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Multimodal imaging of retired professional contact sport athletes does not provide evidence of structural and functional brain damage

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Abstract

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 MRI differences in retired professional contact sport athletes compared to non-contact sport athletes.

Methods—Twenty one (21) male contact sport athletes and 21 age matched non-contact sport athletes were scanned on a 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-

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Conflict of interest:

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.

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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 glutamin 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 (MCI).

Results—No significant differences were found for structural or functional MRI measures between contact sport athletes and non-contact sport athletes.

Conclusions—This multimodal imaging study did not show any microstructural, metabolic brain tissue injury differences in retired contact vs. non-contact sport athletes.

Keywords

concussion; sport athletes; white matter signal abnormalities; brain atrophy; diffusion-imaging; perfusion imaging; susceptibility imaging; spectroscopy; cerebral microbleeds

Introduction

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 sub-concussive head blows without reported symptoms, are occurring particularly frequently in professional players engaging in sports requiring substantial physical head-contacts (e.g. American football and ice hockey).^{1–3}

An increasing number of recent imaging and cognitive studies, conducted in retired contact sport athletes with history of previous concussions,^{4–12,13–17} indicate that 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, 9–12,13–17} 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 non-contact sport athletes, which could have contributed to an important bias when comparing athlete to non-athlete 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 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 to non-contact athletes, in order to examine the continuing effect of sport activities on long-term imaging and cognitive outcomes over long-term.

Material and Methods

Participants

This multimodal MRI sub-study 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. overall description of the study, accompanying this manuscript.

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. 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 (freq $\times$ phase) and field-of-view (FOV) of $25.6\text{cm} \times 19.2\text{cm}$ for an in-plane resolution of $1\text{ mm} \times 1\text{ mm}$. 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 18.4cm, providing for 1mm 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=9/98/5300ms, 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, FA=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 $25.6\text{ cm} \times 25.6\text{ cm}$, 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/mm² image, and 39 diffusion directions with b=900 s/mm². A dual-echo gradient-echo B0 field map was also acquired in order to correct for EPI distortions in the DTI sequence (TE1/TE2/TR=5.0/9.8/34 ms, FOV of $25.6\text{ cm} \times 25.6\text{ cm}$, 64×64 acquisition matrix, 64 slices with a voxel volume of $2 \times 2 \times 2\text{ mm}^3$).

Data for SWI and quantitative susceptibility mapping (QSM) were acquired using an un-accelerated 3D single-echo spoiled GRE sequence with first-order flow compensation in read and slice directions, a matrix of $512 \times 192 \times 64$ and a nominal resolution of $0.5 \times 1 \times 2$

mm³ (FOV=256×192×128 mm³), FLIP = 12°, TE/TR=22ms/40ms, bandwidth=13.89 kHz.
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A PRESS-based single-voxel spectroscopy sequence 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 (WM) signal abnormalities (SAs)—Identification of WM-SAs was done using a semi-automated edge detection contouring/thresholding technique on T2/PD/FLAIR images.²⁷

Global and regional brain atrophy measures—Volumetric measures were determined on the 3D HIRIS that were modified by using an in-house developed inpainting technique to avoid tissue misclassification.²⁵ Structural Image Evaluation using Normalization of Atrophy Cross-sectional (SIENAX) version 2.6²⁸ 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 HIRIS 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, MA) in-house scripts. Diffusion-tensor imaging (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/mm² image and were applied to the DWI images in order to reduce distortion inherent in EPI images.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 inter-group statistical analysis of the DTI data was carried out using Tract-Based-Spatial Statistics (TBSS).³¹

Cerebral microbleeds (CMBs)—The CMB number analysis was performed on SWI minimum intensity projection images and susceptibility maps, as previously reported²⁶ using the Microbleed Anatomical Rating Scale (MARS).³² The CMB volume was calculated on susceptibility maps using a semi-automated edge detection contouring/thresholding technique.²⁶

Quantitative susceptibility mapping (QSM)—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 non-linearity were compensated. Phase images were unwrapped with a best-path algorithm,³⁴ background-field corrected with V-SHARP³⁵ (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—LC-model (version 6.3)^{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-acetylcysteine (NAA), glutamate (Glu) and glutamine (Gln), relative to the concentration of creatine (Cr) and phosphocreatine (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. CBF, CBV and MTT values were relative, based on estimated tissue relaxivity and haematocrit parameters (arterial relaxivity 1.0, L/s/mol, tissue relaxivity 1.0 L/s/mol, arterial haematocrit 0.45, tissue haematocrit 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 interval (CI) are reported for the mean group difference.

A nominal *p*-value of <0.05 was considered statistically significant using two-tailed tests.

Results

A total of 21 contact sport athletes and 21 non-contact 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 non-contact 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 non-contact 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 non-contact controls.

QSM outcomes

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

Cerebral microbleeds

No significant differences were found for various CMBs outcomes between contact sport athletes and non-contact controls. However, more non-contact athlete controls (7, 33%), compared to contact sport athletes (2, 9.5%) presented with at least one CMB ($p=.067$), although this was not significant. The CMB number (.6 vs .3, 95% CI $[-.5 - .9]$, $d=.20$, $p=.542$) and volume (11.2mm^3 vs. 2.3mm^3 , 95% CI $[-.7 - 18.6]$, $d=.58$, $p=.077$) were also somewhat higher in non-contact athletes compared to the contact sport athletes.

MR spectroscopy outcomes

No significant differences in the concentration of the NAA/CrPCr ($d=.41$, 95% CI $[-0.516 - 0.105]$, $p=.119$), Glu/CrPCr ($d=.49$, 95% CI $[-0.044 - 0.332]$, $p=.129$) or Gln/CrPCr ($d=.58$, 95% CI $[-0.049 - 0.624]$, $p=.093$) were found between contact sport athletes and non-contact 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 non-contact 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 non-contact sport, currently exercising controls, we did not find any metabolic, functional or structural differences on brain MRI using a range of advanced conventional and non-conventional imaging techniques. Similar findings were obtained when MCI-contact sport athletes were compared to the MCI-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, Trembley 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 voxel-wise DTI analyses and found no evidence of more advanced microstructural damage in contact sport athletes compared to non-contact controls, in any of the examined regions.

Previous studies reported cortical thinning,⁴² cavum septi pellucidi⁴³ or shrinkage of deep GM volume structures,⁷ as prominent signs of brain atrophy in retired contact sport athletes compared to 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 to non-contact athlete controls. In addition, we found no difference between the two 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 non-contact sport controls, and to determine whether there are susceptibility differences in deep GM structures between the two 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 non-contact 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 non-contact sport athletes. Contrary to our hypothesis, there were no differences between the two 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 non-contact athletes.

One recent study, using PWI, found reduced CBF in former football players with cognitive impairment compared to 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 sub-regions 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 non-contact 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 manuscript. The number of contact sport athletes and non-contact 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 sub-analyses should be carried on the current dataset.

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

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Table 1

Focal white matter signal abnormalities, and global and regional atrophy brain outcomes in the study groups.

	Controls (n=21)	Athletes (n=21)	95% CI	p-value	Effect size*
WM-SA presence, n (%) (Stage 1) [‡]	11 (52.4)	12 (57.1)	NA	.532	0.05
WM-SA volume (Stage 2) [‡]	2.4 (4.5)	1.1 (1.6)	-1.6 – 4.1	.530	0.38
WM-SA volume (total)	1.2 (3.4)	.6 (1.3)	-1.0 – 2.2	.693	0.23
WM-SA number [‡]	10.0 (17.5)	6.3 (11.5)	-5.6 – 12.9	.586	0.25
NBV	1504.4 (72.7)	1483.6 (80.7)	-28.6 – 69.6	.516	0.27
NGMV	728.4 (34.2)	720.1 (40.5)	-15.6 – 32.2	.664	0.22
NWMV	775.7 (45.5)	763.5 (46.9)	-17.4 – 41.8	.221	0.26
NLVV	46.4 (16.3)	39.2 (15.2)	-2.9 – 17.3	.452	0.46
NCV	587.9 (30.5)	578.8 (35.7)	-12.1 – 30.3	.323	0.27
Total DGM	60.1 (4.3)	59.4 (4.7)	-2.2 – 3.5	.555	0.16
Thalamus	20.2 (1.6)	20.5 (1.7)	-1.3 – 0.8	.256	0.18
Caudate	9.1 (.8)	8.7 (1.1)	-0.2 – 1.0	.631	0.42
Putamen	12.8 (1.1)	12.7 (1.3)	-0.7 – 0.9	.645	0.08
Globus pallidus	4.6 (.5)	4.6 (.4)	-0.3 – 0.3	.058	0.03
Hippocampus	9.1 (1.0)	8.8 (.9)	-0.3 – 1.0	.598	0.32
Amygdala	3.2 (.7)	3.1 (.5)	-0.3 – 0.5	.705	0.16
Accumbens	1.1 (.3)	1.1 (.3)	-0.3 – 0.1	.459	0.12

WM-SA – white matter signal abnormality; NBV – normalized brain volume; NGMV – normalized gray matter volume; NWMV – normalized white matter volume; NLVV – normalized lateral ventricle volume; NCV – normalized cortical volume; DGM – deep gray matter; NA – not available.

The values are presented as mean (SD), if not specified otherwise.

The differences between the groups were tested using analysis of co-variance adjusted for age, body-mass-index and education (p-value adjusted). 95% confidence interval (CI) are reported for the mean group difference.

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

[‡] WM-SA volume was modeled in a two-stage fashion. First for presence/absence of WM-SA (binary logistic regression), secondly as a log-transformed general linear model of the remaining positive values.

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

Table 2

Diffusion-tensor imaging brain outcomes in the study groups.

Mean diffusivity	Controls (n=21)	Athletes (n=21)	95% CI	p-value	Effect size*
WM-SA	1.1 (.07)	1.1 (.016)	-0.14 – 0.07	.968	0.29
Whole brain	.99 (.05)	1 (.00006)	-0.05 – 0.02	.545	0.28
GM	1.1 (.06)	1.1 (.07)	-0.05 – 0.03	.745	0.14
WM	.89 (.04)	.90 (.05)	-0.04 – 0.02	.500	0.22
Total DGM	1 (.05)	.97 (.05)	-0.03 – 0.03	.999	0.60
Thalamus	.98 (.06)	.98 (.05)	-0.03 – 0.04	.877	0.03
Caudate	.99 (.08)	.97 (.08)	-0.03 – 0.07	.700	0.25
Putamen	.87 (.06)	.88 (.06)	-0.04 – 0.03	.841	0.17
Globus Pallidus	.5 (.069)	.87 (.03)	-0.05 – 0.02	.127	6.95
Hippocampus	1.1 (.06)	1.1 (.09)	-0.07 – 0.03	.888	0.26
Amygdala	.97 (.06)	.97 (.06)	-0.04 – 0.03	.807	0.06
Accumbens	.89 (.06)	.91 (.08)	-0.06 – 0.03	.350	0.28
Fractional anisotropy	Controls (n=21)	Athletes (n=21)	95% CI	p-value	Effect Size*
WM-SA	.289 (.039)	.277 (.085)	-0.045 – 0.072	.833	0.18
Whole brain	.258 (.013)	.254 (.013)	-0.004 – 0.012	.344	0.31
GM	.171 (.009)	.173 (.013)	-0.007 – 0.005	.613	0.18
WM	.338 (.020)	.323 (.020)	-0.003 – 0.022	.470	0.75
Total DGM	.273 (.017)	.271 (.015)	-0.008 – 0.012	.835	0.12
Thalamus	.326 (.023)	.326 (.013)	-0.012 – 0.012	.620	0.01
Caudate	.252 (.033)	.256 (.034)	-0.025 – 0.017	.441	0.12
Putamen	.249 (.020)	.244 (.018)	-0.006 – 0.018	.337	0.26
Globus Pallidus	.394 (.042)	.371 (.039)	-0.002 – 0.049	.056	0.57
Hippocampus	.180 (.014)	.179 (.018)	-0.009 – 0.011	.399	0.06
Amygdala	.184 (.016)	.179 (.013)	-0.004 – 0.014	.067	0.34
Accumbens	.232 (.022)	.231 (.034)	-0.017 – 0.019	.311	0.03

WM-SA – white matter signal abnormality; GM – gray matter, WM – white matter; DGM – deep gray matter.

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The values are presented as mean (SD). Diffusivity is given in $10^{-3} \text{ mm}^2/\text{sec}$. FA is a dimensionless measure.

The differences between the groups were tested using analysis of co-variance adjusted for age, body-mass-index and education (p-value adjusted). 95% confidence interval (CI) are reported for the mean group difference.

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

Quantitative susceptibility mapping outcomes of the deep-gray matter in the study groups.

Table 3

	Controls (n=21)	Athletes (n=21)	95% CI	p-value	Effect size*
Total DGM	.027 (.006)	.026 (.005)	−0.002 – 0.005	.433	0.18
Thalamus	−.003 (.007)	−.002 (.007)	−0.011 – 0.010	.05	0.14
Caudate	.046 (.009)	.041 (.008)	0 – 0.010	.298	0.59
Putamen	.056 (.013)	.052 (.015)	−0.004 – 0.013	.952	0.28
Globus Pallidus	.106 (.018)	.107 (.015)	−0.005 – 0.003	.814	0.06
Hippocampus	.005 (.005)	.004 (.004)	−0.002 – 0.004	.286	0.22
Amygdala	−.005 (.008)	−.009 (.009)	−0.001 – 0.009	.891	0.47
Accumbens	−.003 (.015)	.011 (.016)	−0.024 – −0.005	.058	0.90

DGM – deep gray matter.

The values are presented as mean (SD). Susceptibility is presented in ppm (parts per million).

The differences between the groups were tested using analysis of co-variance adjusted for age, body-mass-index and education (p-value adjusted). 95% confidence interval (CI) are reported for the mean group difference.

* Effect size estimates calculated using Cohen's *d*.

In bold are shown significant p values.

Table 4

Perfusion-weighted imaging brain outcomes in the study groups.

MTT	Controls (n=21)	Athletes (n=21)	95% CI	p-value	Effect size *
WM-SA	588.8 (1577.5)	5090.7 (1164.9)	-617.7 – 2153.8	.837	0.55
Whole brain	5761.6 (957.7)	5239.4 (836.6)	-117.6 – 1137.3	.790	0.58
GM	5783.6 (940.6)	5201.8 (774.2)	-26.4 – 1176.6	.617	0.68
WM	5744.1 (974.9)	5231.9 (893.6)	-142.5 – 1140.1	.982	0.55
Total DGM	5355.8 (910.2)	5098.4 (859.4)	-375.5 – 890.3	.721	0.29
Thalamus	5857.5 (980.8)	5711.8 (967.5)	-556.7 – 800.3	.496	0.15
Caudate	5321.9 (1020.2)	5199.4 (909.1)	-554.0 – 795.7	.963	0.13
Putamen	4157.7 (946.4)	3662.3 (803.9)	-110.2 – 1101.1	.955	0.56
Globus Pallidus	4245.6 (972.3)	3683.6 (796.5)	-29.8 – 1153.8	.879	0.63
Hippocampus	6517.8 (833.6)	6315.8 (941.9)	-438.4 – 778.5	.459	0.23
Amygdala	5382.1 (885.4)	5087.5 (1083.4)	-404.0 – 993.2	.625	0.30
Accumbens	4592.3 (958.9)	3830.7 (570.21)	169.5 – 1353.7	.210	0.97
CBF	Controls (n=21)	Athletes (n=21)	95% CI	p-value	
WM-SA vol	278.3 (121.4)	354.5 (151.7)	-213.5 – 61.1	.871	0.55
Whole brain	400.1 (153.2)	487.8 (147.9)	-196.1 – 13.7	.570	0.58
GM	445.7 (171.0)	540.3 (178.4)	-221.0 – 22.4	.592	0.54
WM	359.2 (138.8)	435.9 (123.8)	-168.5 – 11.8	.482	0.58
Total DGM	414.1 (177.5)	541.9 (169.7)	-251.9 – -3.8	.719	0.74
Thalamus	407.1 (160.9)	517.1 (146.3)	-216.8 – -2.1	.652	0.72
Caudate	354.7 (141.2)	447.9 (130.3)	-186.9 – 2.8	.548	0.69
Putamen	455.6 (217.0)	601.4 (207.9)	-292.2 – 0.5	.676	0.69
Globus Pallidus	413.9 (209.1)	565.1 (270.4)	-324.6 – 7.3	.574	0.63
Hippocampus	397.6 (173.1)	450.1 (153.4)	-167.2 – 56.9	.789	0.32
Amygdala	526.3 (409.9)	637.6 (277.9)	-365.5 – 142.8	.380	0.32
Accumbens	446.5 (186.9)	558.9 (142.3)	-235.4 – 10.6	.706	0.68

MTT	Controls (n=21)	Athletes (n=21)	95% CI	p-value	Effect size*
CBV	Controls (n=21)	Athletes (n=21)	95% CI	p-value	
WM-SA vol	22.3 (7.4)	17.9 (11.8)	-5.4 – 14.2	.454	0.45
Whole brain	30.2 (7.9)	27.5 (13.7)	-4.8 – 10.8	.409	0.24
GM	33.4 (8.8)	29.8 (14.7)	-4.4 – 12.5	.345	0.30
WM	27.4 (7.3)	25.5 (12.5)	-4.8 – 9.3	.496	0.19
Total DGM	30.2 (8.0)	34.1 (8.4)	-9.2 – 1.5	.666	0.48
Thalamus	35.1 (9.8)	38.0 (12.4)	-5.9 – 4.7	.594	0.26
Caudate	26.8 (8.3)	28.7 (10.4)	-8.0 – 5.4	.567	0.20
Putamen	25.2 (6.5)	26.5 (9.4)	-7.0 – 4.3	.570	0.16
Globus Pallidus	23.0 (26.7)	23.7 (8.6)	-10.6 – 5.5	.689	0.04
Hippocampus	34.4 (11.8)	34.3 (11.8)	-7.5 – 7.8	.635	0.01
Amygdala	28.0 (7.6)	28.4 (5.1)	-5.2 – 4.5	.735	0.06
Accumbens	27.0 (7.5)	25.9 (5.7)	-4.2 – 6.3	.608	0.17

MTT – mean transit time; CBF – cerebral blood flow; CBV = cerebral blood volume; WM-SA – white matter signal abnormality; GM – gray matter; WM – white matter; DGM – deep gray matter.

MTT is presented in seconds. CBF is presented in milliliters blood / 100g tissue / minute. CBV is given as the blood volume as a percentage of the total tissue volume.

The values are presented as mean (SD). The differences between the groups were tested using analysis of co-variance adjusted for age, body-mass-index and education (p-value adjusted). 95% confidence interval (CI) are reported for the mean group difference.

* Effect size estimates calculated using Cohen's *d*.