Cyto- and Myeloarchitectural Alterations in Repetitive Head Impact: A Preliminary Study from the CARE Consortium

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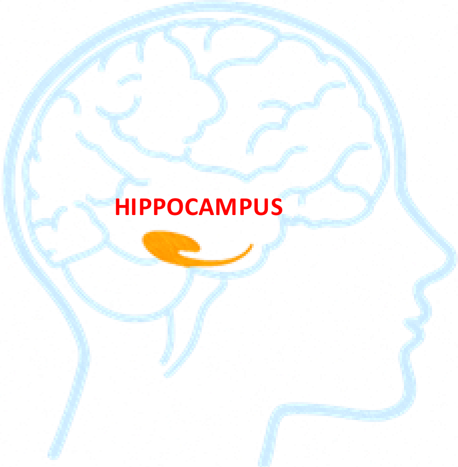

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Non-Disclosure

The presenting author reports no relevant financial relationships or conflicts of interest related to this work

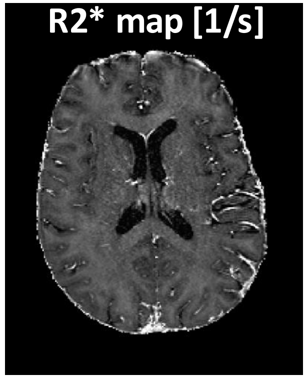
BACKGROUND

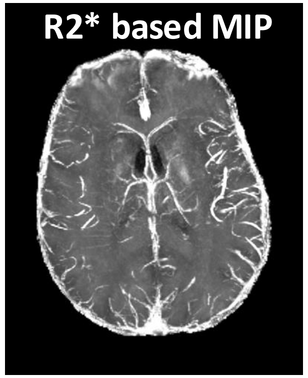
- Repetitive head impact (**RHI**) in collegiate athletes is a growing concern, with evidence suggesting that physiological and metabolic changes follow RHI even in the absence of diagnosed concussion.
- RHIs may cause subtle brain tissue changes in regions such as cortical gray matter and the hippocampus.
- These early cyto- and myelo-architectural alterations may affect mid-to late-life brain health and cognition.
- Conventional structural MRI (macroscale) is not sensitive enough to capture such subtle mesoscale alterations.

OBJECTIVE

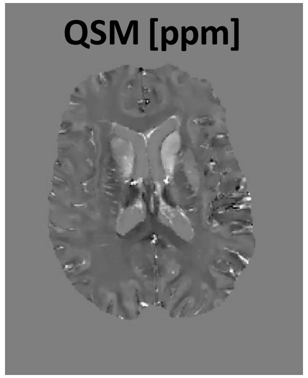
To understand the impact of RHI on brain tissue cyto- and myelo-architectural organization using advanced quantitative MRI (qMRI) techniques.

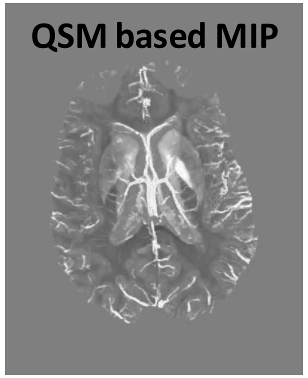
Apparent transverse relaxation rate R2*[1/s]:
R2* is sensitive to microscopic magnetic field inhomogeneity linked to tissue organization, iron/myelin content and cellular composition



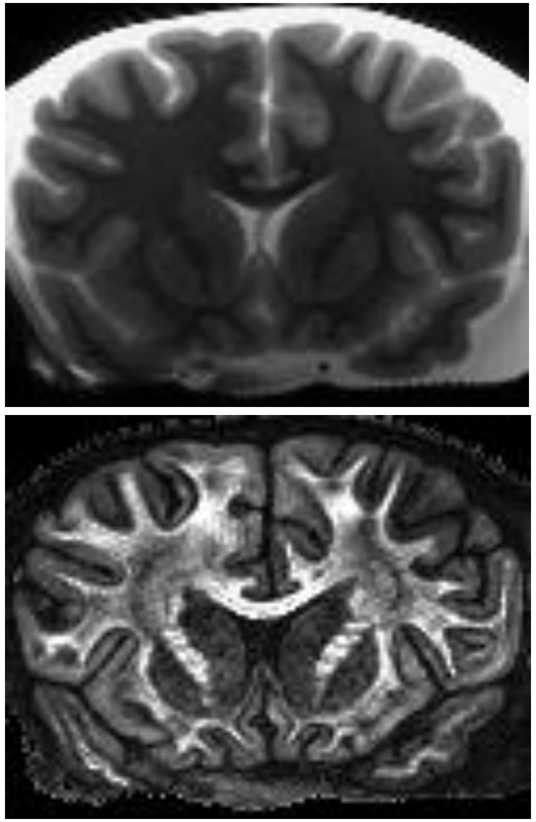


Quantitative susceptibility mapping (QSM) [ppm]:
QSM reflects bulk magnetic susceptibility related to paramagnetic (iron, deoxyhemoglobin) and diamagnetic (calcium, myelin etc.,) substrates

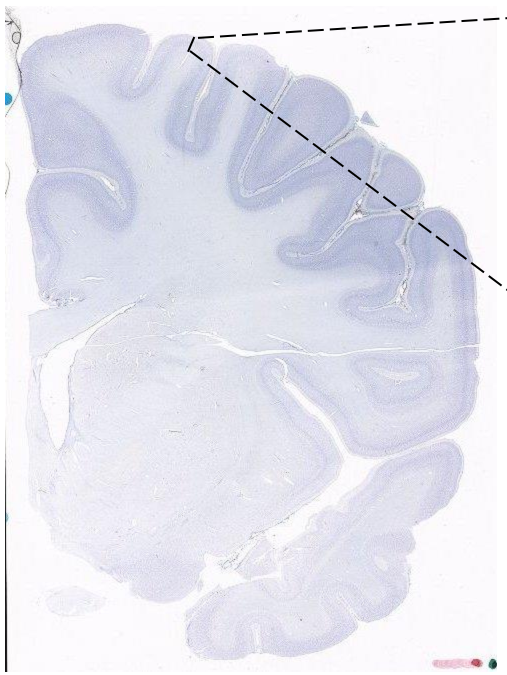




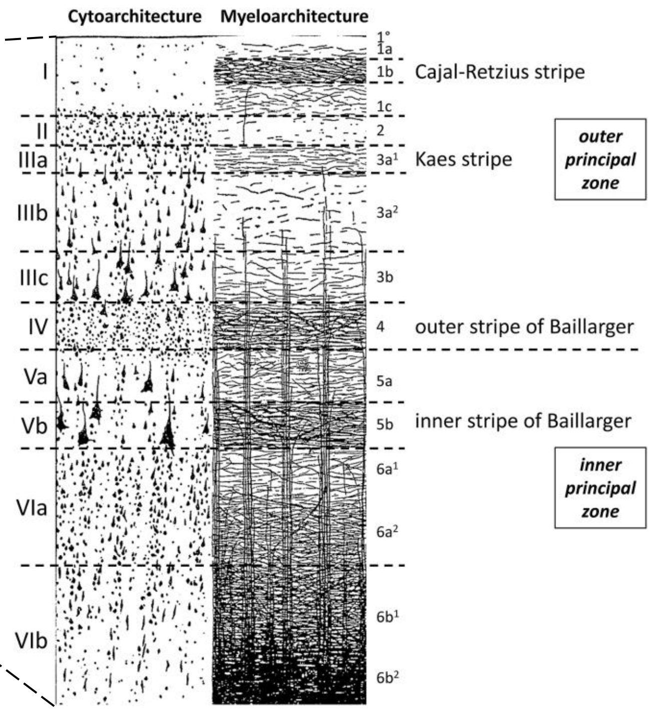
Tissue cyto- and myelo-architectural organization



Source: Allen Human brain atlas
Ex vivo dMRI based b0 and FA map (0.9 x 0.9 x0.9 mm^3)

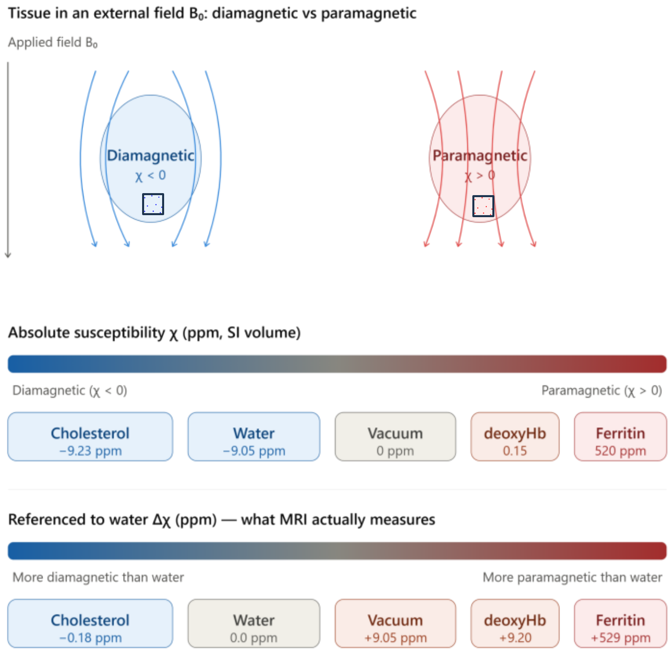


Source: Allen Human brain atlas
ROI: Superior frontal gyrus



Source: Zilles, K., Palomero-Gallagher, N. and Amunts, K., 2015. Myeloarchitecture and maps of the cerebral cortex.

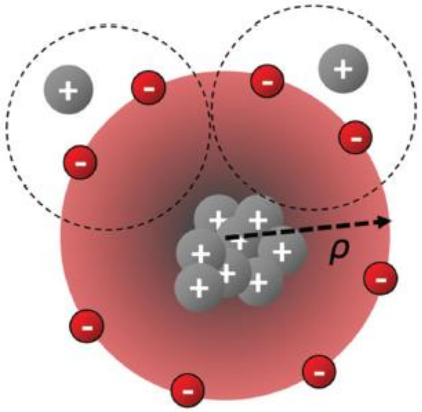
Magnetic susceptibility in MRI



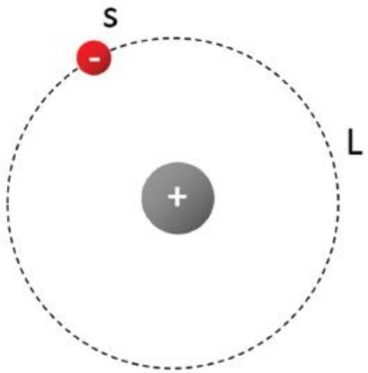
$$\chi = \frac{\underline{m}}{\underline{H}} = \frac{\underline{m}}{B/\mu_0 - \underline{m}} \sim \frac{\mu_0\,\underline{m}}{B_0}$$

Where $\underline{m} = \underline{m}_{para} + \underline{m}_{dia}$

Diamagnetic susceptibility (induction currents)



Paramagnetic susceptibility (spin and orbital angular momentum)

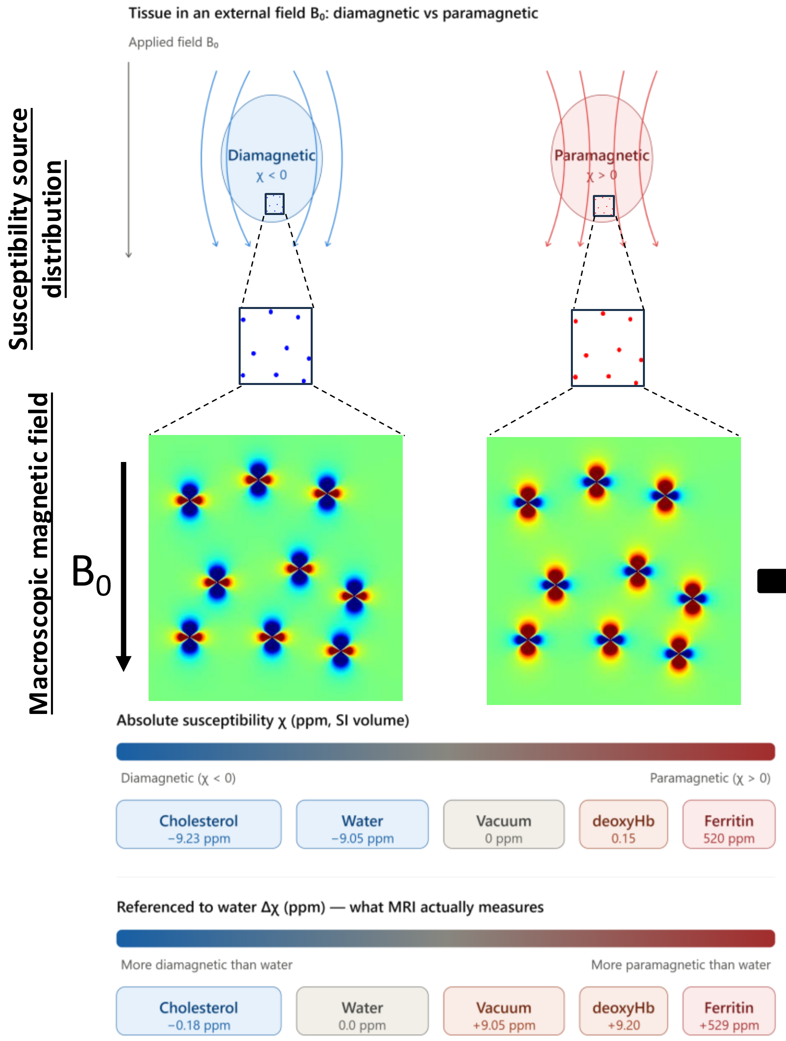


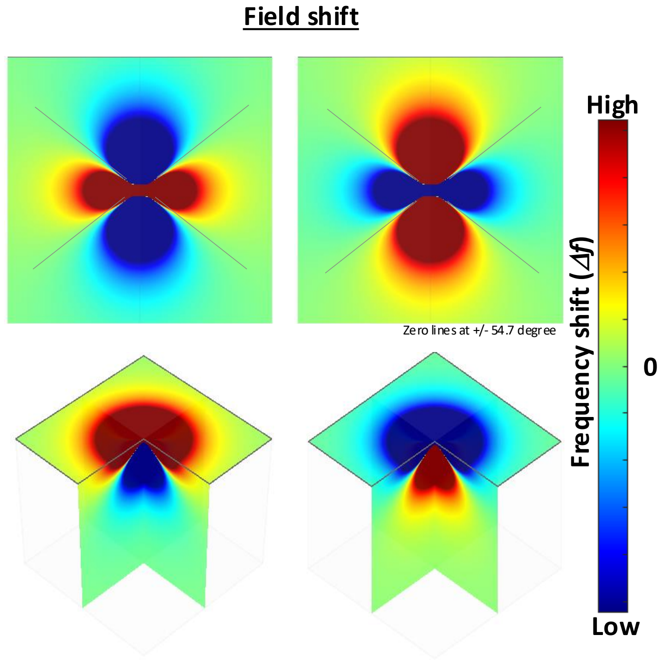
Diamagnetic susceptibility originates from the response of orbital electrons to the applied B_0. The precession of electrons can be modeled as circular current, which generates a secondary field opposing the applied B_0. Thus, the resulting susceptibility is diamagnetic.

Paramagnetic susceptibility originates primarily from spin and orbital angular momentum induced magnetic moments of electrons.

Wang, Principles of Magnetic Resonance Imaging: Physics concepts, pulse sequences and biomedical application, Chapter 5, 2015 .
Chunlei Liu et al, Quantitative Susceptibility Mapping: Contrast Mechanisms and Clinical Applications, 2015, Tomography.

Effect of magnetic susceptibility on magnitude and phase

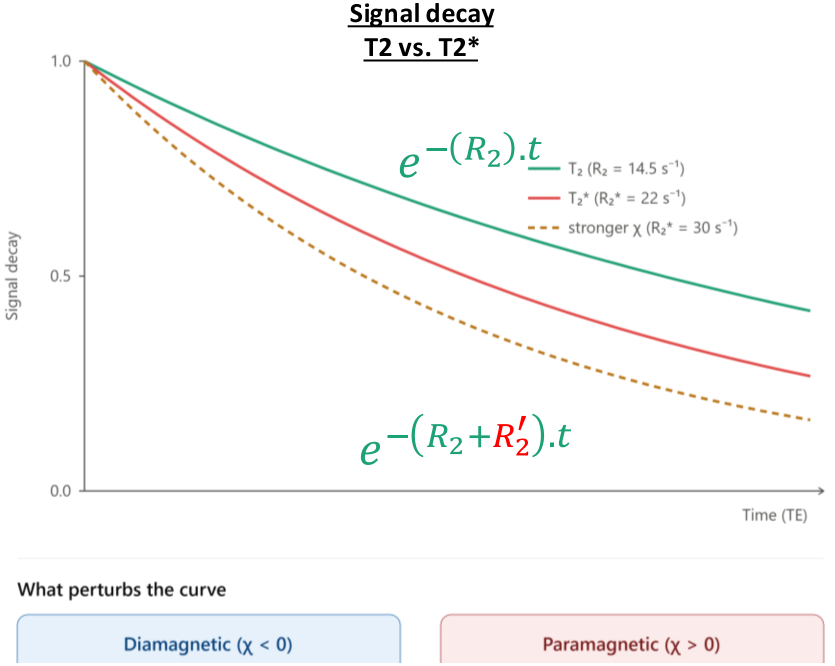




Assuming static dephasing regime and homogeneous isotropic susceptibility with opposite signs

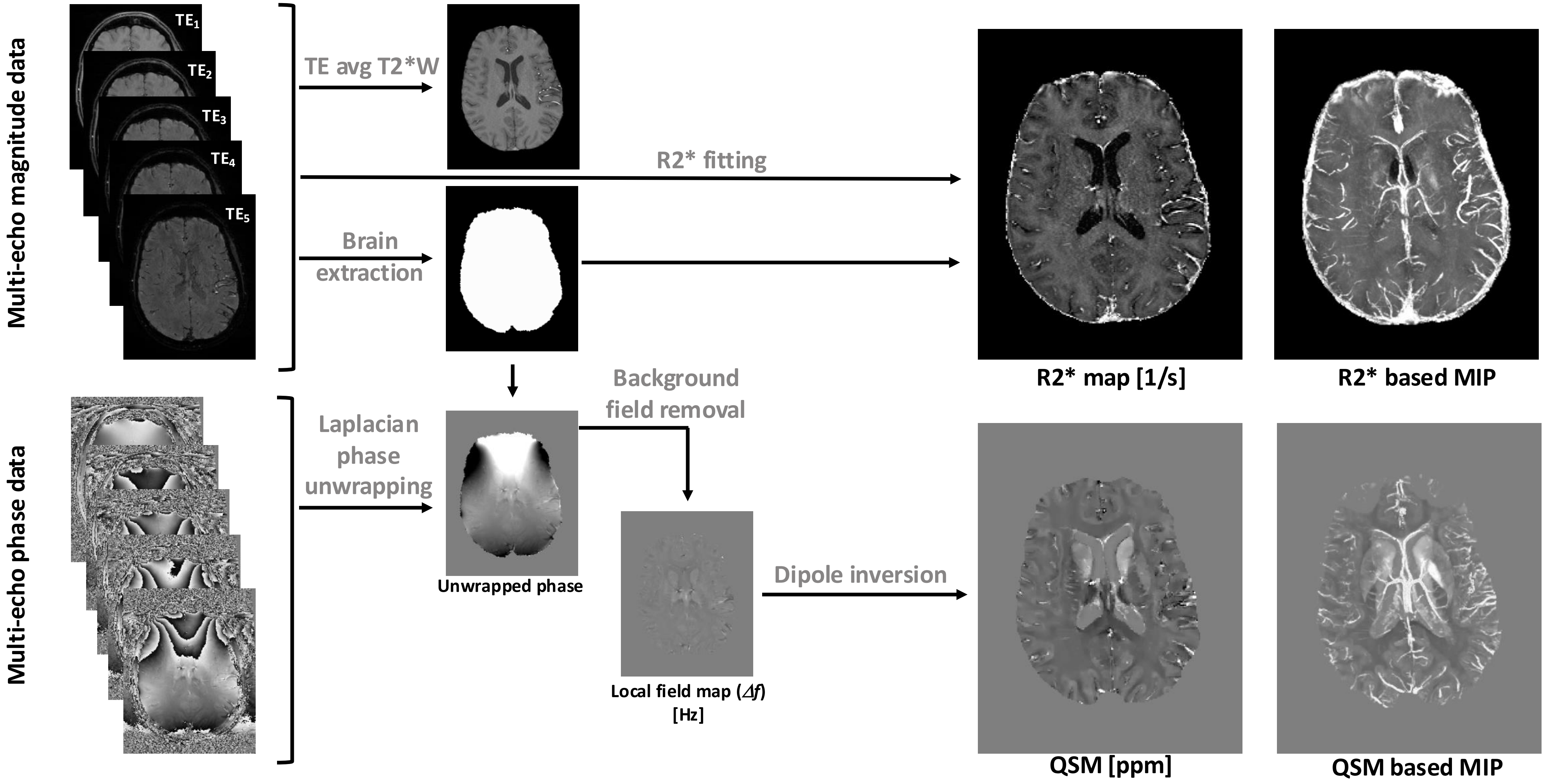
$$R_2' = Dr \cdot |\chi|$$

$$\Delta f = Df * \chi$$



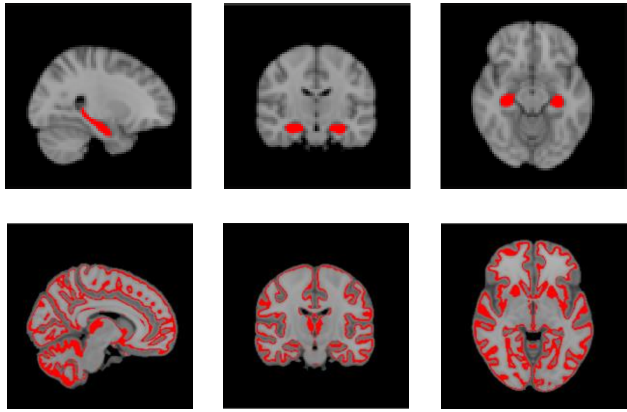
Yablonskiy DA et al. Magnetic resonance in medicine. 1994 Dec;32(6):749-63.
Salomir R, et al. Concepts in Magnetic Resonance Part B: Magnetic Resonance Engineering: An Educational Journal. 2003;19(1):26-34.
Shin HG, Neuroimage. 2021 Oct 15;240:118371.

Quantitative susceptibility mapping reconstruction



SPECIFIC AIMS

To understand the impact of RHI on brain tissue cyto- and myelo-architectural organization using regions of interest-based analysis



Aim 1

Understand the impact of concussion on hippocampal and cerebral gray matter

$$Model\ 1{:}\ MRI\ = \beta_0 + \beta_1 Group + \beta_2 age + \beta_3 sex + \varepsilon$$

Aim 2

Evaluate the effect of exposure level (high vs. low) and its interaction with concussion on hippocampal and cerebral gray matter

$$Model\ 2{:}\ MRI\ = \beta_0 + \beta_1 Exposure + \beta_2 Concussion + \beta_3 Exposure * Concussion + \beta_4 age + \beta_5 sex + \varepsilon$$

Participant demographic and clinical characteristics (IU-scanned participants)

	High Exposure (n=96)	Low Exposure (n=183)	pValue
Age, y	28.80 (1.2)	28.25 (1.08)	**<0.01**
Sex (F : M) *	25 : 71	100 : 85	**< 0.0001**
No. of diagnosed concussion *			**< 0.0001**
0	38	151	
1	24	24	
2	20	6	
3+	14	2	
NIH toolbox Pictures Sequencing Memory	109.73 (19.60)	110.46 (18.50)	**0.6**

Group comparisons were performed using two-sample t-tests, and sex and number of diagnosed concussions were assessed using χ^2 tests.

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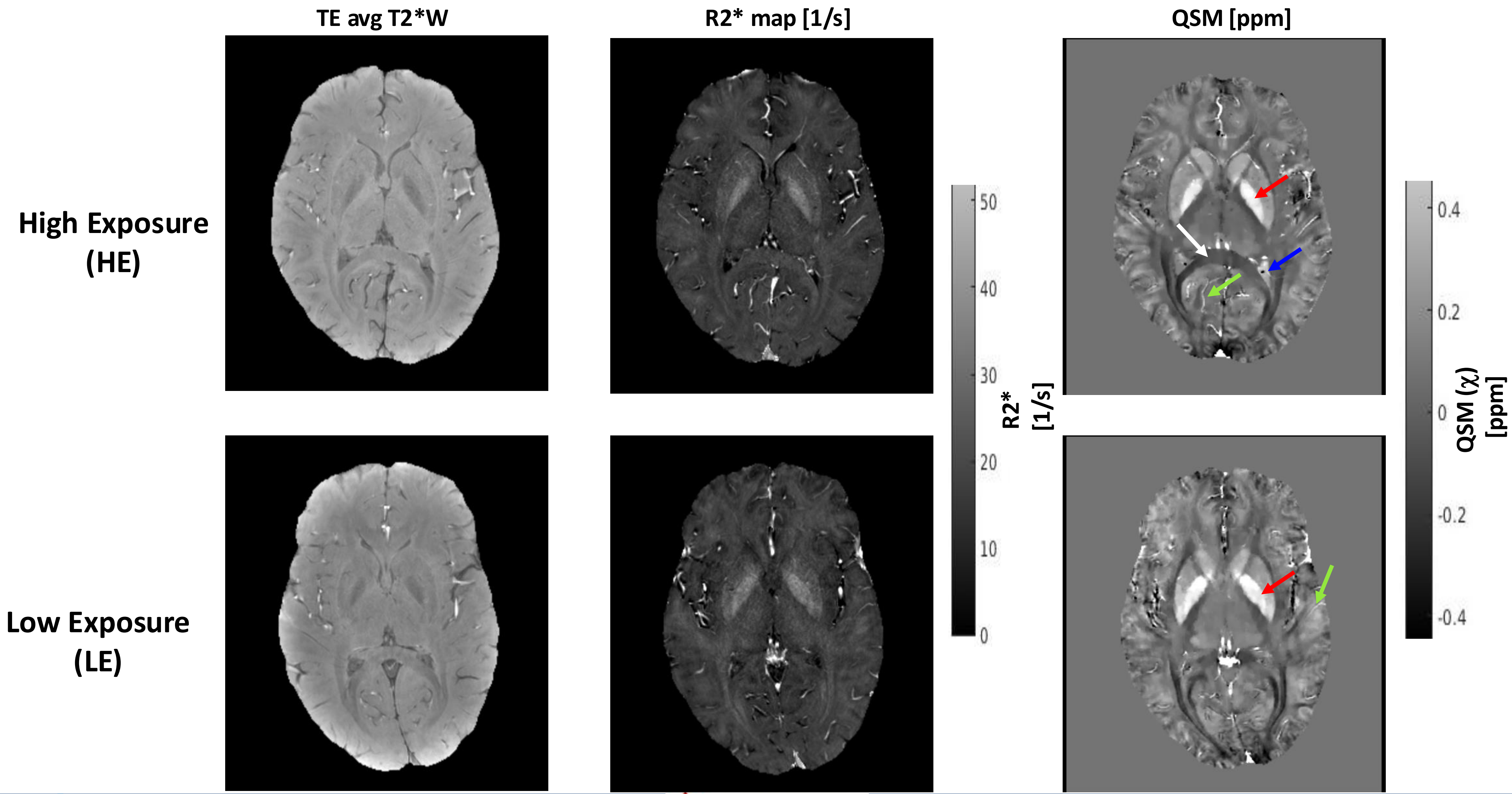
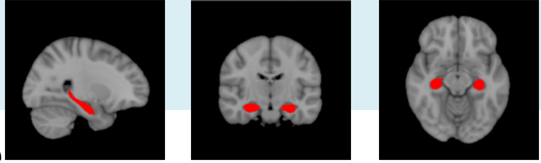

TE avg T2*W
R2* map [1/s]
QSM [ppm]
High Exposure
(HE)
Low Exposure
(LE)
50
40
30
20
10
0
R2* [1/s]
0.4
0.2
0
-0.2
-0.4
QSM (χ) [ppm]

Are the Effects of Sport Exposure Level Reflected in the Brain's Tissue?
qMRI measures in the Hippocampus



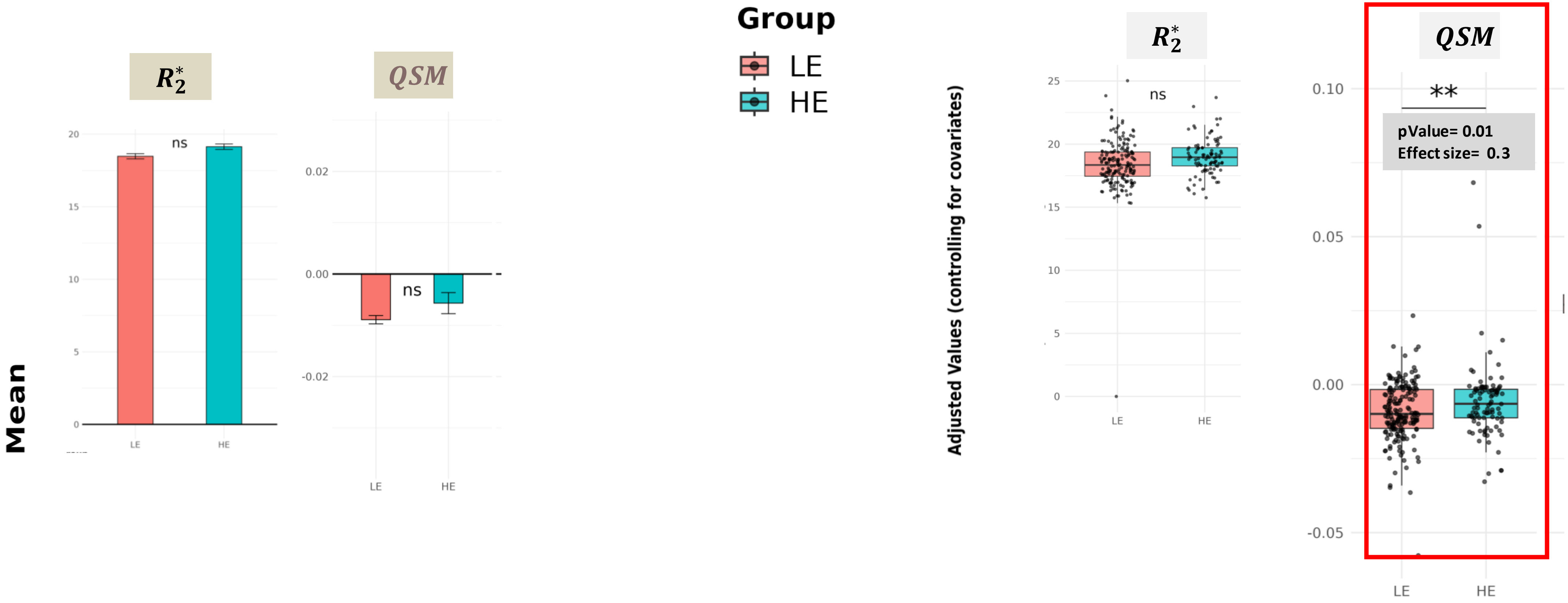
Impact of concussion

$Model\ 1:\ MRI\ = \beta_0 + \beta_1 Group + \beta_2 age + \beta_3 sex + \varepsilon$

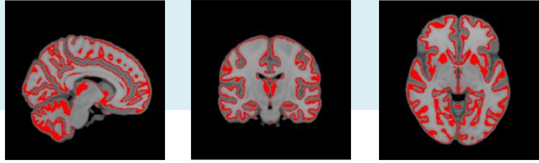
High exposures with concussion and low exposures without concussion

Effect of exposure

$Model\ 2:\ MRI\ = \beta_0 + \beta_1 Exposure + \beta_2 Concussion + \beta_3 Exposure * Concussion + \beta_4 age + \beta_5 sex + \varepsilon$



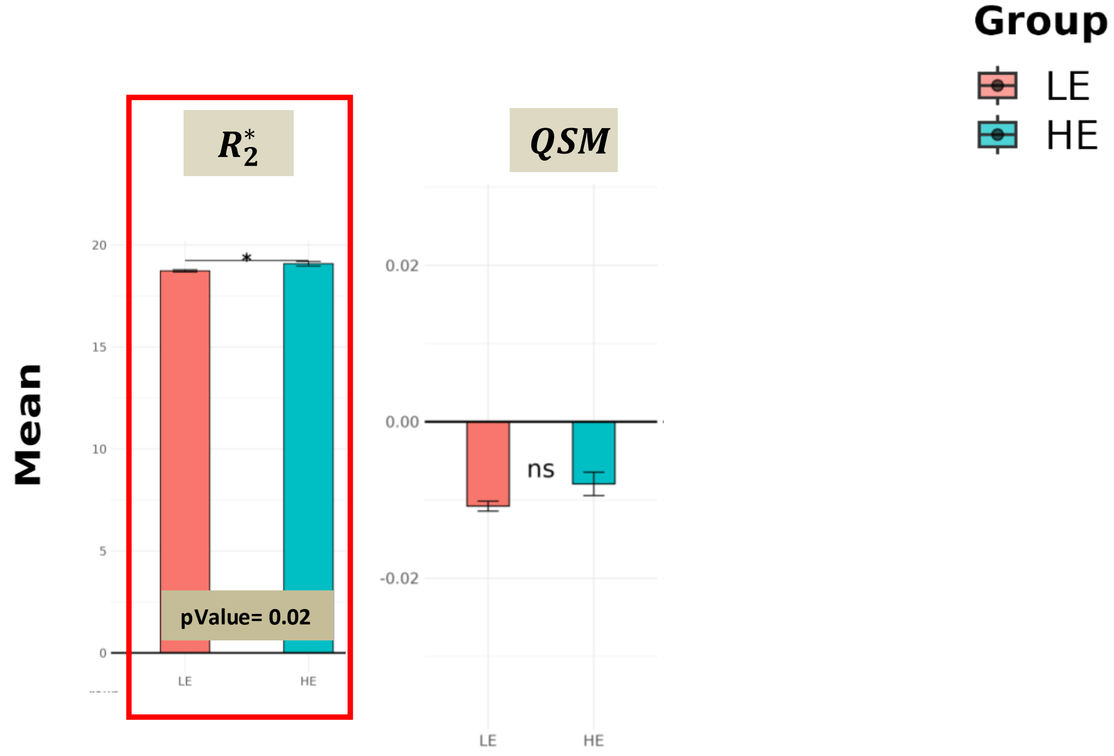
Are the Effects of Sport Exposure Level Reflected in the Brain's Tissue?
qMRI measures in the GM



Impact of concussion

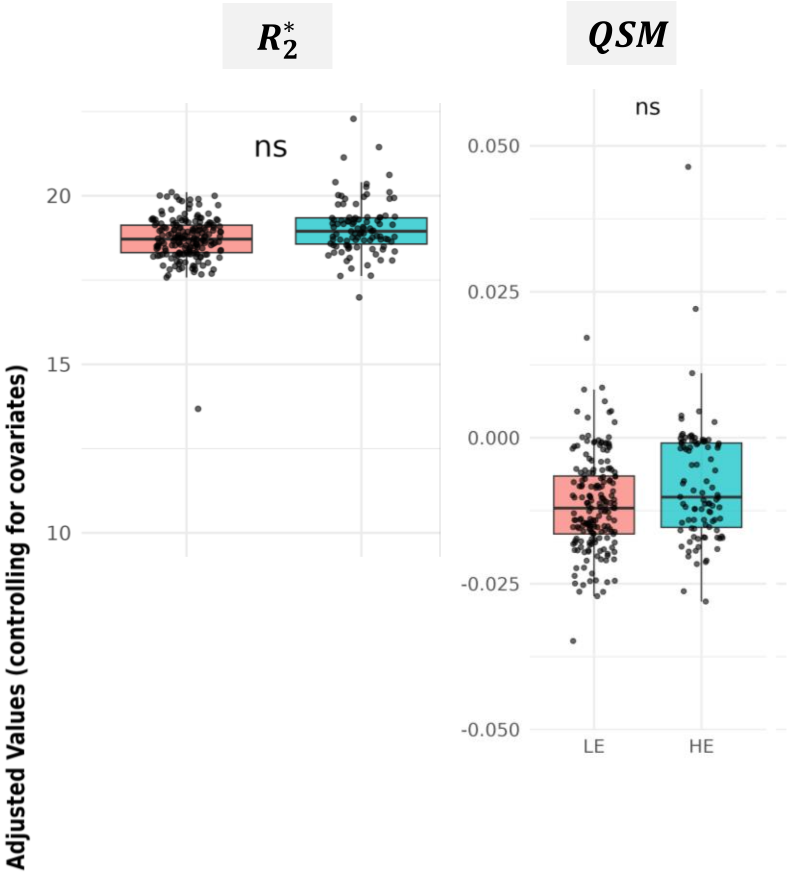
$Model\ 1:\ MRI = \beta_0 + \beta_1 Group + \beta_2 age + \beta_3 sex + \varepsilon$

High exposures with concussion and low exposures without concussion



Effect of exposure

$Model\ 2:\ MRI = \beta_0 + \beta_1 Exposure + \beta_2 Concussion + \beta_3 Exposure * Concussion + \beta_4 age + \beta_5 sex + \varepsilon$



CONCLUSION

- R2* was elevated in GM in **HE participants with concussion**, suggesting increased local magnetic field heterogeneity that may reflect mesoscale cytoarchitectural remodeling.
- QSM showed increased magnetic susceptibility in the hippocampus in HE participants, **independent of concussion history**, suggesting region-specific changes in tissue composition potentially related to iron accumulation.
- Taken together, RHI may be associated with sub-clinical region-specific alterations in cerebral tissue susceptibility properties.

- **Future directions:**
  Expand the analysis to whole-brain ROIs, and examine associations with clinical measures

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