

A Non-invasive Dynamic ^{15}O -water PET/MRI Method to Measure Ventricular CSF Clearance in the Human Brain

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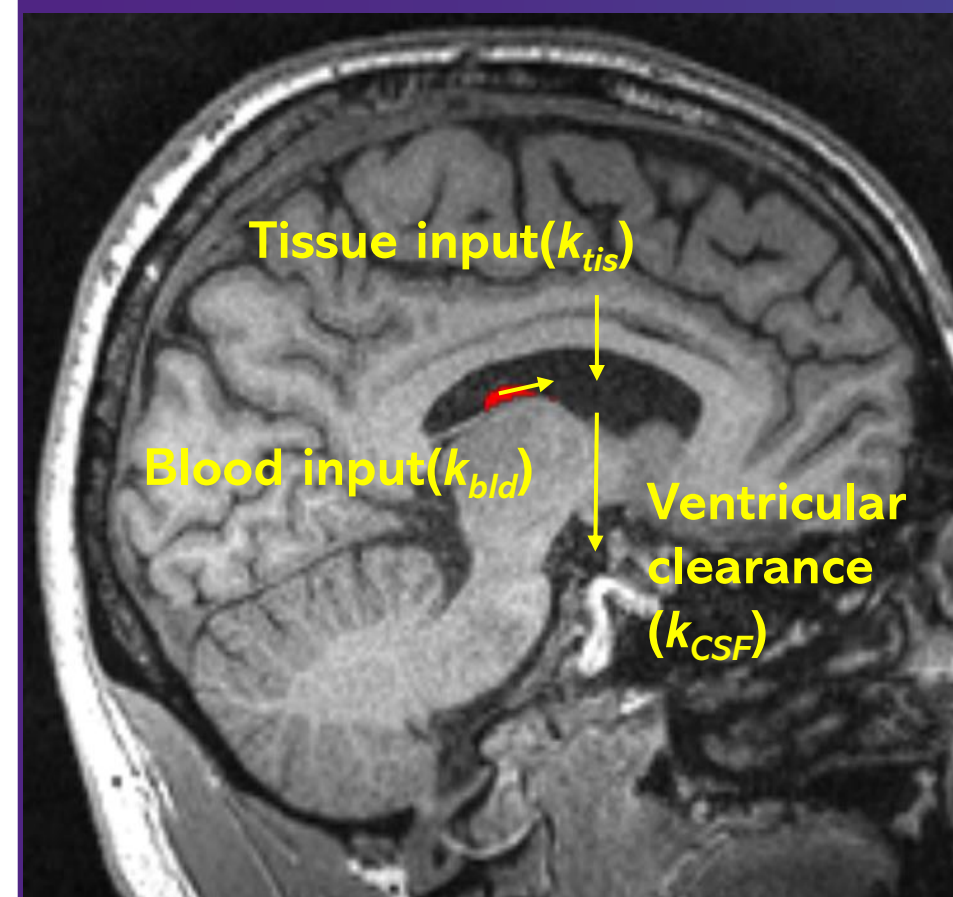
INTRODUCTION

- The majority of CSF is produced by the choroid plexus and secreted into the cerebral ventricles¹
- Ventricular CSF clearance provides a quantitative metric that may reflect glymphatic function
- PET can measure ventricular clearance using intravenously injected low-molecular-weight, diffusible tracers²
- Reduced tracer clearance is associated with increased A β deposition in Alzheimer's Disease (AD)³
- However, quantification requires invasive arterial sampling⁴ and most approaches rely on indirect measures
- Hybrid PET/MRI provides a non-invasive approach to quantify the rate of clearance (k_{CSF}) using radiolabeled water (Figure 1)

OBJECTIVE

To develop and evaluate a [^{15}O]-water based PET/MRI kinetic model for noninvasive quantification of k_{CSF}

METHODS



- The model is characterized by 3 rate constants
 - k_{bld} : input from blood compartment ($C_a(t)$)
 - k_{tis} : input from tissue compartment ($C_t(t)$)
 - k_{CSF} : CSF clearance from ventricular compartment ($C_v(t)$)
- Ventricular time-activity curve ($C_v(t)$) can be expressed as,

$$C_v(t) = \frac{k_{bld}}{f_{wb}} C_{wb}(t) + \frac{k_{bld}}{f_{wb}} \left(\frac{f_{wb}}{\lambda} - k_{CSF} \right) e^{-k_{CSF}t} * C_{wb}(t) + k_{tis} e^{-k_{CSF}t} * C_t(t)$$

λ : partition coefficient of water (0.9 mL/g)

Figure 1. Kinetic model of ventricular time-activity ($C_v(t)$). Arterial input function was eliminated by using whole-brain blood flow (f_{wb}) as a calibration factor. $C_{wb}(t)$: whole-brain tissue time-activity curve;

- Fifteen healthy participants underwent imaging on a hybrid PET/MRI system (Siemens Biograph mMR). Imaging protocol included:
 - Dynamic [^{15}O]-water PET (5 min; 12 min in two subjects)
 - Phase-Contrast (PC) MRI (to measure f_{wb})
 - T1-weighted structural imaging
- Lateral ventricles were segmented from T1 using FastSurfer, and subsequently registered to PET images (Figure 2)
- Ventricular PET activity curves were extracted and fit to the model equation to estimate k_{CSF} , k_{bld} and k_{tis}

DISCUSSION

- Results support the feasibility of noninvasively quantifying ventricular CSF clearance by PET using a highly diffusible tracer
- The proposed compartmental model provided reliable fits to ventricular time-activity curves
- Tracer delivery to ventricles was dominated by exchange with blood with negligible contribution from tissue
- Longer acquisition had minor effect on estimated rate constants
- Future work will include:
 - Evaluate the approach using [^{11}C]-Butanol to better characterize the effect of long imaging windows
 - Apply the approach to AD patients to explore the association between K_{CSF} and amyloid plaque buildup
 - Leverage hybrid PET/MRI to integrate this technique with MRI methods probing other aspects of glymphatic function⁵

RESULTS

Figure 2. Segmented lateral ventricles overlaid on corresponding cerebral blood flow map.

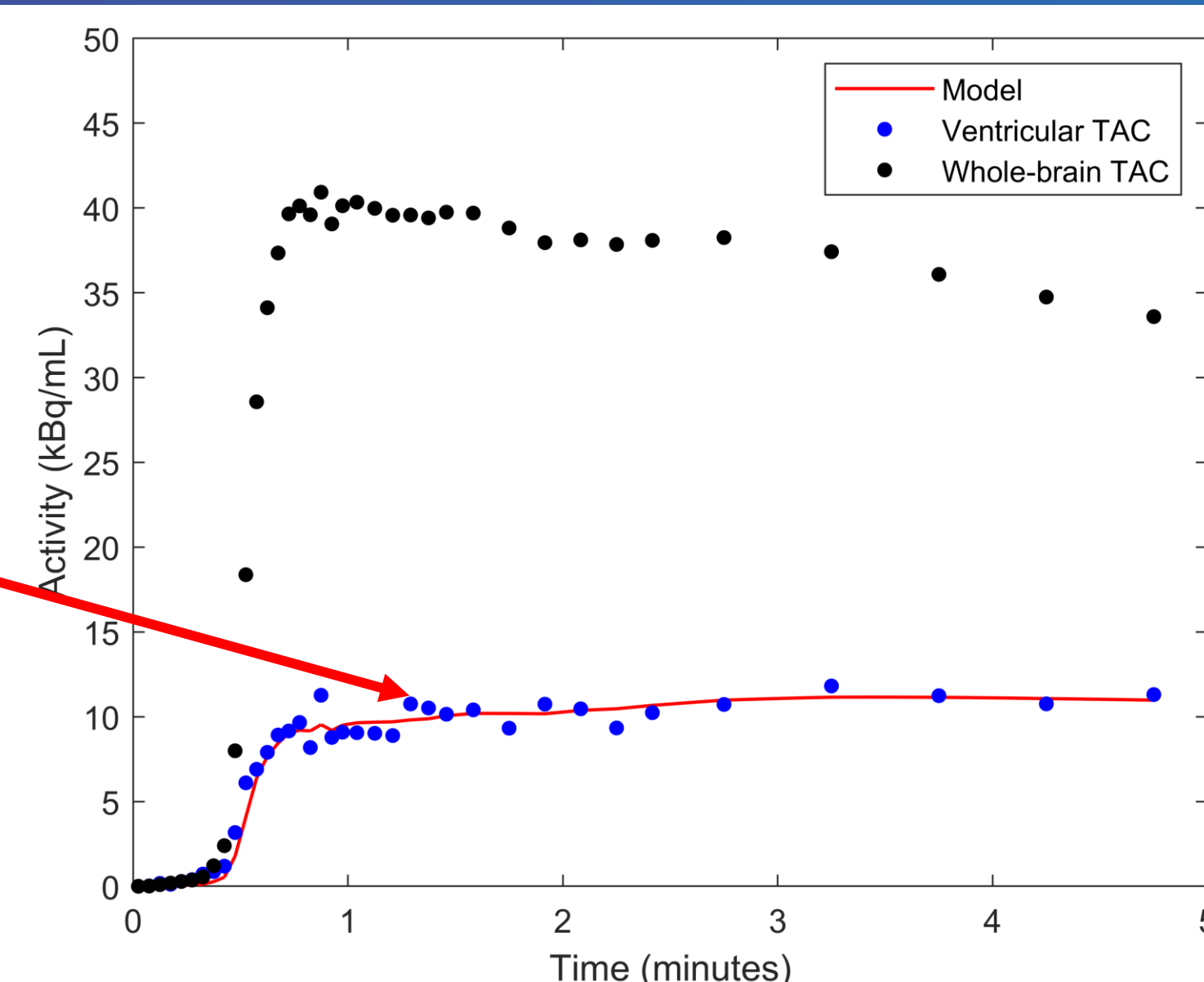
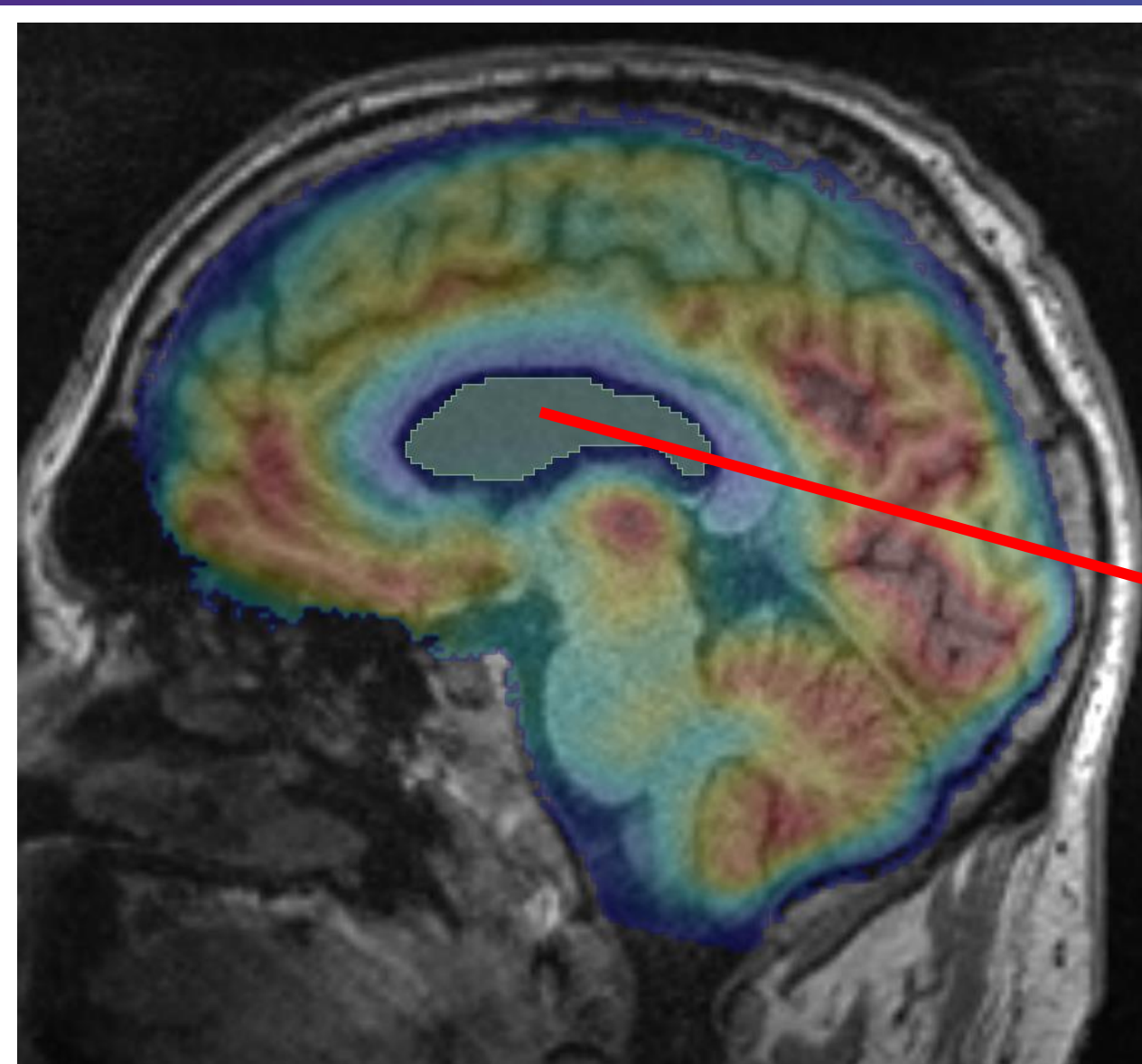


Figure 3. Model fit of the ventricular time-activity curve (TAC) from one subject. Estimated rate constants were $k_{CSF}=0.3 \text{ min}^{-1}$, $k_{bld}=0.1 \text{ min}^{-1}$ and $k_{tis}=0 \text{ min}^{-1}$. f_{wb} measured from PC-MRI was 44.23 ml/100g/min.

- The model displayed reliable fitting to ventricular time-activity ($C_v(t)$) data in all subjects (Figure 3)
- Group-averaged estimates were $k_{CSF} = 0.38 \pm 0.07 \text{ min}^{-1}$ and $k_{bld} = 0.20 \pm 0.07 \text{ min}^{-1}$, while k_{tis} was negligible
- From two subjects with 12-min acquisitions, only minor differences in the rate constants were observed:
 - $k_{CSF} = 0.24$ and 0.29 min^{-1} for 12-min versus 0.27 and 0.29 min^{-1} for 5-min

REFERENCES

- [1] Hablitz et al., (2021). The Glymphatic System: A Novel Component of Fundamental Neurobiology. *The Journal of Neuroscience*
- [2] Zhou et al., (2024). Multimodal Assessment of Brain Fluid Clearance is Associated with Amyloid-Beta Deposition in Humans. *Journal of Neuroradiology*
- [3] Li et al., (2022). Decreased CSF Clearance and Increased Brain Amyloid in Alzheimer's Disease. *Fluids and Barriers of the CNS*
- [4] Schubert et al., (2019). Dynamic ^{11}C -PiB PET Shows Cerebrospinal Fluid Flow Alterations in Alzheimer Disease and Multiple Sclerosis. *The Journal of Nuclear Medicine*
- [5] Naganawa et al., (2023). The Glymphatic System in Humans: Investigations With Magnetic Resonance Imaging. *Investigative Radiology*

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