USC Stevens Neuroimaging and Informatics Institute

INI Microstructural Imaging Group

Effect of glycated hemoglobin level on brain clearance morphology

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Disclosure

- CEO and co-founder of NeuroScope Inc
- Co-inventor of the patent related to the neuroimaging technique

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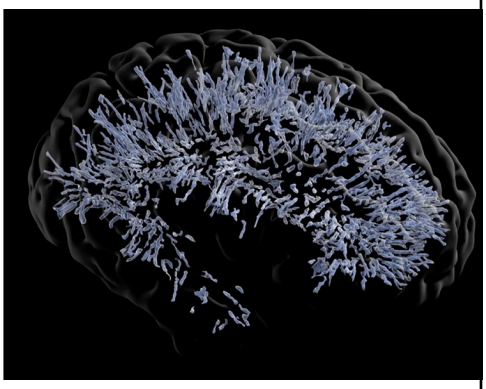
Introduction

- Brain clearance is important (homeostasis)
- Brain clearance dysfunction in AD and vascular dementia
- Perivascular spaces (PVS) morphology have been used as a proxy to brain clearance health
- Several modifiable and non-modifiable risk factors have been reported for alteration of PVS
  - Age, BMI, sleep, neuro-vascular health
- High blood sugar over time damages blood vessels in the brain, but the link between blood sugar and brain clearance in human is understudied
- In this work we studied the association between PVS volume and blood sugar



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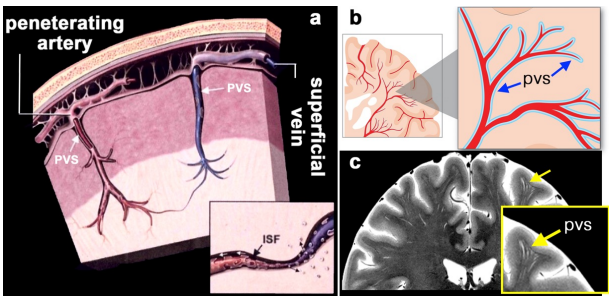
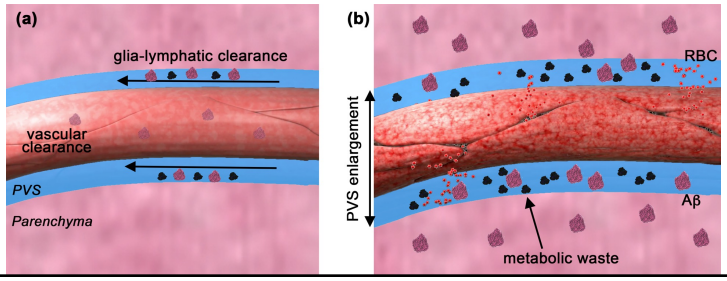
Brain clearance system (glia-lymphatic system)

- Macroscopic waste clearance system
- A system of perivascular tunnels, formed by astroglial cells
- Elimination of soluble proteins and metabolites – brain homeostasis
- **Perivascular space (PVS)** are sites for:
  - Influx of CSF through peri-arterial space
  - Drainage of CSF plus interstitial fluid/waste through peri-venous space





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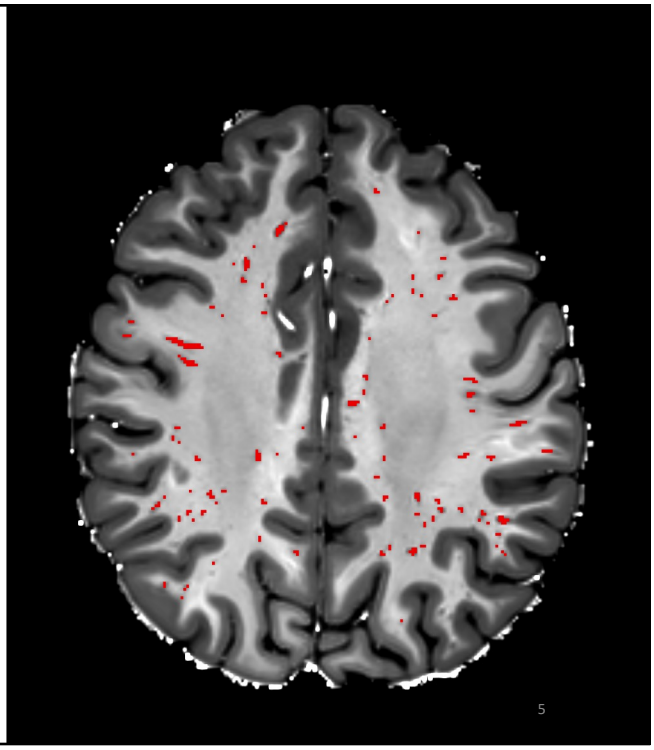
Automated PVS mapping

- Current clinical routine
  - Categorical scoring system (Wardlaw scale)
  - Counting number of visible PVS in:
    - Centrum semi-ovale
    - Basal ganglia
    - Brainstem
- Laborious
- Image resolution / quality dependent
- Morphology and distribution is ignored
- The focus is limited to “large” PVS
  - Most pathologies starts at micro-level
- Detecting PVS vs. noise can be challenging



Sepehrband, Choupan, et al *Nature Scientific Reports 2019*
Sepehrband, Choupan *US Patent* 2021 (*pending*)

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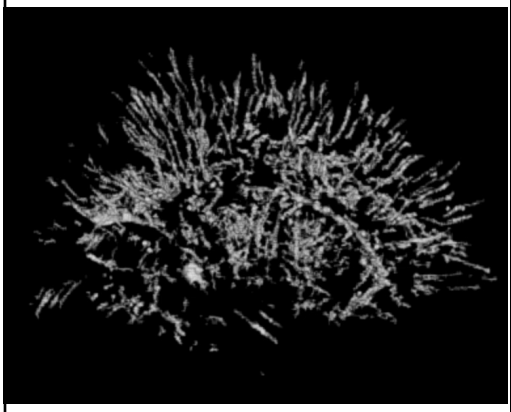
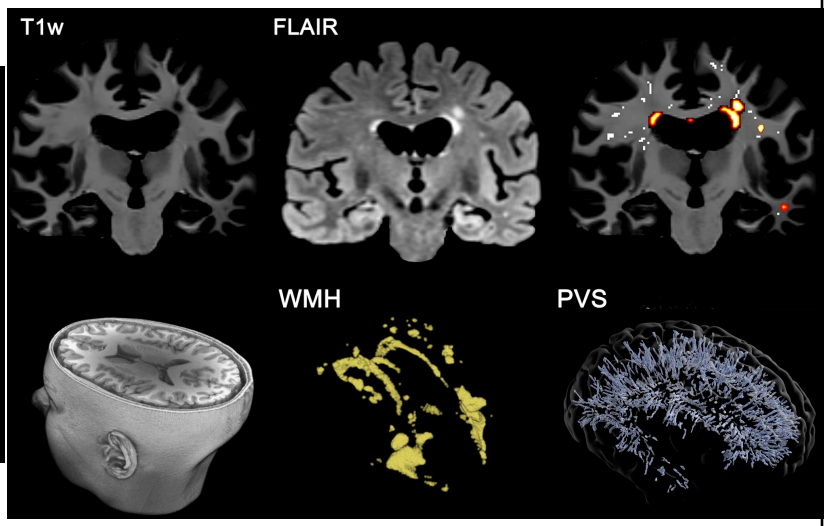
Removing white matter hyperintensities from PVS masks improves the accuracy of the PVS segmentation





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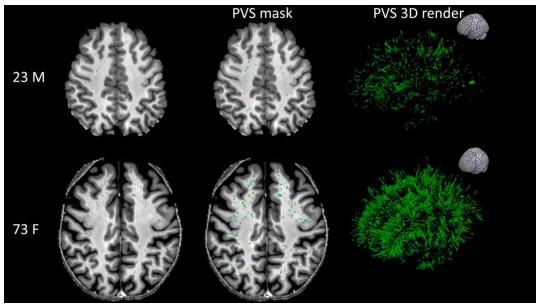
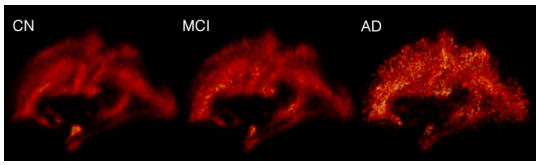
Perivascular space in health and neurological disorders





Condition	Neuroimaging PVS analysis	Finding
Healthy Aging	Visual (Francis et al., 2019; Gutierrez et al., 2013; Huang et al., 2021; Laveskog et al., 2018; Yakushiji et al., 2014; Zhu et al., 2010b, 2011) Quantitative (Barisano et al., 2021b; Ramirez et al., 2015)	Higher PVS burden is associated with aging
Gender	Visual (Zhu et al., 2010b, 2011) Quantitative (Barisano et al., 2021b; Ramirez et al., 2015)	Higher PVS burden is associated with male sex
BMI	Visual (Ozato et al., 2021) Quantitative (Barisano et al., 2021b)	Higher PVS burden is associated with higher BMI (Barisano et al., 2021b) and higher visceral fat (Ozato et al., 2021)
Time of day	Quantitative (Barisano et al., 2021b)	Higher PVS burden is visible on MRI at later time of day
Long-duration spaceflight	Quantitative (Barisano et al., 2022)	Increased PVS volume in the white matter (WM-PVS) and basal ganglia after long-duration spaceflight on the International Space Station, but not short-duration spaceflight on the Space Shuttle. Preflight and postflight WM-PVS volumes are associated with the spaceflight-associated neuro-ocular syndrome.
Genetics	Visual (Duperron et al., 2018) Quantitative (Barisano et al., 2021b; Choi et al., 2020)	Significant heritability estimates for PVS burden in older community-dwelling people. Healthy young twins show similar amount of PVS.
Sleep	Visual (Aribisala et al., 2020; Del Brutto et al., 2019; Song et al., 2017) Quantitative (Berezuk et al., 2015)	Higher PVS burden is associated with sleep dysfunction (Aribisala et al., 2020; Berezuk et al., 2015; Del Brutto et al., 2019) and obstructive sleep apnea (Song et al., 2017)
Hypertension	Visual (Gutierrez et al., 2013; Martinez-Ramirez et al., 2013; Yakushiji et al., 2014; Zhu et al., 2010b) Quantitative (Dubost et al., 2019; Sepehrband et al., 2021) Meta-analysis (Francis et al., 2019)	Hypertension is associated with higher PVS burden, especially in the basal ganglia
MCI	Quantitative (Sepehrband et al., 2021)	Female MCI subjects have higher PVS volume fraction in centrum semiovale. MCI subjects have lower PVS volume fraction in the anterosuperior medial temporal lobe.
AD	Visual (Banerjee et al., 2017; Chen et al., 2011; Roher et al., 2003) Quantitative (Cai et al., 2015; Ramirez et al., 2015)	AD is significantly associated with increased PVS volume (Cai et al., 2015; Ramírez et al., 2015), count (Roher et al., 2003), and visually-rated severity (Banerjee et al., 2017; Chen et al., 2011) in the subcortical white matter
CAA	Visual (Charidimou et al., 2014; van Veluw et al., 2016)	CAA is associated with greater burden of PVS in white matter (Charidimou et al., 2014; van Veluw et al., 2016)
MS	Visual (Achiron and Faibel, 2002; Conforti et al., 2014; Etemadifar et al., 2011; Ge et al., 2005; Kilsdonk et al., 2015) Quantitative (Wuerfel et al., 2008)	MS is associated with higher PVS burden in white matter
PD	Visual (Conforti et al., 2018; Duker and Espay, 2007; Fénelon et al., 1995; Lee et al., 2015; Mancardi et al., 1988; Mehta et al., 2013) Quantitative (Donahue et al., 2021)	PD is associated with higher PVS burden in the basal ganglia (Conforti et al., 2018; Duker and Espay, 2007; Fénelon et al., 1995; Lee et al., 2015; Mancardi et al., 1988; Mehta et al., 2013) and certain regions of the subcortical white matter (Donahue et al., 2021)

Review paper: Barisano, et al. *NeuroImage 2022*

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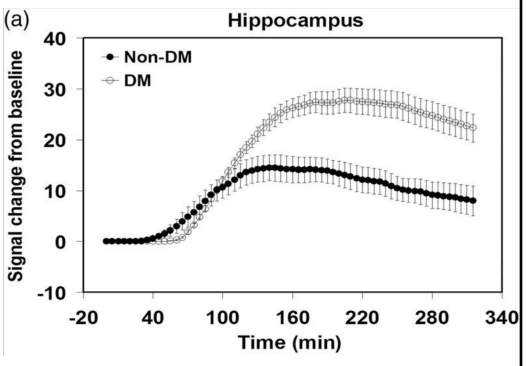
Blood sugar and perivascular spaces

- High blood sugar damages brain vessels and therefore could affect brain clearance
- Pre-clinical data has shown that diabetes impairs brain clearance system [Jiang Q, et al., 2016],
  - The clearance of gadolinium contrast agent in CSF from the interstitial space was slowed in Type-2 diabetes mellitus rats.



Here we used data from **MarkVCID data** to study the link between blood sugar level (HbA1C) and PVS volume.

- PVS was segmented as described
- The association between PVS and HbA1C was assessed
- We controlled for age, sex, ICV, and handedness
- Bonferroni correction and post-hoc analysis

Table 1. Participant summary information.

	Diabetics	***Non-diabetics***	***P value***
N	16	33	
Age	69.0 +/- 5.6	68.8 +/- 6.7	0.92
Gender	11 females	25 females	
HbAIC	8.03 +/- 1.1	5.8 +/- 0.36	1.5 e-14

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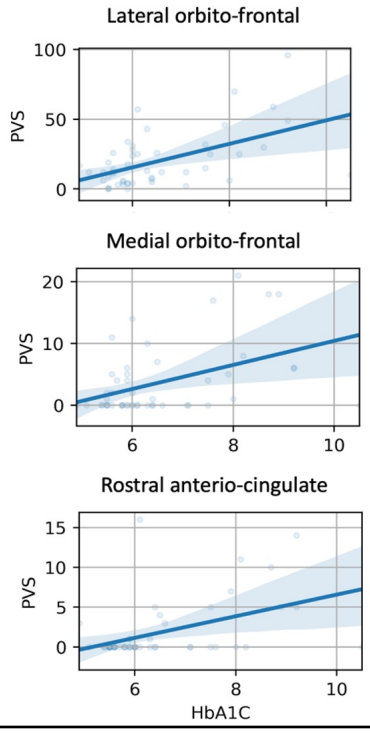
Patients with high HbA1C have higher PVS volume in the frontal regions in left hemisphere

- Lateral orbito-frontal region
  - t=3.98, p<0.0001;
  - OLS: F(49,4)=4.48, R^2=0.29
- Medial orbito-frontal region
  - t=2.91, p=0.006;
  - OLS: F(49,4)=2.63, R^2=0.19
- Rostral anterio-cingulate region
  - t=3.11, p=0.003;
  - OLS: F(49,4)=2.94, R^2=0.21



Choupan et al, unpublished

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Summary

- We show the first results of the association between blood sugar level and perivascular space integrity in human
- Higher HbA1C was associated with higher volume of PVS
- It's been shown that high blood sugar damages small vessels and affect BBB integrity, which may explain the observed PVS changes
  - It is unclear why PVS change is localized rather than global
  - Larger studies and longitudinal data is required to better understand the underlying mechanism

No causal relation can be uncovered yet

Given the cross-sectional nature of the analysis

We speculate that HbA1C drives the observed PVS change, rather than the opposite direction.

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Thank you

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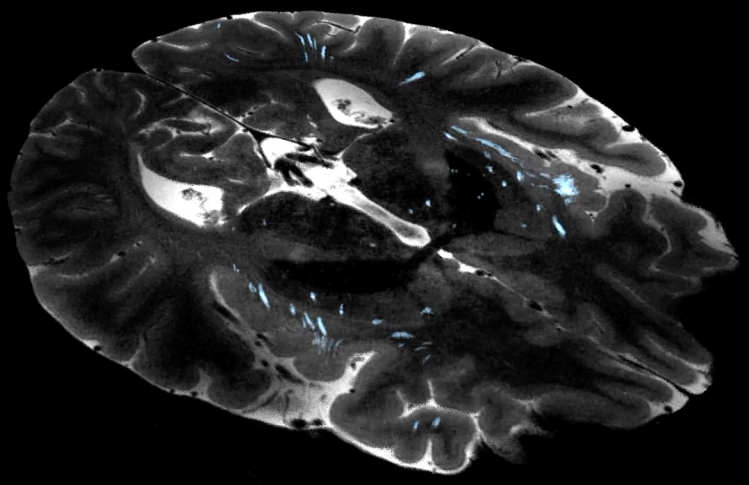

Grants
R01: AG07082501
RF1: MH12322301
R41: AG07302401

UH3-NS100614

Postdoc positions available