaluation of neurocognitive performance.

Robert Zivadinov received personal compensation from EMD Serono, Novartis, Celgene, Genentech, Claret Medical, and Sanofi-Genzyme for speaking and consultant fees. R. Zivadinov received financial support for research activities from Biogen Idec, Teva Pharmaceuticals, Sanofi-Genzyme, Novartis, Claret Medical, and Coherus-Intekrin.

Michael G. Dwyer received personal compensation from Claret Medical for speaking and consultant fees. He received financial support for research activities from Novartis.

The authors declare no conflicts of interest.

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DOI: 10.1097/HTR.0000000000000422

there is some microscopic and macroscopic localized brain injury in different brain structures that may be associated with cognitive decline, characterized by impairment in memory, executive function, mood and behavior, among others.

While a majority of these studies showed some evidence of chronic brain injury in retired contact sport athletes,[4–7,9–17] a number of them also showed no prominent clinical, functional, or structural signs of chronic brain damage in these players.[7,8,10,18–20] Moreover, most of these studies[4–11,15–18] were based on a small sample of subjects, used only players who had a history of concussions, did not correct for multiple comparisons, and compared retired contact sport athletes with age- and sex-matched healthy individuals, and not to noncontact sport athletes, which could have contributed to an important bias when comparing athlete to nonathlete groups. In addition, only a few studies used multimodal imaging approaches to determine the extent of metabolic and structural chronic brain damage.[17,21–24]

Based on this background, the aim of this study was to apply a multimodal metabolic and structural imaging approach to investigate brain tissue injury by using different conventional and non-conventional magnetic resonance imaging (MRI) techniques, in an attempt to better understand the possible long-term consequences of professional football and ice hockey playing. In particular, we chose to compare contact athletes with noncontact athletes, to examine the continuing effect of sport activities on long-term imaging and cognitive outcomes over the long-term.

MATERIAL AND METHODS

Participants

This multimodal MRI substudy was completed as part of a larger research project of retired athletes at the University at Buffalo, which has been described in detail in the Willer et al[25] overall description of the study, accompanying this article.

Ethical approval was obtained prior to the study from the local institutional review board committee.

MRI acquisition

All scans were acquired on a 3T GE Signa Excite HD 12.0 Twin Speed 8-channel scanner (General Electric, Milwaukee, Wisconsin). The following sequences were acquired: proton-density/T2-weighted image (PD/T2-WI); fluid-attenuated inversion recovery (FLAIR); 3D high-resolution (HIRES) T1-WI using a fast spoiled gradient echo (FSPGR) with magnetization-prepared inversion recovery (IR) pulse (3D HIRES), diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), magnetic resonance spectroscopy (MRS), and perfusion-weighted imaging (PWI).

Conventional scans were prescribed in an axial-oblique orientation, parallel to the subcallosal line, and one average was used for all acquisitions. Conventional sequences were acquired with a 256 × 192 matrix (frequency × phase) and field-of-view (FOV) of 25.6 cm × 19.2 cm for an in-plane resolution of 1 mm × 1 mm. For the PD/T2 and FLAIR scans, 48 slices were collected, thickness of 3 mm, no gap between slices. For the 3D HIRES, 184 locations were acquired with a slab of 18.4 cm, providing for 1-mm isotropic resolution. Other relevant parameters were as follows: for dual fast spin-echo PD/T2, echo and repetition times (TE and TR) TE1/TE2/TR = 9/98/5300 ms, flip angle (FLIP) = 90°, echo train length (ETL) = 14; for FLAIR, TE/inversion time (TI)/TR = 120/2100/8500 ms (inversion time, TI), FLIP = 90°, ETL = 24; for 3D HIRES, TE/TI/TR = 2.8/900/5.9 ms, FLIP = 10°.

The DWI sequence was a 2D spin-echo, echo planar imaging (EPI), axial sequence, with the following sequence parameters: TE/TR = 92.8/7000 ms, FOV of 25.6 cm × 25.6 cm, number of averages: 2, 27 slices, thickness of 4 mm, slices acquired with a 0.5-mm gap between slices. The acquisition matrix was 128 × 128, frequency encoding in the right/left direction. A parallel imaging factor of 2 was applied. Diffusion parameters were – 1 b = 0 s/mm^2 image, and 39 diffusion directions with b = 900 s/mm^2. A dual-echo gradient-echo B0 field map was also acquired in order to correct for EPI distortions in the diffusion-tensor imaging (DTI) sequence (TE1/TE2/TR = 5.0/9.8/34 ms, FOV of 25.6 cm × 25.6 cm, 64 × 64 acquisition matrix, 64 slices with a voxel volume of 2 × 2 × 2 mm^3).

Data for SWI and quantitative susceptibility mapping (QSM) were acquired using an unaccelerated 3D single-echo spoiled GRE sequence with first-order flow compensation in read and slice directions, a matrix of 512 × 192 × 64 and a nominal resolution of 0.5 × 1 × 2 mm^3 (FOV = 256 × 192 × 128 mm^3), FLIP = 12°, TE/TR = 22 ms/40 ms, bandwidth = 13.89 kHz.[26,27]

A point-resolved spectroscopy sequence (PRESS)-based single-voxel spectroscopy with TR/TR = 35/3000 ms, bandwidth 5.0 kHz, was also acquired. The voxel was prescribed axially, with a slice thickness of 18.7 mm, centered superior to the ventricles, angulated parallel to the callosal line, and positioned with the bottom edge of the voxel at the intersection of the corpus callosum and the fornix, and the anterior edge of the voxel aligned with the anterior tip of the genu. The voxel was adjusted for each subject, having an average of 75 mm left to right, and 100 mm anterior to posterior.

Dynamic susceptibility contrast-enhanced PWI was acquired during and after injection of gadobutrol (0.1 mmol/kg) with an MRI-compatible power injector at a speed of 2 mL/s. A single-shot gradient-echo EPI was used with the following parameters:

TE/TR = 45/2275 ms, FOV 26 × 26 cm, matrix 96 × 96 (resulting in in-plane voxel sizes of 2.71 mm × 2.71 mm), 36 slices (4-mm thick) with no gap. Forty time points were acquired per slice.

MRI analyses

Image analysts were blinded to the subjects' demographic, clinical characteristics, and group status.

White matter signal abnormalities

Identification of white matter signal abnormalities (WM-SAs) was done using a semiautomated edge-detection contouring/thresholding technique on T2/PD/FLAIR images.[26]

Global and regional brain atrophy measures

Volumetric measures were determined on the 3D HIRES that were modified by using an in-house developed inpainting technique to avoid tissue misclassification.[27] Structural Image Evaluation using Normalisation of Atrophy Cross-sectional (SIENAX) version 2.6 (FMRIB, Oxford, UK)[28] was used to obtain normalized brain volume (NBV), gray matter (GM) volume (NGMV), WM volume (NWMV), cortical volume (NCV), and lateral ventricle volume (NLVV).

FMRIB's Integrated Registration and Segmentation Tool (FIRST) on the 3D HIRES was used to calculate volume of the deep GM.[29] The following structures were segmented: total deep GM, thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, and accumbens.

DTI measures

B0 field maps were created with the use of MATLAB (MATLAB, Natick, Massachusetts) in-house scripts. DTI analysis was performed using the tools from the FSL software package (http://www.fmrib.ox.ac.uk/fsl). Initially, DWI data were checked for adequate signal-to-noise and motion artifacts–poor-quality data were eliminated from further processing. After eddy-current correction and brain extraction, the B0 field maps were linearly registered to b = 0 s/mm^2 image and were applied to the DWI images to reduce distortion inherent in EPIs.[30] A fully automated processing pipeline was used to calculate mean diffusivity (MD) and fractional anisotropy (FA) for WM-SA volume, SIENAX, and FIRST global and regional segmented structures. In addition, voxelwise intergroup statistical analysis of the DTI data was carried out using tract-based-spatial statistics (TBSS).[31]

Cerebral microbleeds

The cerebral microbleed (CMB) number analysis was performed on SWI minimum-intensity projection images and susceptibility maps, as previously reported[27] using the Microbleed Anatomical Rating Scale.[32] The CMB volume was calculated on susceptibility maps using a semiautomated edge-detection contouring/thresholding technique.[27]

Quantitative susceptibility mapping

Magnitude and phase GRE images were reconstructed offline using sum-of-squares and scalar phase matching,[33] respectively. In-plane distortions due to imaging gradient nonlinearity were compensated. Phase images were unwrapped with a best-path algorithm,[34] background field corrected with V-SHARP[35] (radius 5mm; TSVD threshold 0.05), and converted to magnetic susceptibility maps using the HEIDI algorithm.[36] Magnetic susceptibility was referenced (0 ppb) to the average susceptibility of the brain.

MR spectroscopy measures

LCModel (version 6.3, Stephen Provencher, Oakville, Canada)[37,38] was used to process the single-voxel spectroscopy data in the intersection of the corpus callosum and the fornix, and the anterior edge of the voxel aligned with the anterior tip of the genu, based on the relative concentrations of *N*-acetylaspartate (NAA), glutamate (Glu), and glutamine (Gln), relative to the concentration of creatine (Cr) and phosphor creatine (PCr).

PWI measures

Calculation of perfusion cerebral blood flow (CBF), blood volume (CBV), and mean transit time (MTT) within areas of WM-SA, SIENAX, and FIRST global and regional segmented structures was performed as previously described.[39] Briefly, we used the Java Image Manipulation software package (Xinapse Systems, Thorpe Waterville, UK) with automated method for arterial input function detection (searching 500 "artery-like" candidate voxels and retaining the 40 best fitting voxels) and singular value decomposition (cutoff at 20% of maximum singular value) for perfusion curve fitting.[40] CBF, CBV, and MTT values were relative, based on estimated tissue relaxivity and hematocrit parameters (arterial relaxivity 1.0, L/s/mol, tissue relaxivity 1.0 L/s/mol, arterial hematocrit 0.45, tissue hematocrit 0.45).

Statistical analysis

All data analyses were performed using SPSS version 23.0 (IBM, Armonk, New York). MRI differences between the study groups were assessed using the analysis of covariance (ANCOVA), adjusted for age, body mass index, and education. Effect size estimates were calculated using Cohen's *d* and Cramer's *V*; 95%

confidence intervals (CIs) are reported for the mean group difference.

A nominal *P* value of <.05 was considered statistically significant using 2-tailed tests.

RESULTS

A total of 21 contact sport athletes and 21 noncontact sport athletes participated in the MRI portion of the study.

Focal WM-SA outcomes

Table 1 shows that 12 (57.1%) of contact sport athletes and 11 (52.4%) of noncontact controls presented with WM-SAs. There were no significant differences between contact sport athletes and non-contact controls for the total number and volume of WM-SAs.

Global and regional brain volume outcomes

Table 1 also shows global and regional brain volume outcomes in both groups of athletes. There were no significant differences between the study groups in global or regional brain volume measures.

DTI outcomes

Table 2 shows DTI MD and FA values in WM-SAs, global and regional GM, and WM brain structures between contact sport athletes and noncontact athlete controls. There were no significant differences between the study groups in DTI measures.

No significant differences in TBSS-DTI outcomes were detected between contact sport athletes and noncontact controls.

QSM outcomes

Table 3 shows QSM values in deep GM structures between contact sport athletes and noncontact controls. There were no significant differences between the study groups in QSM measures.

Cerebral microbleeds

No significant differences were found for various CMB outcomes between contact sport athletes and noncontact controls. However, more noncontact athlete controls (7, 33%), compared with contact sport athletes (2, 9.5%) presented with at least 1 CMB ($P = .067$), although this was not significant. The CMB number (0.6 vs 0.3, 95% CI = −0.5 to 0.9, $d = 0.20$, $P = .542$)

TABLE 1 *Focal white matter signal abnormalities, and global and regional atrophy brain outcomes in the study groups*[a]

	Controls ($n = 21$)	Athletes ($n = 21$)	95% CI	*P* value	Effect size[b]
WM-SA presence (stage 1),[c] *n* (%)	11 (52.4)	12 (57.1)	NA	.532	0.05
WM-SA volume (stage 2)[c]	2.4 (4.5)	1.1 (1.6)	−1.6 to 4.1	.530	0.38
WM-SA volume (total)	1.2 (3.4)	0.6 (1.3)	−1.0 to 2.2	.693	0.23
WM-SA number[d]	10.0 (17.5)	6.3 (11.5)	−5.6 to 12.9	.586	0.25
NBV	1504.4 (72.7)	1483.6 (80.7)	−28.6 to 69.6	.516	0.27
NGMV	728.4 (34.2)	720.1 (40.5)	−15.6 to 32.2	.664	0.22
NWMV	775.7 (45.5)	763.5 (46.9)	−17.4 to 41.8	.221	0.26
NLVV	46.4 (16.3)	39.2 (15.2)	−2.9 to 17.3	.452	0.46
NCV	587.9 (30.5)	578.8 (35.7)	−12.1 to 30.3	.323	0.27
Total DGM	60.1 (4.3)	59.4 (4.7)	−2.2 to 3.5	.555	0.16
Thalamus	20.2 (1.6)	20.5 (1.7)	−1.3 to 0.8	.256	0.18
Caudate	9.1 (0.8)	8.7 (1.1)	−0.2 to 1.0	.631	0.42
Putamen	12.8 (1.1)	12.7 (1.3)	−0.7 to 0.9	.645	0.08
Globus pallidus	4.6 (0.5)	4.6 (0.4)	−0.3 to 0.3	.058	0.03
Hippocampus	9.1 (1.0)	8.8 (0.9)	−0.3 to 1.0	.598	0.32
Amygdala	3.2 (0.7)	3.1 (0.5)	−0.3 to 0.5	.705	0.16
Accumbens	1.1 (0.3)	1.1 (0.3)	−0.3 to 0.1	.459	0.12

Abbreviations: CI, confidence interval; DGM, deep gray matter; NA, not available; NBV, normalized brain volume; NCV, normalized cortical volume; NGMV, normalized gray matter volume; NLVV, normalized lateral ventricle volume; NWMV, normalized white matter volume; WM-SA, white matter signal abnormality.

[a]The values are presented as mean (standard deviation), if not specified otherwise. Volumes are presented in milliliters. The differences between the groups were tested using analysis of covariance adjusted for age, body mass index, and education (*P* value adjusted); 95% confidence intervals are reported for the mean group difference.

[b]Effect size estimates calculated using Cohen's *d* and Cramer's *V*.

[c]WM-SA volume was modeled in a 2-stage fashion: first for presence/absence of WM-SA (binary logistic regression), second as a log-transformed general linear model of the remaining positive values.

[d]WM-SA number was calculated using a negative binomial model.

TABLE 2 *Diffusion-tensor imaging brain outcomes in the study groups*[a]

	Controls ($n = 21$)	Athletes ($n = 21$)	95% CI	*P* value	Effect size[b]
Mean diffusivity					
WM-SA	1.1 (0.07)	1.1 (0.016)	−0.14 to 0.07	.968	0.29
Whole brain	0.99 (0.05)	1 (0.00006)	−0.05 to 0.02	.545	0.28
GM	1.1 (0.06)	1.1 (0.07)	−0.05 to 0.03	.745	0.14
WM	0.89 (0.04)	0.90 (0.05)	−0.04 to 0.02	.500	0.22
Total DGM	1 (0.05)	0.97 (0.05)	−0.03 to 0.03	.999	0.60
Thalamus	0.98 (0.06)	0.98 (0.05)	−0.03 to 0.04	.877	0.03
Caudate	0.99 (0.08)	0.97 (0.08)	−0.03 to 0.07	.700	0.25
Putamen	0.87 (0.06)	0.88 (0.06)	−0.04 to 0.03	.841	0.17
Globus Pallidus	0.5 (0.069)	0.87 (0.03)	−0.05 to 0.02	.127	6.95
Hippocampus	1.1 (0.06)	1.1 (0.09)	−0.07 to 0.03	.888	0.26
Amygdala	0.97 (0.06)	0.97 (0.06)	−0.04 to 0.03	.807	0.06
Accumbens	0.89 (0.06)	0.91 (0.08)	−0.06 to 0.03	.350	0.28
Fractional anisotropy					
WM-SA	0.289 (0.039)	0.277 (0.085)	−0.045 to 0.072	.833	0.18
Whole brain	0.258 (0.013)	0.254 (0.013)	−0.004 to 0.012	.344	0.31
GM	0.171 (0.009)	0.173 (0.013)	−0.007 to 0.005	.613	0.18
WM	0.338 (0.020)	0.323 (0.020)	−0.003 to 0.022	.470	0.75
Total DGM	0.273 (0.017)	0.271 (0.015)	−0.008 to 0.012	.835	0.12
Thalamus	0.326 (0.023)	0.326 (0.013)	−0.012 to 0.012	.620	0.01
Caudate	0.252 (0.033)	0.256 (0.034)	−0.025 to 0.017	.441	0.12
Putamen	0.249 (0.020)	0.244 (0.018)	−0.006 to 0.018	.337	0.26
Globus pallidus	0.394 (0.042)	0.371 (0.039)	−0.002 to 0.049	.056	0.57
Hippocampus	0.180 (0.014)	0.179 (0.018)	−0.009 to 0.011	.399	0.06
Amygdala	0.184 (0.016)	0.179 (0.013)	−0.004 to 0.014	.067	0.34
Accumbens	0.232 (0.022)	0.231 (0.034)	−0.017 to 0.019	.311	0.03

Abbreviations: CI, confidence interval; DGM, deep gray matter; GM, gray matter; WM, white matter; WM-SA, white matter signal abnormality.

[a]The values are presented as mean (standard deviation). Diffusivity is given in 10^{-3} mm^2/s. Fractional anisotropy is a dimensionless measure. The differences between the groups were tested using analysis of covariance adjusted for age, body mass index, and education (*P* value adjusted); 95% confidence intervals are reported for the mean group difference.

[b]Effect size estimates calculated using Cohen's *d* and Cramer's *V*.

TABLE 3 *Quantitative susceptibility mapping outcomes of the deep gray matter in the study groups*[a]

	Controls (n = 21)	Athletes (n = 21)	95% CI	*P* value	Effect size[b]
Total DGM	0.027 (0.006)	0.026 (0.005)	−0.002 to 0.005	.433	0.18
Thalamus	− 0.003 (0.007)	− 0.002 (0.007)	−0.011 to 0.010	.05	0.14
Caudate	0.046 (0.009)	0.041 (0.008)	0 to 0.010	.298	0.59
Putamen	0.056 (0.013)	0.052 (0.015)	−0.004 to 0.013	.952	0.28
Globus pallidus	0.106 (0.018)	0.107 (0.015)	−0.005 to 0.003	.814	0.06
Hippocampus	0.005 (0.005)	0.004 (0.004)	−0.002 to 0.004	.286	0.22
Amygdala	− 0.005 (0.008)	− 0.009 (0.009)	−0.001 to 0.009	.891	0.47
Accumbens	− 0.003 (0.015)	0.011 (0.016)	−0.024 to −0.005	.058	0.90

Abbreviations: CI, confidence interval; DGM, deep gray matter.

[a]The values are presented as mean (standard deviation). Susceptibility is presented in ppm (parts per million). The differences between the groups were tested using analysis of covariance adjusted for age, body mass index, and education (*P* value adjusted); 95% confidence intervals are reported for the mean group difference.

[b]Effect size estimates calculated using Cohen's *d*.

and volume (11.2 mm^3 vs 2.3 mm^3, 95% CI = −0.7 to 18.6, $d = 0.58$, $P = .077$) were also somewhat higher in noncontact athletes compared with the contact sport athletes.

MR spectroscopy outcomes

No significant differences in the concentration of the NAA/CrPCr ($d = 0.41$, 95% CI = −0.516 to 0.105, $P = .119$), Glu/CrPCr ($d = 0.49$, 95% CI = −0.044 to 0.332, $P = 0.129$) or Gln/CrPCr ($d = 0.58$, 95% CI = −0.049 to 0.624, $P = .093$) were found between contact sport athletes and noncontact controls.

PWI outcomes

Table 4 shows PWI MTT, CBF, and CBV values in WM-SAs, global and regional GM, and WM brain structures between contact sport athletes and noncontact

TABLE 4 *Perfusion-weighted imaging brain outcomes in the study groups*[a]

	Controls ($n = 21$)	Athletes ($n = 21$)	95% CI	*P* value	Effect size[b]
MTT					
WM-SA	5858.8 (1577.5)	5090.7 (1164.9)	−617.7 to 2153.8	.837	0.55
Whole brain	5761.6 (957.7)	5239.4 (836.6)	−117.6 to 1137.3	.790	0.58
GM	5783.6 (940.6)	5201.8 (774.2)	−26.4 to 1176.6	.617	0.68
WM	5744.1 (974.9)	5231.9 (893.6)	−142.5 to 1140.1	.982	0.55
Total DGM	5355.8 (910.2)	5098.4 (859.4)	−375.5 to 890.3	.721	0.29
Thalamus	5857.5 (980.8)	5711.8 (967.5)	−556.7 to 800.3	.496	0.15
Caudate	5321.9 (1020.2)	5199.4 (909.1)	−554.0 to 795.7	.963	0.13
Putamen	4157.7 (946.4)	3662.3 (803.9)	−110.2 to 1101.1	.955	0.56
Globus pallidus	4245.6 (972.3)	3683.6 (796.5)	−29.8 to 1153.8	.879	0.63
Hippocampus	6517.8 (833.6)	6315.8 (941.9)	−438.4 to 778.5	.459	0.23
Amygdala	5382.1 (885.4)	5087.5 (1083.4)	−404.0 to 993.2	.625	0.30
Accumbens	4592.3 (958.9)	3830.7 (570.21)	169.5 to 1353.7	.210	0.97
CBF					
WM-SA volume	278.3 (121.4)	354.5 (151.7)	−213.5 to 61.1	.871	0.55
Whole brain	400.1 (153.2)	487.8 (147.9)	−196.1 to 13.7	.570	0.58
GM	445.7 (171.0)	540.3 (178.4)	−221.0 to 22.4	.592	0.54
WM	359.2 (138.8)	435.9 (123.8)	−168.5 to 11.8	.482	0.58
Total DGM	414.1 (177.5)	541.9 (169.7)	−251.9 to −3.8	.719	0.74
Thalamus	407.1 (160.9)	517.1 (146.3)	−216.8 to −2.1	.652	0.72
Caudate	354.7 (141.2)	447.9 (130.3)	−186.9 to 2.8	.548	0.69
Putamen	455.6 (217.0)	601.4 (207.9)	−292.2 to 0.5	.676	0.69
Globus pallidus	413.9 (209.1)	565.1 (270.4)	−324.6 to 7.3	.574	0.63
Hippocampus	397.6 (173.1)	450.1 (153.4)	−167.2 to 56.9	.789	0.32
Amygdala	526.3 (409.9)	637.6 (277.9)	−365.5 to 142.8	.380	0.32
Accumbens	446.5 (186.9)	558.9 (142.3)	−235.4 to 10.6	.706	0.68
CBV					
WM-SA volume	22.3 (7.4)	17.9 (11.8)	−5.4 to 14.2	.454	0.45
Whole brain	30.2 (7.9)	27.5 (13.7)	−4.8 to 10.8	.409	0.24
GM	33.4 (8.8)	29.8 (14.7)	−4.4 to 12.5	.345	0.30
WM	27.4 (7.3)	25.5 (12.5)	−4.8 to 9.3	.496	0.19
Total DGM	30.2 (8.0)	34.1 (8.4)	−9.2 to 1.5	.666	0.48
Thalamus	35.1 (9.8)	38.0 (12.4)	−5.9 to 4.7	.594	0.26
Caudate	26.8 (8.3)	28.7 (10.4)	−8.0 to 5.4	.567	0.20
Putamen	25.2 (6.5)	26.5 (9.4)	−7.0 to 4.3	.570	0.16
Globus pallidus	23.0 (26.7)	23.7 (8.6)	−10.6 to 5.5	.689	0.04
Hippocampus	34.4 (11.8)	34.3 (11.8)	−7.5 to 7.8	.635	0.01
Amygdala	28.0 (7.6)	28.4 (5.1)	−5.2 to 4.5	.735	0.06
Accumbens	27.0 (7.5)	25.9 (5.7)	−4.2 to 6.3	.608	0.17

Abbreviations: CBF, cerebral blood flow; CBV, cerebral blood volume; CI, confidence interval; DGM, deep gray matter; GM, gray matter, MTT, mean transit time; WM, white matter; WM-SA, white matter signal abnormality.

[a]MTT is presented in seconds. CBF is presented in milliliters blood/100-g tissue/min. CBV is given as the blood volume as a percentage of the total tissue volume. The values are presented as mean (standard deviation). The differences between the groups were tested using analysis of covariance adjusted for age, body mass index, and education (*P* value adjusted); 95% confidence intervals are reported for the mean group difference.

[b]Effect size estimates calculated using Cohen's *d*.

controls. There were no significant differences between the study groups in PWI measures.

DISCUSSION

In this multimodal imaging study between retired contact sport professional athletes and noncontact sport, currently exercising controls, we did not find any metabolic, functional, or structural differences on brain MRI using a range of advanced conventional and nonconventional imaging techniques. Similar findings were obtained when mild cognitive impairment-contact sport athletes were compared with the mild cognitive impairment-non-contact controls.

Although the long-term consequences of sport-related head injuries have received much attention,[1,2,41] many questions remain to be elucidated. For example, Tremblay et al[17] found that retired athletes with a history of concussions exhibited widespread damage along many major association, interhemispheric, and projection tracts, using TBSS-DTI analysis, which were associated with cognitive symptoms. On the contrary, another DTI study found no difference between clinically normal retired sport athletes with a history of concussions and matched controls.[10] Yet, other studies reported that the majority of retired players had normal cognitive status and that DTI abnormalities were more pronounced only in those players who reported a higher number of concussions.[8,19] In the present study, we examined global and tissue-specific GM and WM structures, including WM-SAs, by standard and voxelwise DTI analyses and found no evidence of more advanced microstructural damage in contact sport athletes compared with noncontact controls, in any of the examined regions.

Previous studies reported cortical thinning,[42] cavum septi pellucidi,[43] or shrinkage of deep GM volume structures,[7] as prominent signs of brain atrophy in retired contact sport athletes compared with controls. We investigated cortical and deep GM, as well as WM and central signs of brain atrophy in the current study, and detected no evidence of more advanced brain volume loss in contact sport athletes compared with noncontact athlete controls. In addition, we found no difference between the 2 groups in presence, number, and volume of WM-SAs, indicating that there was no more focal lesion burden, due to contact sport playing, in contact sport athletes.

This is one of the first studies to examine the effect of contact sport playing on QSM, a new imaging technique that measures subtle changes of the magnetic susceptibility of tissue and that is regarded as one of the most sensitive techniques for studying tissue iron in vivo.[35,36] We hypothesized that repetitive subconcussive events would lead to increased iron deposition in deep GM structures, due to a higher degree of neurodegeneration. To the best of our knowledge, only one previous study used SWI to determine an association between number of concussions and altered SWI measures in 45 retired former players.[8,19] It found that 4 (9%) of the athletes presented with CMBs on SWI. In the present study, we used SWI and QSM to investigate number and volume of CMBs between contact sport athletes and noncontact sport controls, and to determine whether there are susceptibility differences in deep GM structures between the 2 groups. Because CMBs have been associated with mTBI in subjects with subconcussive and concussive injury,[44] we hypothesized that athletes would have a higher frequency of CMBs. Surprisingly, the findings showed that 33% of the noncontact athlete controls and only 9.5% of the contact sport athletes had CMBs, and the number and volume of CMBs were also slightly higher in the noncontact sport athletes. Contrary to our hypothesis, there were no differences between the 2 groups in deposited iron in the deep GM structures, as measured by QSM.

While a number of previous studies used MR spectroscopy to study the effect of concussion in contact sport athletes,[1] only one used MR spectroscopy to investigate changes in retired sport athletes with a history of concussion.[24] It revealed various neurometabolic anomalies across studied regions of interest. In the present study, we used a single-voxel spectroscopy sequence that examined a large region of interest above the lateral ventricles and found no differences in the concentrations of metabolites of cellular integrity and neurotransmission between contact sport athletes and noncontact athletes.

One recent study, using PWI, found reduced CBF in former football players with cognitive impairment compared with matched healthy controls.[10] Another study, using single-photon emission computed tomography, compared retired and current NFL players and healthy controls, and found that hypoperfusion in the orbital frontal, anterior cingulate, anterior temporal, hippocampal, amygdala, insular, caudate, superior/mid occipital, and cerebellar subregions separated NFL players from controls with 90% sensitivity, 86% specificity, and 94% accuracy.[45] We obtained MTT, CBF, and CBV PWI measures in contact sport athletes and noncontact athletes, examining global and tissue-specific GM and WM structures, and detected no differences between the groups.

There are a number of limitations of this study that are discussed in more detail in Willer et al, accompanying this article. The number of contact sport athletes and noncontact athlete controls was too small to detect differences between brain MRI measures we examined in this study, but the effect sizes and 95% CI that were provided should help the reader to interpret better the magnitude of the differences between the study

groups. We did not investigate in more detail injury of other brain regions (beyond using the TBSS analysis), which might be associated with repetitive subconcussive events, such as the corpus callosum, brainstem, or front-orbital structures, [6,8,10,15,17,24] and therefore future subanalyses should be carried out on the current dataset.

In conclusion, this multimodal imaging study, which used a range of established functional and structural MRI measures, did not show any microscopic or macroscopic brain tissue injury differences in retired contact versus noncontact sport athletes.

REFERENCES

1. Koerte IK, Lin AP, Willems A, et al. A review of neuroimaging findings in repetitive brain trauma. *Brain Pathol*. 2015;25:318–349.
2. Williams VB, Danan IJ. A historical perspective on sports concussion: where we have been and where we are going. *Curr Pain Headache Rep*. 2016;20:43.
3. McKee AC, Daneshvar DH, Alvarez VE, Stein TD. The neuropathology of sport. *Acta Neuropathol*. 2014;127:29–51.
4. Goswami R, Dufort P, Tartaglia MC, et al. Frontotemporal correlates of impulsivity and machine learning in retired professional athletes with a history of multiple concussions. *Brain Struct Funct*. 2016;221:1911–1925.
5. Gardner RC, Hess CP, Brus-Ramer M, et al. Cavum Septum Pellucidum in Retired American Pro Football Players. *J Neurotrauma*. 2016;33:157–161.
6. Coughlin JM, Wang Y, Minn I, et al. Imaging of Glial cell activation and white matter integrity in brains of active and recently retired National Football League players. *JAMA Neurol*. 2017;74(1):67–74.
7. Strain JF, Womack KB, Didehbani N, et al. Imaging correlates of memory and concussion history in retired National Football League athletes. *JAMA Neurol*. 2015;72:773–780.
8. Casson IR, Viano DC, Haacke EM, Kou Z, LeStrange DG. Is there chronic brain damage in retired NFL players? Neuroradiology, neuropsychology, and neurology examinations of 45 retired players. *Sports Health*. 2014;6:384–395.
9. Strain J, Didehbani N, Cullum CM, et al. Depressive symptoms and white matter dysfunction in retired NFL players with concussion history. *Neurology*. 2013;81:25–32.
10. Hart J Jr, Kraut MA, Womack KB, et al. Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study. *JAMA Neurol*. 2013;70:326–335.
11. Hampshire A, MacDonald A, Owen AM. Hypoconnectivity and hyperfrontality in retired American football players. *Sci Rep*. 2013;3:2972.
12. Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin Sports Med*. 2011;30:179–188, xi.
13. Seichepine DR, Stamm JM, Daneshvar DH, et al. Profile of self-reported problems with executive functioning in college and professional football players. *J Neurotrauma* 2013;30:1299–1304.
14. Stern RA, Daneshvar DH, Baugh CM, et al. Clinical presentation of chronic traumatic encephalopathy. *Neurology*. 2013;81:1122–1129.
15. Broglio SP, Eckner JT, Paulson HL, Kutcher JS. Cognitive decline and aging: the role of concussive and subconcussive impacts. *Exerc Sport Sci Rev*. 2012;40:138–144.
16. De Beaumont L, Theoret H, Mongeon D, et al. Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain*. 2009;132:695–708.
17. Tremblay S, Henry LC, Bedetti C, et al. Diffuse white matter tract abnormalities in clinically normal ageing retired athletes with a history of sports-related concussions. *Brain*. 2014;137:2997–3011.
18. Solomon GS, Kuhn AW, Zuckerman SL, et al. Participation in Pre-High School Football and Neurological, Neuroradiological, and Neuropsychological Findings in Later Life: a study of 45 retired National Football League players. *Am J Sports Med*. 2016;44:1106–1115.
19. Kuhn A, Zuckerman S, Solomon G, et al. Interrelationships among neuroimaging, neuropsychological test data and symptom reporting in a cohort of retired National Football League players. *Sports Health*. 2017;9:30–40.
20. Lewis GN, Hume PA, Stavric V, Brown SR, Taylor D. New Zealand rugby health study: motor cortex excitability in retired elite and community level rugby players. *N Z Med J*. 2017;130:34–44.
21. Bartnik-Olson BL, Holshouser B, Wang H, et al. Impaired neurovascular unit function contributes to persistent symptoms after concussion: a pilot study. *J Neurotrauma*. 2014;31:1497–1506.
22. Dean PJ, Sato JR, Vieira G, McNamara A, Sterr A. Multimodal imaging of mild traumatic brain injury and persistent postconcussion syndrome. *Brain Behav*. 2015;5:45–61.
23. Keightley ML, Chen JK, Ptito A. Examining the neural impact of pediatric concussion: a scoping review of multimodal and integrative approaches using functional and structural MRI techniques. *Curr Opin Pediatr*. 2012;24:709–716.
24. Tremblay S, De Beaumont L, Henry LC, et al. Sports concussions and aging: a neuroimaging investigation. *Cereb Cortex*. 2013;23:1159–1166.
25. Willer B, Zivadinov R, Haider MN, Miecznikowski JC, Leddy JJ. A preliminary study of early-onset dementia of former professional football and hockey players. *J Head Trauma Rehabil*. 2018 [Published ahead of print].
26. Zivadinov R, Heininen-Brown M, Schirda CV, et al. Abnormal subcortical deep-gray matter susceptibility-weighted imaging filtered phase measurements in patients with multiple sclerosis: a case-control study. *Neuroimage*. 2012;59:331–339.
27. Zivadinov R, Ramasamy DP, Benedict RR, et al. Cerebral microbleeds in multiple sclerosis evaluated on susceptibility-weighted images and quantitative susceptibility maps: a case-control study. *Radiology*. 2016;281(3):884–895.
28. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage*. 2002;17:479–489.
29. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage*. 2011;56:907–922.
30. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004;23(suppl 1):S208–S219.
31. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*. 2006;31:1487–1505.

32. Gregoire SM, Chaudhary UJ, Brown MM, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. *Neurology*. 2009;73:1759–1766.
33. Hammond KE, Lupo JM, Xu D, et al. Development of a robust method for generating 7.0 T multichannel phase images of the brain with application to normal volunteers and patients with neurological diseases. *Neuroimage*. 2008;39:1682–1692.
34. Abdul-Rahman HS, Gdeisat MA, Burton DR, Lalor MJ, Lilley F, Moore CJ. Fast and robust three-dimensional best path phase unwrapping algorithm. *Appl Opt*. 2007;46:6623–6635.
35. Schweser F, Deistung A, Lehr BW, Reichenbach JR. Quantitative imaging of intrinsic magnetic tissue properties using MRI signal phase: an approach to in vivo brain iron metabolism? *Neuroimage*. 2011;54:2789–2807.
36. Schweser F, Sommer K, Deistung A, Reichenbach JR. Quantitative susceptibility mapping for investigating subtle susceptibility variations in the human brain. *Neuroimage*. 2012;62:2083–2100.
37. Tkáč I, Henry PG, Andersen P, Keene CD, Low WC, Gruetter R. Highly resolved in vivo 1H NMR spectroscopy of the mouse brain at 9.4 T. *Magn Reson Med*. 2004;52:478–484.
38. Provencher S. Automatic quantitation of localized in vivo1H spectra with LCModel. *NMR Biomed*. 2001;14:26–64.
39. Dwyer MG, Bergsland N, Saluste E, et al. Application of hidden Markov random field approach for quantification of perfusion/diffusion mismatch in acute ischemic stroke. *Neurol Res*. 2008;30:827–834.
40. Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: mathematical approach and statistical analysis. *Magn Reson Med*. 1996;36:715–725.
41. McKee AC, Stein TD, Kiernan PT, Alvarez VE. The neuropathology of chronic traumatic encephalopathy. *Brain Pathol*. 2015;25:350–364.
42. Adler CM, DelBello MP, Weber W, et al. MRI evidence of neuropathic changes in former college football players. *Clin J Sport Med*. 2018;28(2):100–105.
43. Koerte IK, Hufschmidt J, Muehlmann M, et al. Cavum Septi Pellucidi in Symptomatic Former Professional Football Players. *J Neurotrauma*. 2016;33:346–353.
44. Helmer KG, Pasternak O, Fredman E, et al. Hockey Concussion Education Project, Part 1. Susceptibility-weighted imaging study in male and female ice hockey players over a single season. *J Neurosurg*. 2014;120:864–872.
45. Amen DG, Willeumier K, Omalu B, Newberg A, Raghavendra C, Raji CA. Perfusion neuroimaging abnormalities alone distinguish National Football League Players from a healthy population. *J Alzheimers Dis*. 2016;53:237–241.