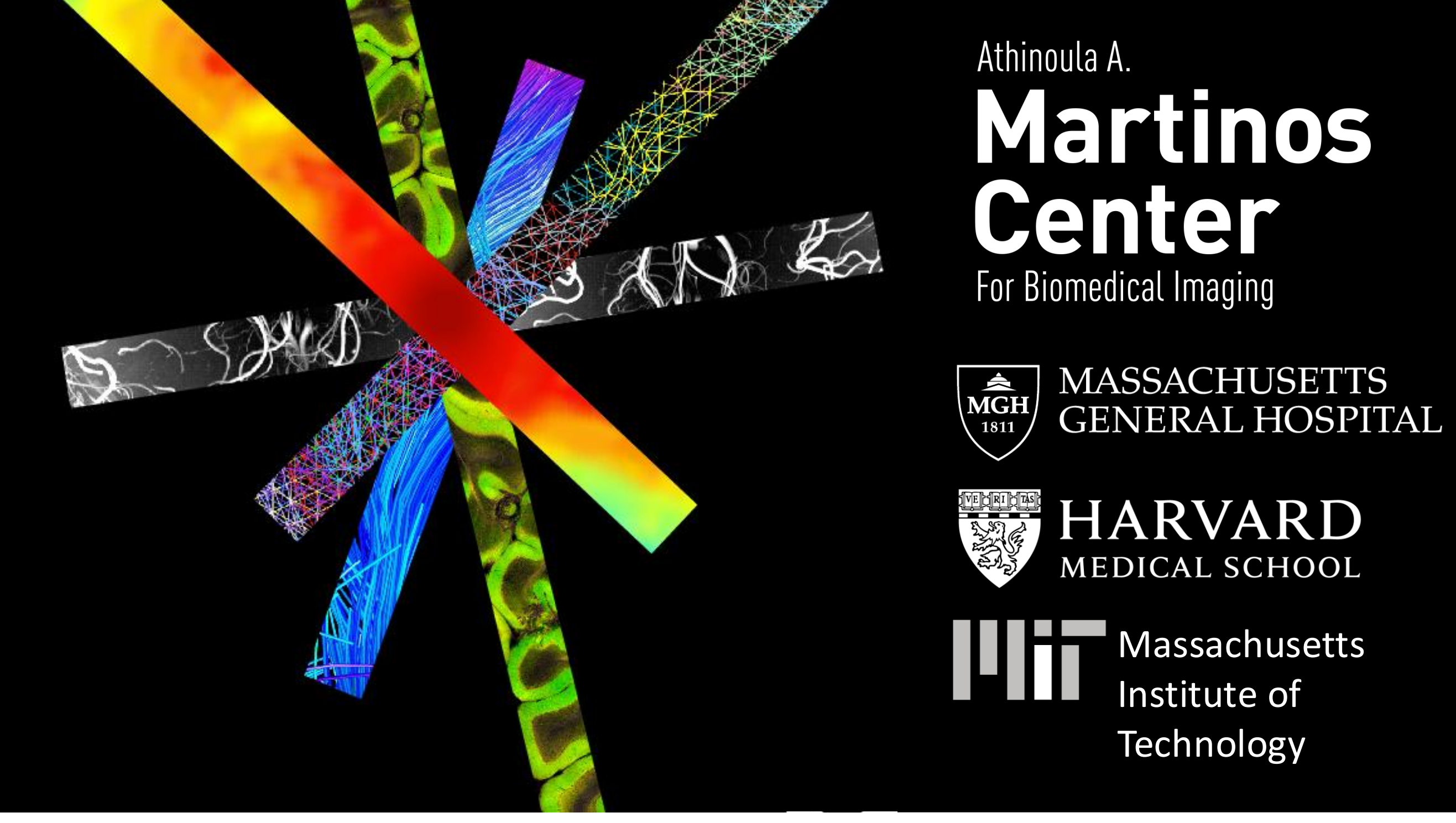


# Two distinct sources of <sup>18</sup>F-MK-6240 off-target signal identified by individualized head modeling and PET kinetics

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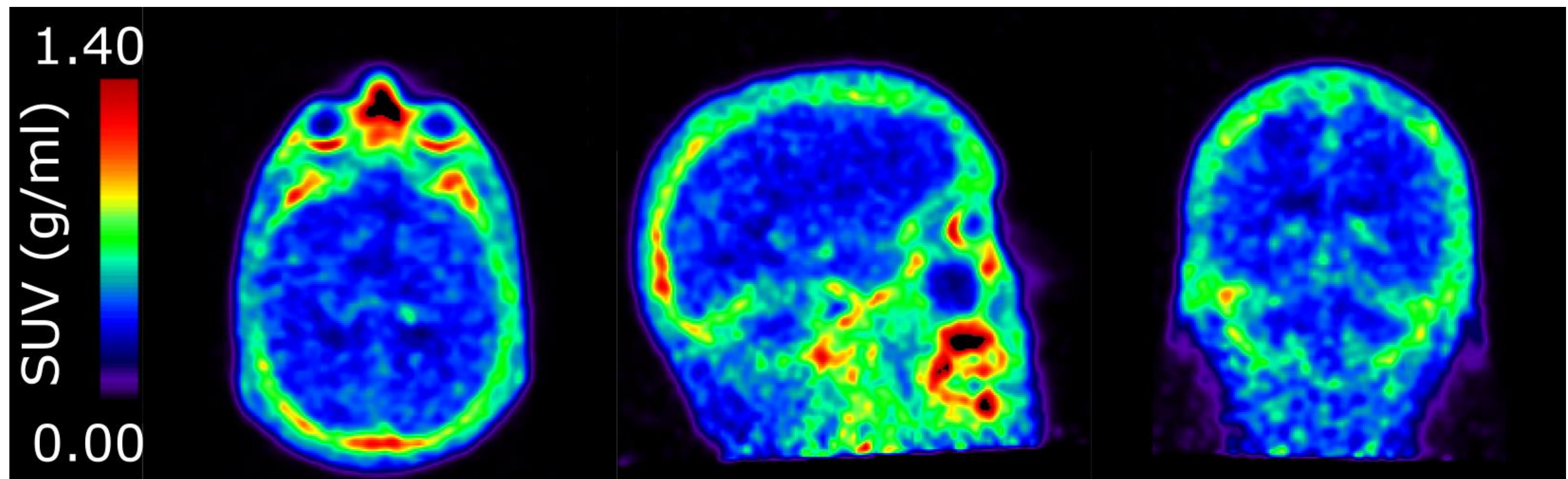
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## Background

- <sup>18</sup>F-MK-6240 PET is a powerful tool for imaging the spread of tau neurofibrillary tangles (NFTs) across cerebral cortex in Alzheimer disease (AD).
- However, off-target signal (OTS) in the meninges can spill into cerebral and cerebellar cortices.
- Characterizing meningeal OTS will be important for correcting OTS spill-in, but studying the meninges directly is challenging due to their thin structure.
- Instead, prior approaches have used the FreeSurfer-defined skull mask (FS skull, Mertens et al. JCBFM 2022) and a dilated FS cortical ribbon (Fu et al. JCBFM 2023) to approximate the meningeal OTS.
- Herein, we describe an approach that uses individualized head modeling and PET kinetics to more precisely identify meningeal OTS.

**Figure 1: Meningeal OTS in <sup>18</sup>F-MK-6240 PET.** <sup>18</sup>F-MK-6240 PET SUV<sub>90-110</sub> (g/ml) in a male participant in his 60s with low cortical but high meningeal <sup>18</sup>F-MK-6240 uptake and no cognitive impairment (**Participant #1**).



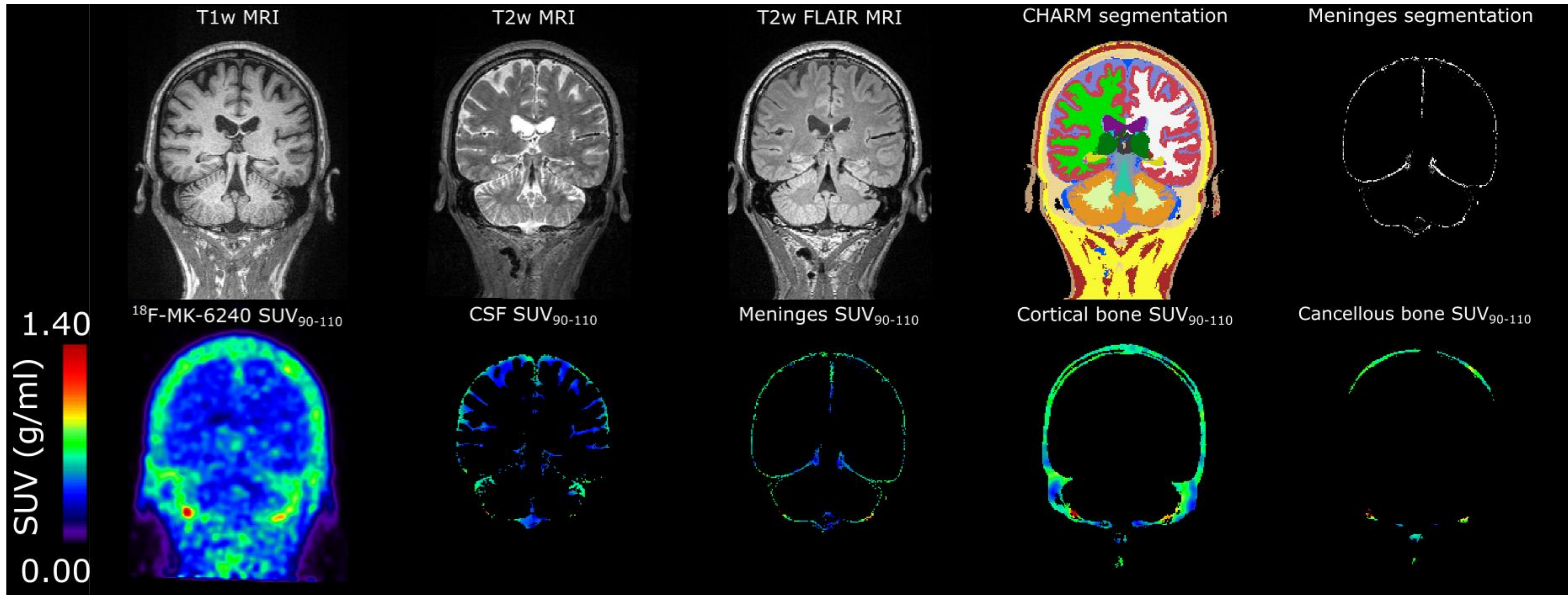
## Methods

- Applied the Complete Head Anatomy Reconstruction Method (CHARM, Puonti et al. NeuroImage 2020) to segment the whole head from T1w, T2w, and T2w FLAIR MRIs in our test-retest dataset (Lois et al. Imaging Neuroscience 2024) of dynamic (0-120 min) <sup>18</sup>F-MK-6240 PET/MRI in seven older adults (**Table 1 and Fig. 2**).
- Created T1w/T2w ratio images from T1w and T2w MRIs to separate meninges from CSF. This enables us to generate time-activity curves (TACs) for cerebral and cerebellar cortices, CSF, meninges, and skull, and compare these to TACs generated using FS-defined skull.
- Applied Diebold-Mariano test (Diebold and Mariano JBES 1995) to compare TACs and identify whether CHARM+T1w/T2w-defined meninges and skull TACs have equivalent accuracy in predicting FS skull TAC.

**Table 1: Participant demographics.** Continuous values are summarized as median [1<sup>st</sup> quartile 3<sup>rd</sup> quartile]. MMSE=mini-mental state examination.

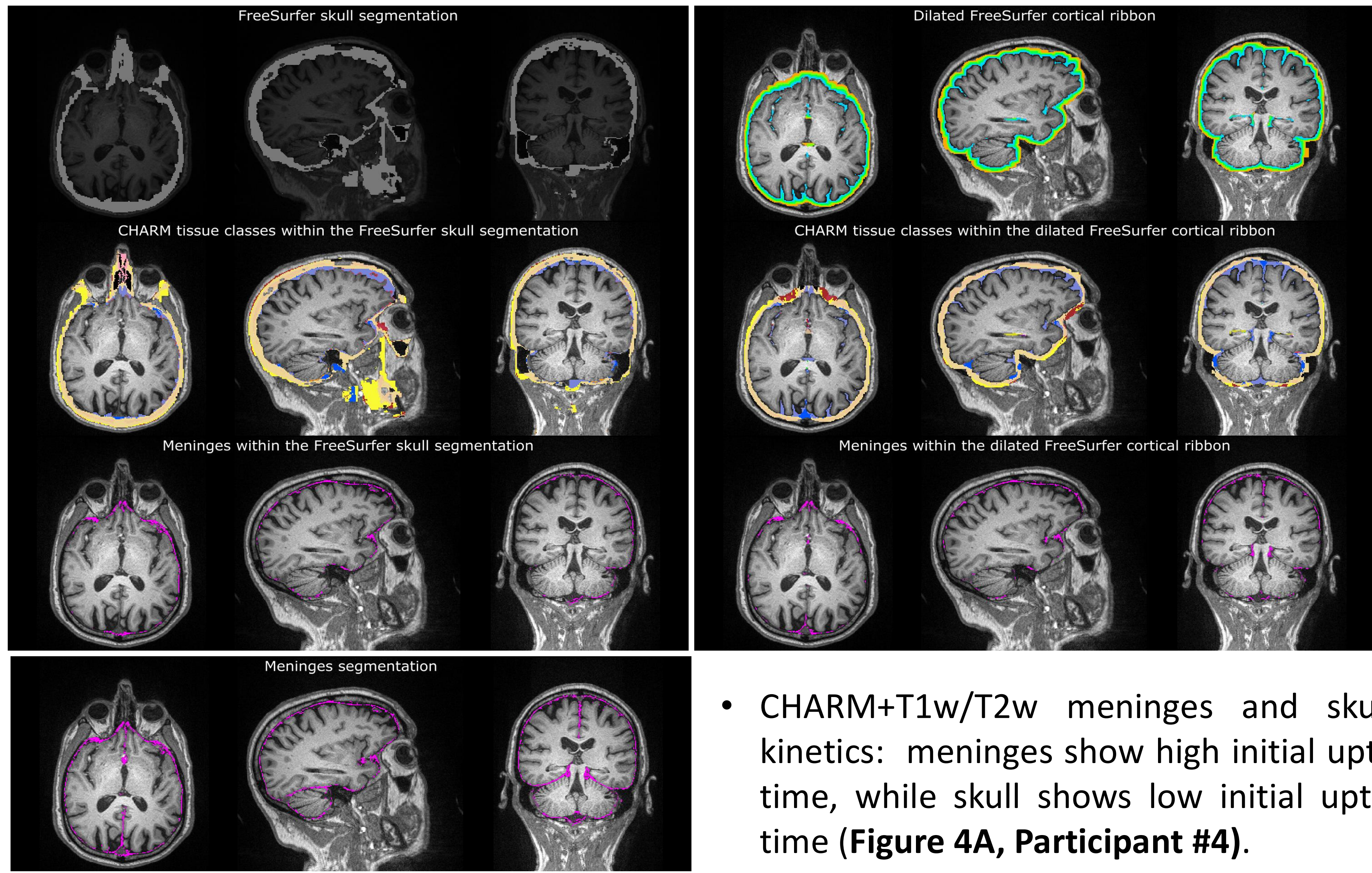
	Cognitively normal (n=6)	AD diagnosis (n=1)
Test-retest interval (days)	25 [14 30]	30
Age (years)	66 [63 71]	54
Sex	Male=4, Female=2	Male=1
MMSE	29.5 [29 30]	22

**Fig. 2: CHARM+T1w/T2w segmentation workflow (Participant #1)**



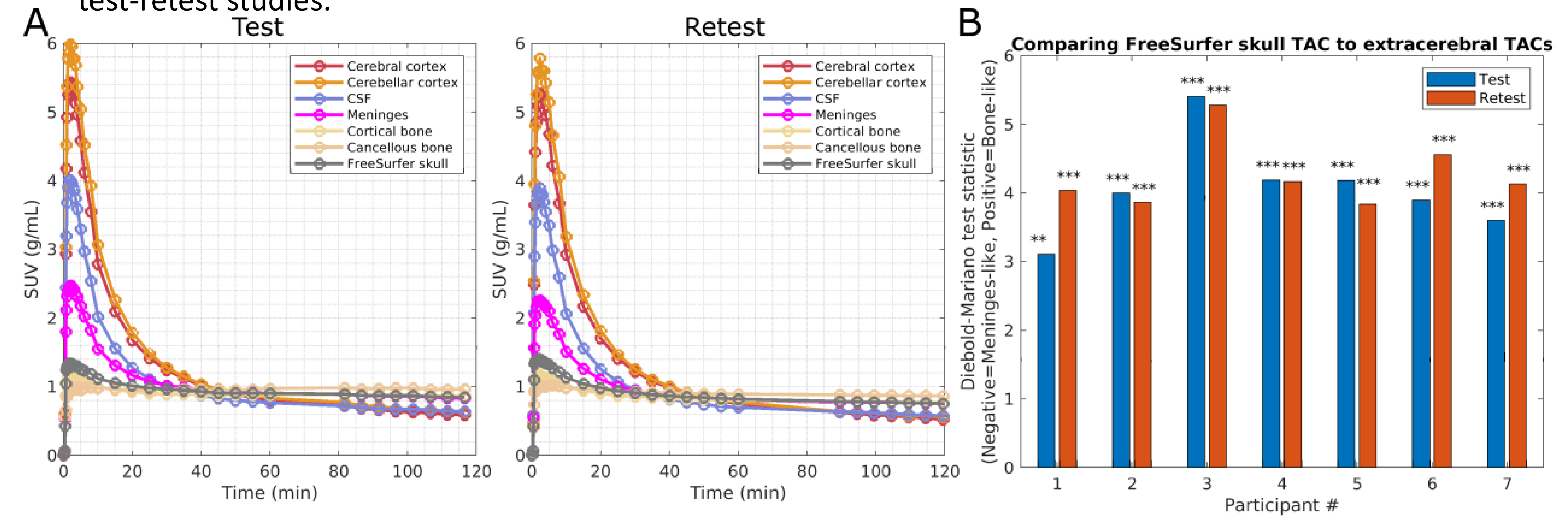
## Results

- FS skull and dilated FS cortical ribbon overlap inconsistently with CHARM+T1w/T2w meninges, especially near the tentorium (**Figure 3**).



**Figure 3: Comparing CHARM+T1w/T2w meninges with FS skull and dilated FS cortical ribbon.**

- CHARM+T1w/T2w meninges and skull show differing TAC kinetics: meninges show high initial uptake that decreases over time, while skull shows low initial uptake that increases over time (**Figure 4A, Participant #4**).
- CHARM+T1w/T2w meninges and skull TACs do not have equivalent accuracy in predicting FS skull TAC; FS skull TACs are more similar to CHARM+T1w/T2w skull (**Figure 4B**). Findings are consistent across participants and test-retest studies.



**Figure 4: (A) Test and Retest TACs (0-120 min). (B) Diebold-Mariano test (\*\*=p<0.01, \*\*\*=p<0.001)**

## Conclusions and Future Directions

- In this work, meninges and skull were found to represent two spatiotemporally distinct sources of <sup>18</sup>F-MK-6240 OTS.
- FreeSurfer-defined skull TACs are more similar to CHARM+T1w/T2w-defined skull than meninges TACs
- Future Directions:* [1] Perform evaluation in larger study sample; [2] Use information to correct for OTS spill-in and assess impact on <sup>18</sup>F-MK-6240 quantification; [3] investigate CHARM+T1w/T2w-defined TACs of retina, mucosa, choroid plexus, and other OTS areas.

## \* Acknowledgments \*

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