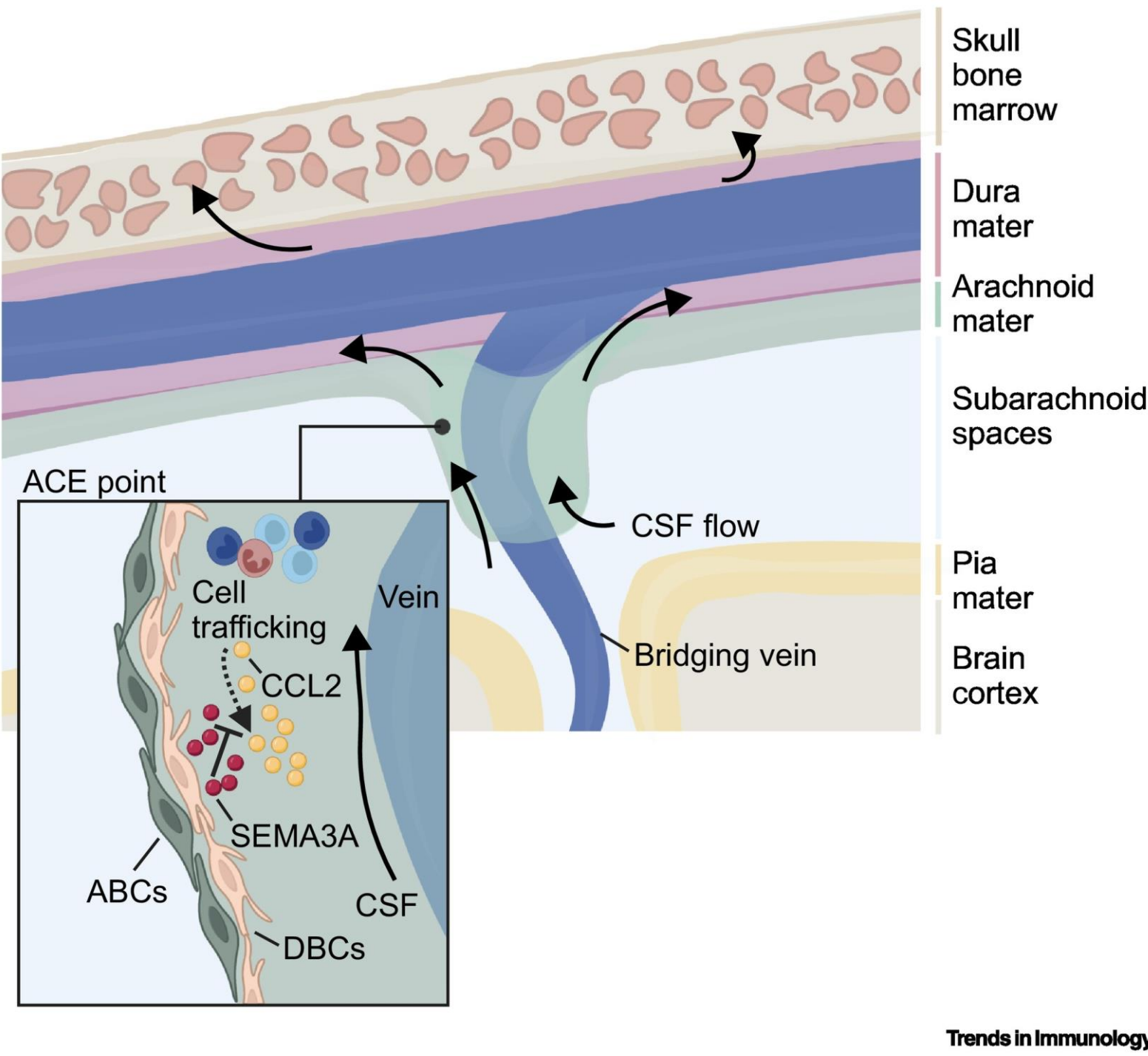


Characterizing Arachnoid Cutoff Exit Points in Aging and Alzheimer’s Disease.

Background

- Specialized barriers, including the blood-brain barrier, shield the central nervous systems (CNS) from the peripheral immune system. Yet, CNS-dura communication is vital for immune surveillance and waste clearance.

Arachnoid Cutoff Exit (ACE) Points

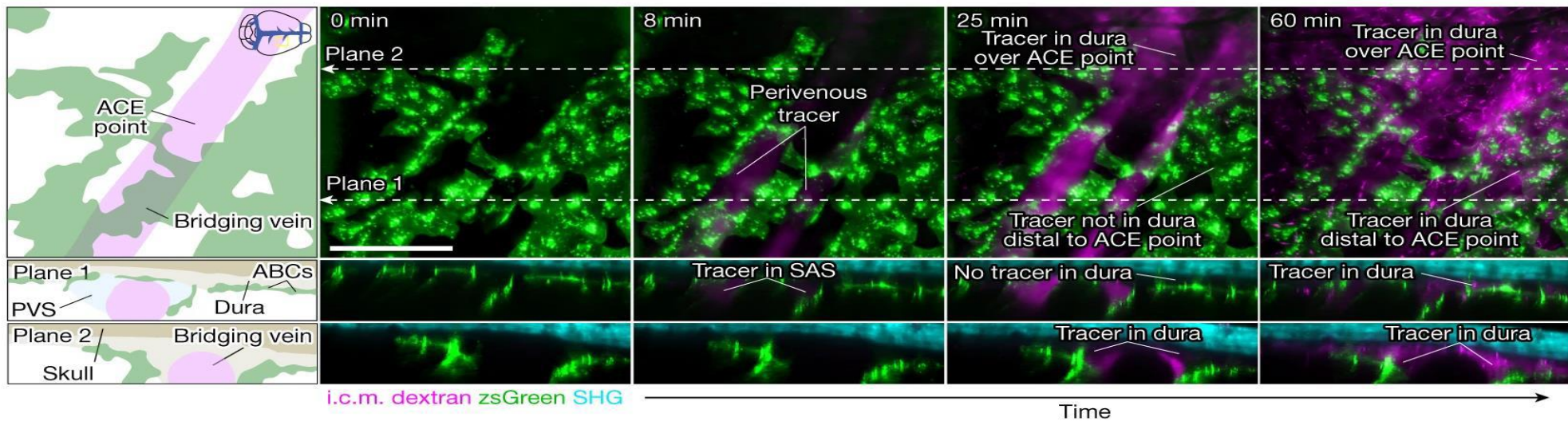


Trends in Immunology

ACE points are sites where bridging veins cross the arachnoid into the parasagittal dura as potential routes for waste and immune cell transport.

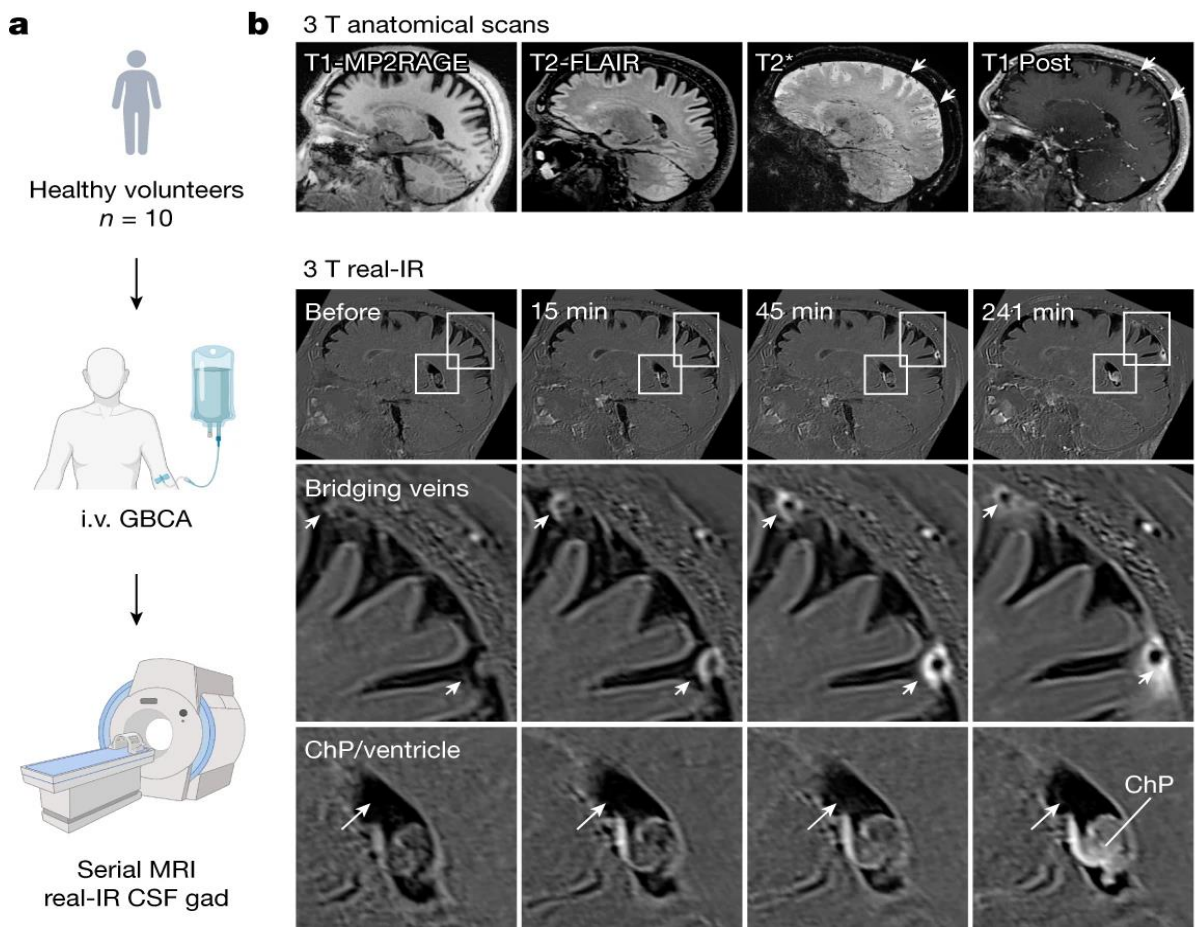
Preliminary Studies

ACE Points in Mice



- Smyth et al. (2024) applied two-photon intravital imaging of dextran flow to the dura mater through an ACE point in mice.
- Follow up work by Smyth et al. (2025) established ACE point amyloidosis as a neuropathological feature of Alzheimer's disease (AD).

ACE Points in Humans



Smyth et al. (2024) further found ACE points in the human brain by applying contrast-enhanced MRI in a sample of (n = 10) healthy participants.

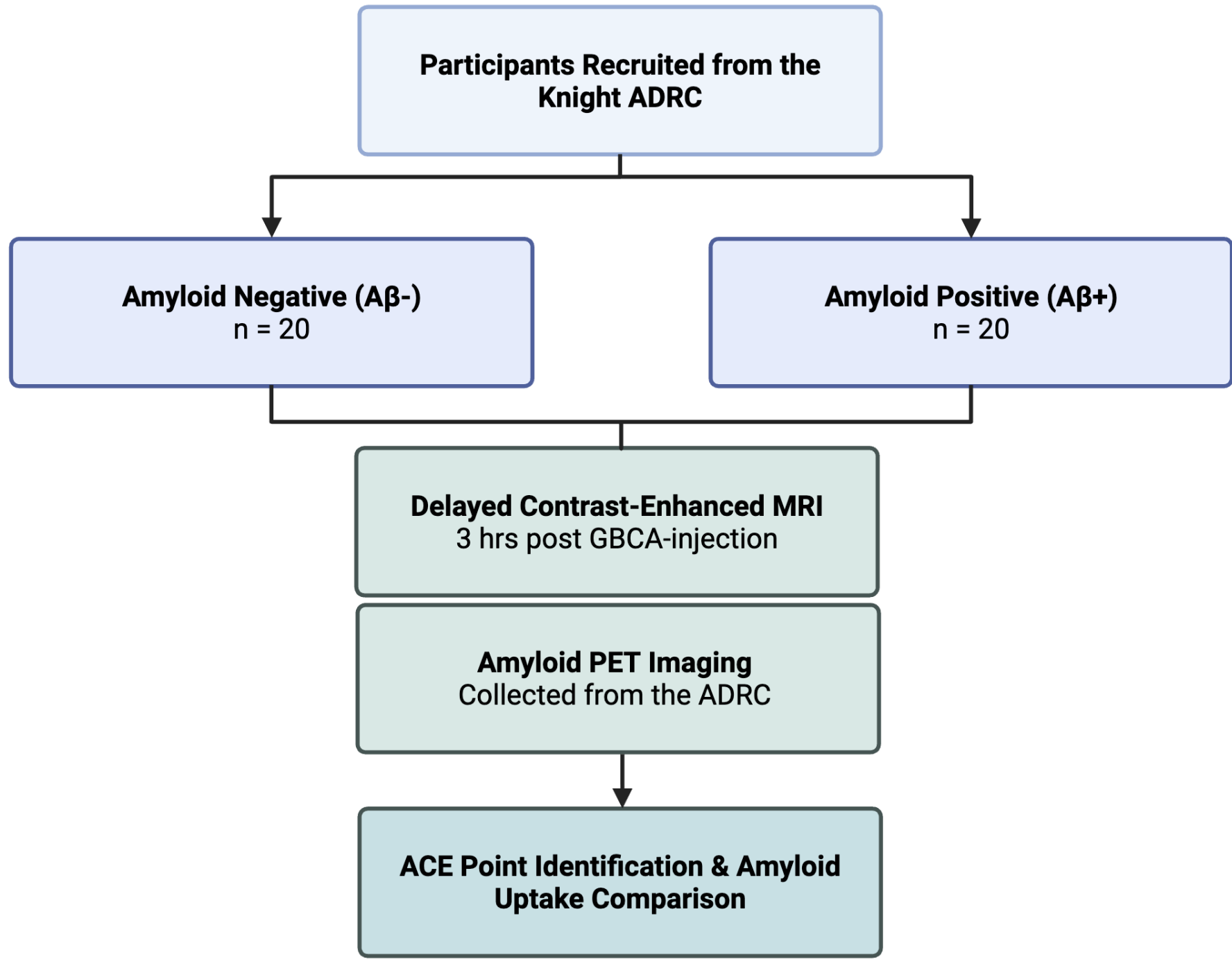
Aims

Overarching Aim: To investigate the presence of ACE points in a cohort of individuals with and without amyloid-pathology to further elucidate their role in AD.

Aim	Objective	Hypothesis
Aim 1	Identify the existence of ACE points in a sample of older adults.	ACE points will be identified in this cohort of older adults, validating earlier work.
Aim 2	Test whether amyloid accumulates in ACE points.	There will be greater amyloid uptake at ACE points in older adults with amyloid pathology compared to healthy older adults.
Aim 3	Determine if the level of amyloid accumulation at ACE points predicts overall amount of amyloid in the brain.	Increasing levels of amyloid present at ACE points will be positively associated with amyloid levels in the brain.

Methods

Older adults (65+) from the **Knight Alzheimer’s Disease Research Center (ADRC)** will undergo a pre- and post-contrast MRI that will be aligned with their existing amyloid PET scan.



Self-Reports & Cognitive Assessments Administered:

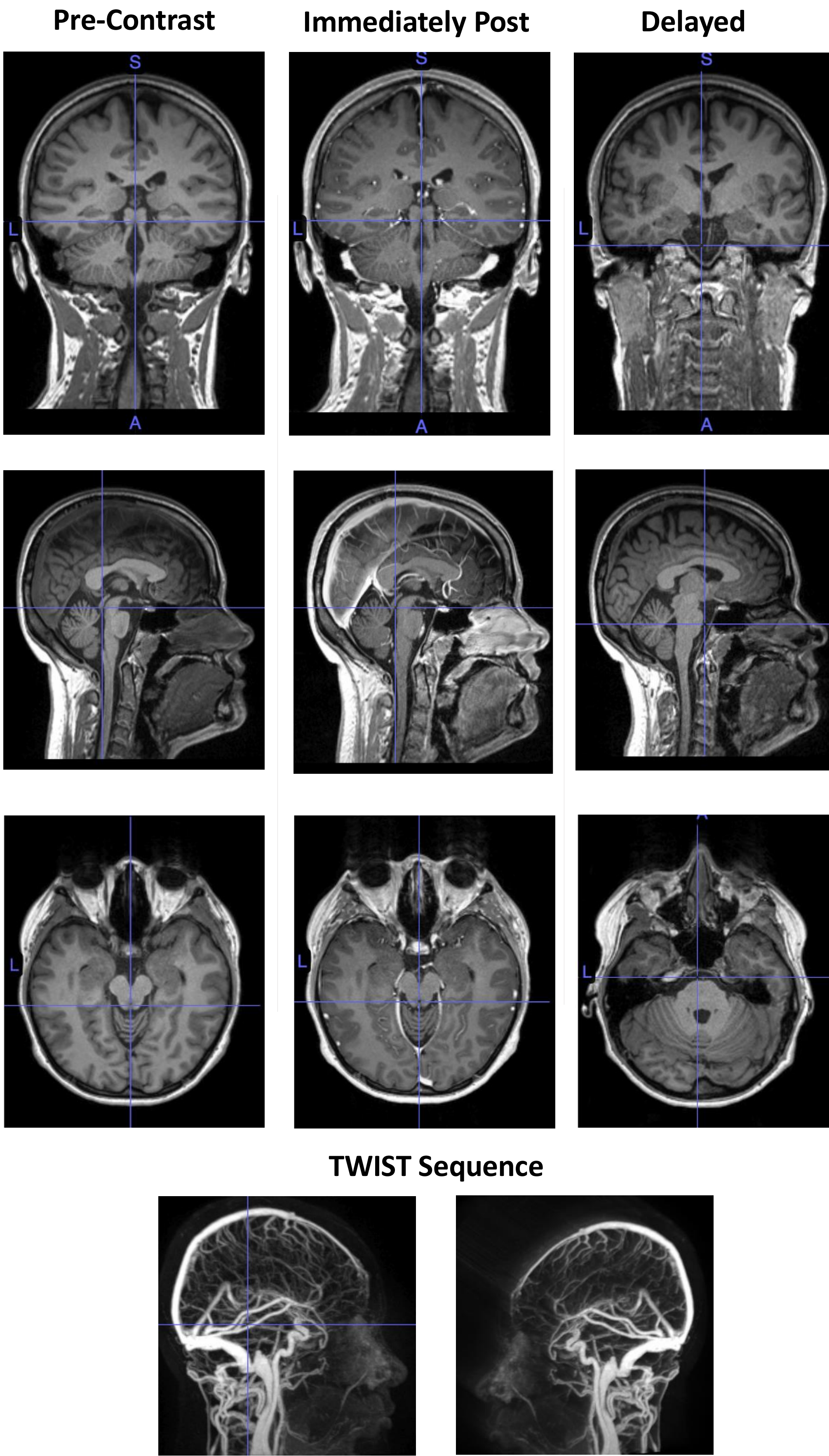
- Physical Activity Scale for the Elderly
- Non-Laboratory Based INTERHEART Modifiable Risk Score
- Pittsburgh Sleep Quality Index
- Geriatric Depression Scale - Short Form
- Montreal Cognitive Assessment

Neuroimaging Sequences

Scan name	Category	Timing
T1 sagittal	T1	[Pre] [Post] [Delay]
T1-SPACE	T1	[Pre] [Post] [Delay]
Real-IR-FLAIR	FLAIR	[Pre] [Post] [Delay]
SURF-EPI	Low b-value	[Pre]
DWI	Low b-value	[Delay]
PCSF	PCSF	[Pre]
T2*-EPI	T2	[Pre]
T2	T2	[Pre]
TWIST	Other	[During bolus]
BOLD resting state	fMRI	[Delay]

Timing key: [Pre] Pre-contrast; [Post] Post-contrast; [Delay] after delay; [During bolus] During injection

Example Images (T1 MPRAGE)



Implications

These findings may:

- Provide further evidence for the existence of ACE points in humans and, further in the setting of AD.
- Reveal whether impaired clearance at ACE points contributes to amyloid accumulation.
- Offer new insights into CSF waste clearance in aging and AD and inform for early diagnosis and targeted intervention.

Funding & Citations

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National Science Foundation Graduate Research Fellowship Program

- Citations:
- Castellani, Giulia, et al. "Bridging anatomical gaps between brain and immune system." *Trends in Immunology*, vol. 45, no. 5, May 2024, pp. 318–319, <https://doi.org/10.1016/j.it.2024.04.006>.
 - Smyth, Leon C., et al. "Identification of direct connections between the Dura and the brain." *Nature*, vol. 627, no. 8002, 7 Feb. 2024, pp. 165–173, <https://doi.org/10.1038/s41586-023-06993-7>.
 - Smyth, Leon C.D., et al. "Amyloidosis of bridging veins is a pathologic feature of alzheimer's disease." *Journal of Experimental Medicine*, vol. 223, no. 2, 2 Dec. 2025, <https://doi.org/10.1084/jem.20251860>.

