From Diffusion to Magnetization Transfer: A Progressive Journey Through Tissue Microstructure



Evgenios Kornaropoulos, PhD

Affiliations:

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Multidimensional diffusion MRI Group, Lund University



My background



.... my scientific parkour

Probing tissue microstructure to study neurodegeneration



nai cora imagi with 3T MRI

Inferring tissue properties at the sub-voxel scale



Image modified from Edwards et al., Neuroimage 2018

Inferring tissue properties at the sub-voxel scale



heterogeneous spin systems:

- free water
- macromolecule-bound water
- lipid protons
- protein protons etc

Image modified from Edwards et al., Neuroimage (2018)

Inferring tissue properties at the sub-voxel scale



heterogeneous spin systems:

- free water
- macromolecule-bound water
- lipid protons
- protein protons etc



Fig. 1. Schematic representation of a dynamically heterogeneous system. Image modified from Edwards et al., Neuroimage (2018)

Inferring tissue properties at the sub-voxel scale



Volume element of the image On the order of $(0.5 - 1 \text{ mm})^3$



Very active research, many groups (qMRI, *in vivo* histology, microstructure...)

Goal of microstructural MRI

Goal: go beyond the voxel level and <u>infer what's happening at</u> <u>the subvoxel scale.</u>



Volume element of the image On the order of (0.5 - 1 mm)³



From macro- to micro-

MRI signal mostly detected from water protons

Water protons are **local probes** of their microscopic environment (**magnetic sensors**)

Complementary contrast mechanism arises at different scales

Biophysical modeling of the MRI signal consists in **building effective models** for averaged parameters in a bottom-up approach (coarse graining)

Effective MRI model: understand the timescales of fundamental Nuclear Magnetic Resonance properties & the NMR they produce to resonate with the motions occurring in the timescale of interest.



Image modified from Weiskopf et al., Nat Rev Phys (2021)



- → water (around 70%)
- → cell membranes
- \rightarrow solute proteins
- → insolute proteins (e.g. myelin)
- → iron
- → metabolites

. . . .

→

Various compartments



Image modified from Howes et al., Neuropsychopharmacology (2023) Image modified from Schyboll et al., Sci Report (2019)

Many kinds of protons, molecules and compartments coexists within biological tissues



Specific timescales associated with nuclear spin dynamics and magnetic resonance phenomena



Specific timescales of molecular motion that dominates each environment



Adapted from Calucci and Forte. PNMRS (2009)



Adapted from Calucci and Forte. PNMRS (2009)

Specialized MRI techniques for microstructural imaging

- DWI, MT, and ihMT are sensitive to cell membrane properties
- MT and **ihMT** also probe insoluble proteins (e.g. **myelin**)
- SWI and QSM target iron-bound complexes
- CEST and MRS help us detect low-concentration metabolites

The theory of ihMT:

<u>Nice survey:</u> Alsop DC, Ercan E, Girard OM, Mackay AL, Michal CA, Varma G, Vinogradov E, Duhamel G. Inhomogeneous magnetization transfer imaging: Concepts and directions for further development. NMR in Biomedicine. 2023 Jun;36(6):e4808.

ihMT probes:

- dipole-dipole interactions (dipolar order)
- good for imaging myelin



at thermal equilibrium





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ihMT probes:

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ix*Marseille



Adapted from Calucci and Forte. PNMRS (2009)



off-resonance RF excitation

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Dipolar Order β 1/T_{1D} R_{RFB} R_{FB} R_{FB}

Semisolid (macromolecular) pool

Liquid pool

ihMT model

Varma, G., Girard, O.M., Prevost, V.H., Grant, A.K., Duhamel, G. and Alsop, D.C., 2015. Interpretation of magnetization transfer from inhomogeneously broadened lines (ihMT) in tissues as a dipolar order effect within motion restricted molecules. Journal of magnetic resonance, 260, pp.67-76.

- **R1f:** longitudinal relaxation rate of the free pool
- **T2f:** transverse relaxation time of the free pool
- **T2b:** transverse relaxation time of the bound pool
- **R:** exchange rate
- MOb: equilibrium magnetization of the bound pool
- T1d: longitudinal relaxation time in the presence of dipolar interaction

Zeeman Order

MZA

R_{1A}

R_{RFA}









Our results: myelin imaging via ihMT

presented at the **ISMRM 2024 conference** in the process towards publication...



The Cardiac Conduction System (CCS) regulates normal heartbeat of its normal pattern (e.g. ventricular fibrillation) could cause sudden cardiac death







- - simulated muscle area - - - simulated insertion fiber area - - - simulated free running fiber area



v

The ihMT biophysical	Predefined range	Mean value & Std
parameters	of values	(muscle, fiber _{insertion} , fiber _{free})
M_0^A	-	1.00, 1.00, 1.00
$R_1^A(s^{-1})$	[0.001, 5]	$\textbf{3.34} \pm \textbf{1.65}, \textbf{4.36} \pm \textbf{0.03}, \textbf{3.73} \pm \textbf{0.12}$
$T_2^A(ms)$	[1, 5000]	$\textbf{1.09} \pm \textbf{0.36}, \textbf{2.34} \pm \textbf{0.33}, \textbf{1.52} \pm \textbf{0.14}$
R	[0.01, 100]	40.04 ± 10.96 , 21.62 \pm 0.16, 30.33 \pm 1.46
M_0^B	[0.1, 50]	$\textbf{5.73} \pm \textbf{2.91}, \textbf{3.99} \pm \textbf{0.28}, \textbf{6.14} \pm \textbf{0.53}$
$R_1^B(s^{-1})$		0.99, 0.99, 0.99
$T_2^B(\mu s)$	[3, 20]	$\textbf{7.20} \pm \textbf{0.13}, \textbf{7.42} \pm \textbf{0.17}, \textbf{7.62} \pm \textbf{0.13}$
$T_{1D}(ms)$	[0.001, 50]	$\textbf{2.03} \pm \textbf{0.20}, \textbf{4.51} \pm \textbf{0.65}, \textbf{3.28} \pm \textbf{0.35}$

Conclusions on that study:

- via fitting acquired data -> a cardiac ihMT model
- higher T1D values in PF compared to muscle
- lower exchange rate in PF compared to muscle
- better contrast in ihMT compared to T2w or MT

presented at the

ISMRM 2024 conference

in the process towards publication...

ORIGINAL ARTICLE

Inhomogeneous Magnetization transfer (ihMT) as an alternative source of MRI contrast for the cardiac conduction system: ex-vivo assessment of the ihMT biophysical model in differentiating cardiac muscle from Purkinje fibers

Evgenios N. Kornaropoulos, PhD^{1+†} | Arash Forodighasemabadi, PhD^{2†} | Lucas Soustelle, PhD¹ | Timothy Andersson¹ | Bruno Quesson, PhD^{2,3} | Gopal Varma, PhD⁴ | David Alsop, PhD⁴ | Olivier Girard, PhD^{1‡} | Julie Magat, PhD^{2,3‡} | Guillaume Duhamel, PhD^{1‡}

¹Aix-Marseille Univ, CNRS, CRMBM, Marseille, France ²IHU LIRYC, Univ of Bordeaux, Pessac, France

³CRMSB, UMR 5536 CNRS/Université de Bordeaux, Bordeaux, France

⁴Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA

Correspondence Evgenios N. Kornaropoulos PhD, Center for Magnetic Resonance in Biology and Medicine, Aix-Marseille University, Marseille, France Email: ekornaropoulos@uliege.be

HARVARD MEDICAL SCHOOL







Imaging of the cardiac conduction system for the prevention and treatment of lethal arrhythmias is of high importance. Nonetheless, such an endeavour remains challenging, since conventional structural MRI (i.e. T1w, T2w and proton density) has not managed to provide good contrast between the cardiac muscles and one of the main components of the cardiac conduction system: the Purkinje network of fibers within the myocardium, that regulate ventricular electrical impulse formation and conduction. Instead, inhomogeneous Magnetization Transfer (ihMT) shows great

Main lines of research in DWI:

Diffusion encoding strategy

- FEXI (isolate exchange)
- Free-waveform DWI (flexible sensitivity to microstructure)
- Tensor-values DWI
 - Linear Tensor Encoding (LTE)
 - Spherical Tensor Encoding (STE)
 - Planar Tensor Encoding (PTE)

(C) Waveforms for the 300 mT/m Application protocol



Biophysical modelling

- DTI
- DKI
- NODDI
- CHARMED
- SANDI
- NEXI

• CEXI b) **PROPOSED** MODEL OF BRAIN MICROSTRUCTURE



Palombo et al., Neuroimage (2020) - SANDI

Chakwizira et al., Neuroimage (2023)

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Biophysical modelling

- DTIDKI
- NODDI
- CHARMED
- SANDI
- NEXI
- CEXI

Pulsed Gradient Spin Echo (PGSE)

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Diffusion encoding strategy

- FEXI (isolate exchange)
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Biophysical modelling



Pulsed Gradient Spin Echo (PGSE)

2 different pathologies in neurodegeneration:

Systemic Lupus Erythematosus (SLE)



Traumatic Brain Injury (TBI)



2 different pathologies in neurodegeneration:

Systemic Lupus Erythematosus (SLE)

Frontiers | Frontiers in Neurology

ORIGINAL RESEARCH published: 26 April 2022 doi: 10.3389/fneur.2022.837385



Traumatic Brain Injury (TBI)

Journal of Neurotrauma 39:829-840 (June 2022) Mary Ann Liebert, Inc. DOI: 10.1089/neu.2021.044

Journal of Neurotrauma

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ORIGINAL ARTICLE

CLINICAL STUDIES

Post-Concussive Vestibular Dysfunction Is Related to Injury to the Inferior Vestibular Nerve

Anna Gard^{1,*} Ali Al-Husseini¹, Evgenios N. Kornaropoulos,² Alessandro De Maio,³ Yelverton Tegner,⁴ Isabella Björkman-Burtscher,⁵ Karin Markenroth Bloch,⁶ Markus Nilsson,² Måns Magnusson,⁷ and Niklas Marklund¹

Journal of Neurotrauma 41:1533–1549 (July 2024) Mary Ann Liebert, Inc. DOI: 10.1089/neu.2023.0099

Journal of Neurotrauma

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ORIGINAL ARTICLE

IMAGING

Widespread White Matter Abnormalities in Concussed Athletes Detected by 7T Diffusion Magnetic Resonance Imaging

Sensitivity of Diffusion MRI to White Matter Pathology: Influence of Diffusion Protocol, Magnetic Field Strength, and Processing Pipeline in Systemic Lupus Erythematosus

OPEN ACCESS

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Evgenios N. Kornaropoulos^{1,2*}, Stefan Winzeck^{2,3}, Theodor Rumetshofer¹, Anna Wikstrom¹, Linda Knutsson^{4,5,6}, Marta M. Correia⁷, Pia C. Sundgren^{1,8,et} and Markus Nilsson¹⁷

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SLE study



Difference (SLE versus HC) in diffusion parameters measured within WM tracts

Kornaropoulos et al., frontiers in Neurology (2022)

SLE study

TABLE 1 | Demographics and image acquisition parameters.

Image acquisition	#SLE, #HC	Mean age (std) of HC, SLE	Image resolution (isotropic, in <i>mm</i> ³)	<i>b</i> -values in s/ <i>mm</i> ² (# of directions)	TR/TE in ms/ms	
3T-DTI	63, 20	37 (9) , 36 (9)	2.0	0 (8), 1,000 (64)	7,300/73	
3T-DKI	56, 20	37 (9) , 35 (9)	2.3	0 (3), 250 (6), 500 (6), 1,000 (20), 2750 (30)	7,500/103	
7T-DTI	54, 21	40 (10) , 40 (9)	2.0	0 (3), 1,000 (30)	8,816/62	

Rows show the three protocols: # corresponds to the number of, SLE, patients with systemic lupus erythematosus; HC, human controls; TR, repetition time; TE, echo time. In total 106 subjects participated in this study: 76 patients with SLE and 30 HC. Out of the 106 subjects, 47 were scanned with all three image acquisition protocols (3T-DTI and 3T-DKI and 7T-DTI): 37 patients with SLE and 10 HC.

SLE study



SLE study



TractSeg (Deep Learning): 72 white matter bundles automatic segmentation





with

 $s = \sqrt{((n_{HC} - 1)s_{HC}^2 + (n_{SLE} - 1)s_{SLE}^2)/(n_{HC} + n_{SLE} - 2)}$ (2)

SLE study

Pipelines comparison:

- minuscule differences across the data processing pipelines
- correcting for distortions from motion and eddy currents (Eddy) was the most beneficial
 - gross smoothing reduced effect sizes by up to 20% !



with

 $s = \sqrt{((n_{HC} - 1)s_{HC}^2 + (n_{SLE} - 1)s_{SLE}^2)/(n_{HC} + n_{SLE} - 2)}$ (2)

 $d = (u_{HC} - u_{SLE})/s$

SLE study

Diffusion protocols & magnetic field strength comparison:

- the **diffusion protocol** had the strongest influence on effect sizes among the ones examined
- **DKI is less sensitive than DTI** to WM pathology in SLE



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- FA was the parameter displaying the highest effect sizes in all the protocols.

Effect size of diffusion parameters over whole brain								
3T-DTI	*	frest.		*		森		1.0 0.8 25 0.6 55 0.4 20 0.2 0.0
FA 3T-DKI	a t	ful.		华		森		1.0 0.825 0.65 0.43 0.220 0.0
7T-DTI	a t	fint		袋		森		1.0 0.82/5 0.6 t10 0.42 0.0
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	A	1.1		*		森		1.0 0.8 0.6 0.4 0.2 0.0 0.0
зт-рті 🛃		f.		*		料		1.0 0.8 az 0.6 to 0.4 a 0.2 a 0.0
AD 3T-DKI		1		**		林		1.0 0.825 0.61 0.220 0.0
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зт-рті 🌑	*			袋		禁		1.0 0.8 ± 2 0.6 ± 2 0.4 ± 0 0.2 ± 0 0.0
RD 3T-DKI	**	1.1		谷		料		1.0 0.8 az 0.6 tp 0.4 au 0.2 b 0.0
7T-DTI	t t	1.1		**		森		1.0 0.8 825 0.4 910 0.210 0.0

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- no substantial increase in sensitivity came with the use of more demanding acquisitions (DKI and 7T)

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MD 3T-DKI	t at	for t		华		幕			1.0 0.8 gi 0.6 tt 0.4 gi 0.2 to 0.2 to 0.0
7T-DTI	and the second s	1-1-1		*		莽			1.0 0.8 2 3 0.6 5 1 3 0.6 2 1 3 0.6 5 1 3 0.6 5 1 3 0.2 1 0 0.2 1 0 0.2 1 0 0.2 1 0 0.2 1 0 0.0 1 0 0.0 1 0 0.0 0 0.0 1 0 0.0 0 0 0.0 0 0 0.0 0 0 0.0 0 0 0
3T-DTI		for t		*		森			1.0 0.8350 0.61 0.24 0.2 0.0
AD 3T-DKI		1.01				森			1.0 0.8 a 0.6 t 0.4 a 0.2 a 0.0
7T-DTI	4	1.1				森			1.0 0.82is 0.6 tJ 0.24 0.2 0.0
зт-рті 💽	**	for t		*		禁			1.0 0.8 av 0.6 to 0.4 av 0.2 to 0.0
RD 3T-DKI	***	1.1		谷		禁			1.0 0.8 z 0.6 t 0.4 t 0.2 t 0.0
7T-DTI	and	1		**		森			1.0 0.8 az 0.6 t) 0.4 at 0.2 a 0.0

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Effect size of diffusion parameters over whole brain 3T-DTI 📲 3T-DKI 7T-DTI 3T-DTI MD 3T-DKI 7T-DTI 3T-DTI 3T-DKI -AD 7T-DTI

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2 different pathologies in neurodegeneration:

Traumatic Brain Injury (TBI)



Study cohorts & neuroimaging Athletes, 7T



7T MRI (Lund)



• T1w

- FOV: 230×230×180 mm³
- resolution: 0.80×0.80×0.80 mm³
- TR/TE: 6/0.39132 ms

• T2w

- FOV: 230×230×180 mm³
- resolution: 0.80×0.80×0.80 mm³
- TR/TE: 3.2/0.25 ms

• FLAIR

- FOV: 230×230×180 mm³
- resolution: 0.70×0.70×0.70 mm³
- TR/TE: 6/0.39132 ms

• DT

- FOV: 224×224×110 mm³
- resolution: 2.00×2.00×2.00 mm³
- TR/TE: 9200/65 ms
- 6 b = 100 s/mm²
- 30 b = 1000 s/mm²
- TOPUP (2 b = 0 with opposing polarities of the phase-encode blips)

• DKI

- FOV: 224×224×120 mm³
- resolution: 2.00×2.00×2.00 mm³
- TR/TE: 9800/76 ms
- 6 b = 100 s/mm²
- 6 b = 500 s/mm²
- 10 b = 1000 s/mm²
- 30 b = 2000 s/mm²
- TOPUP (2 b = 0 with opposing polarities of the phase-encode blips)

So far 2 publications:

- Gard, Al-Husseini, Kornaropoulos et al., **Post-concussive vestibular dysfunction is related to injury to the inferior vestibular nerve**, Journal of neurotrauma 39 (11-12), 829-840
- Gard, Kornaropoulos et al., Widespread White Matter Abnormalities in Concussed Athletes Detected by 7T Diffusion Magnetic Resonance Imaging, Journal of Neurotrauma 41 (13-14), 1533-1549

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IMAGING

ORIGINAL ARTICLE

CLINICAL STUDIES

Post-Concussive Vestibular Dysfunction Is Related to Injury to the Inferior Vestibular Nerve

Anna Gard^{1,*} Ali Al-Husseini¹, Evgenios N. Kornaropoulos², Alessandro De Maio³, Yelverton Tegner⁴, Isabella Björkman-Burtscher⁵, Karin Markenroth Bloch⁶, Markus Nilsson², Måns Magnusson⁷, and Niklas Marklund¹

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Widespread White Matter Abnormalities in Concussed Athletes Detected by 7T Diffusion Magnetic Resonance Imaging

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- No significant differences in DTI/DKI metrics of cerebellar white matter tracts
- Cerebellar gray and white matter volumes were similar in athletes with SRC and control subjects.

So far 2 publications:

- Gard, Kornaropoulos et al., Widespread White Matter Abnormalities in Concussed Athletes Detected by 7T Diffusion Magnetic Resonance Imaging, Journal of Neurotrauma 41 (13-14), 1533-1549
- Widespread microstructural alterations in the white matter that correlated with CSF markers of axonal injury
- DKI was more sensitive, detecting more white matter changes than DTI

Journal of Neurotrauma 41:1533–1549 (July 2024) Mary Ann Liebert, Inc. DOI: 10.1089/neu.2023.0099

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IMAGING

ORIGINAL ARTICLE

Widespread White Matter Abnormalities in Concussed Athletes Detected by 7T Diffusion Magnetic Resonance Imaging

Ongoing project: A proxy for glymphatic system malfunction after mild TBI



Lohela et al., 2022

Representative PVS masks 3D rendering

PVS automatic method 1: *Sepehrband et al.*

PVS automatic method 2: *Duarte Coelle et al.*

Journal of Neuroscience Methods 403 (2024) 110039



Check for updates



Roberto Duarte Coello ^a, Maria del C. Valdés Hernández^{*,*}, Jaco J.M. Zwanenburg^b, Moniek van der Velden^b, Hugo J. Kuijf^b, Alberto De Luca^b, José Bernal Moyano^{*,c,d}, Lucia Ballerini^{*,e}, Francesca M. Chappell^a, Rosalind Brown^{*}, Geet Jan Biessels^b, Joanna M. Wardlaw^{*}

⁴ Centre (or Clinical Brain Sciences, Department of Neuroimaging Sciences, University of Edinburgh, Edinburgh, UK ⁵ Image Sciences Institute, UMC Urecht, Urtecht, Netherlands German Centre (or Neurodegaranizub Dissues, Magdhurg, Germany ⁶ Institute of Cognitive Neurology and Demonito Research, Onto-ton-Guiricke University Magdeburg, Magdeburg, Germany



They use Frangi or RORPO filtering

ABSTRACT

Background: Magnetic Resonance Imaging (MRI) visible perivascular spaces (PVS) have been associated with age, decline in cognitive abilities, interrupted sleep, and markers of small vessel disease. But the limits of validity of their quantification have not been established.

New method: We use a purpose-built digital reference object to construct an in-silico phantom for addressing this need, and validate it using a physical phantom. We use cylindeer of different sizes as models for PVS. We also evaluate the influence of PVS' orientation, and different sets of parameters of the two vesselness filters that have been used for enhancing tubular structures, samely Frangi and RORFO filters, in the messurements' accuracy, *Readue*: PVS measurements in MRI are only a proxy of their true dimensions, as the boundaries of their representation are consistently overestimated. The success in the use of the Frangi filter relies on a careful tuning of several parameters. Applas – 0.5, beta= 0.5 and (= 500 yielded the best results. RORFO does not have these requirements and allows detecting smaller cylinders in their entirety more consistently in the absence of noise and contounding artefacts. The Frangi filter seems to be best studie for vossi size sequal or larger than 0.4 mm isotropic and cylinders larger than 1 mm diameter and 2 mm length. PVS' orientation did not affect messurements in data with listorgic voxels.

Comparison with existent methods: Does not apply.

Conclusions: The in-silico and physical phantoms presented are useful for establishing the validity of quantification methods of tubular small structures.

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> They use EPC after NL means filtering

OPEN Image processing approaches to enhance perivascular space visibility and quantification using MRI

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Imaging the perivascular spaces (PVS), also known as Virchow-Robin space, has significant clinical value, but there remains a need for neuroimaging techniques to improve mapping and quantification of the PVS. Current technique for PVS evaluation is a scoring system based on visual reading of visible PVS in regions of interest, and often limited to large caliber PVS. Enhancing the visibility of the PVS could support medical diagnosis and enable novel neuroscientific investigations. Increasing the MRI resolution is one approach to enhance the visibility of PVS but is limited by acquisition time and physica constraints. Alternatively, image processing approaches can be utilized to improve the contrast ratio between PVS and surrounding tissue. Here we combine T1- and T2-weighted images to enhance PVS contrast, intensifying the visibility of PVS. The Enhanced PVS Contrast (EPC) was achieved by combining T1- and T2-weighted images that were adaptively filtered to remove non-structured high-frequency spatial noise. EPC was evaluated on healthy young adults by presenting them to two expert readers and also through automated quantification. We found that EPC improves the conspicuity of the PVS. We also present a highly reliable automated PVS quantification approach, which was optimized using expert readings.

Representative PVS masks 3D rendering

PVS automatic method 1: Sepehrband et al.

more robust across scanners



PVS automatic method 2: *Duarte Coelle et al.*

more precise for our data



Representative PVS masks 3D rendering



Ongoing collaborations Multicenter mild TBI dataset for glymphatic measures & correlations

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PVSF & Diffusivity

Cerebrovascular burden

Fluid biomarkers

Cognition

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