

Impaired Ventricular CSF flow and Its Associations with Amyloid/Tau Pathology and Cognitive Decline

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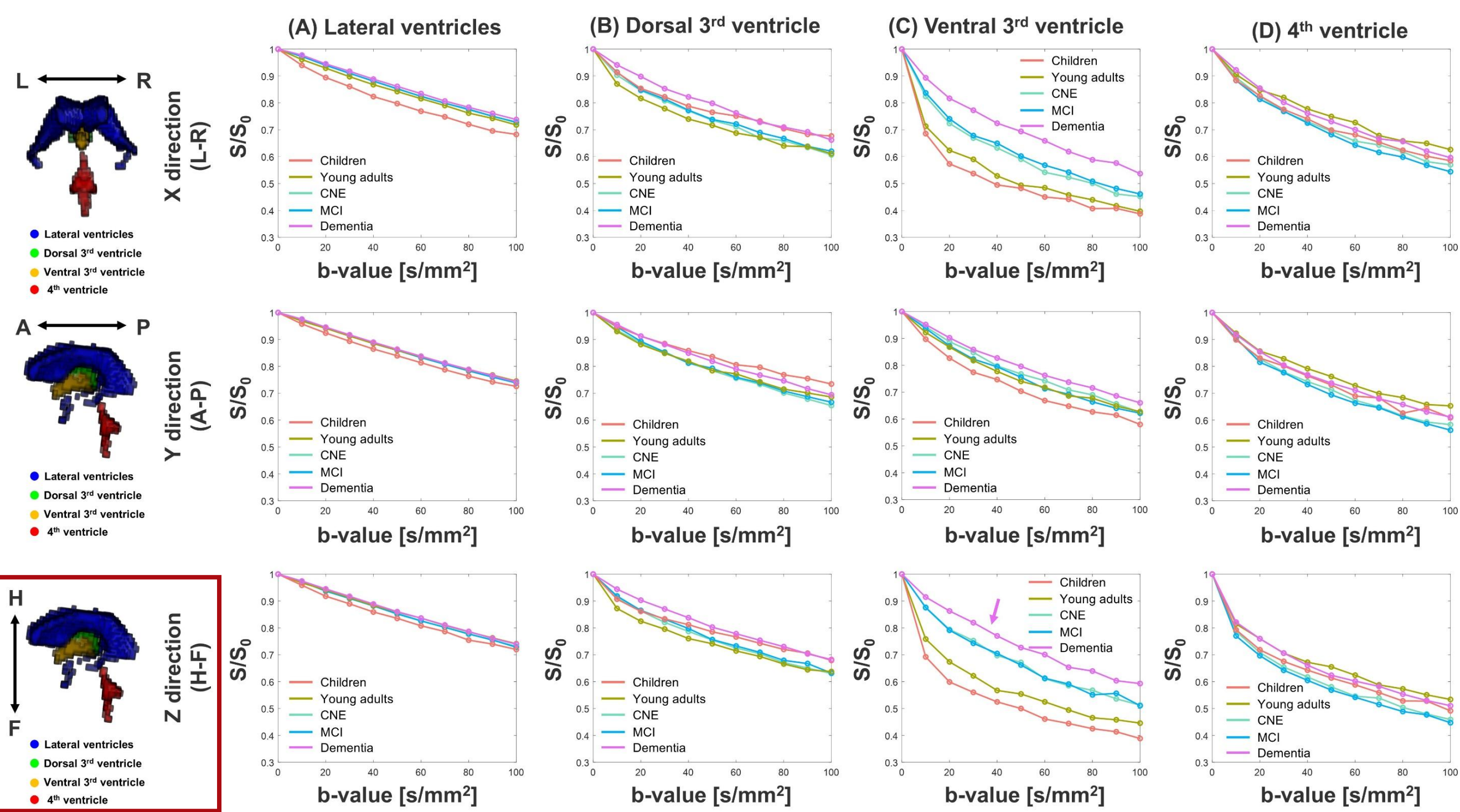
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Introduction

- The Role of CSF in Brain Homeostasis**
Pulsatile forces drive CSF movement, which is crucial for clearing metabolic waste and maintaining the brain's "Glymphatic" health^[1].
- The Problem:** Altered CSF dynamics are increasingly recognized as a putative driver of the pathological cascade underlying cognitive decline and Alzheimer's disease (AD). However, comprehensive **lifespan investigations** and the **mechanistic interplay** with AD proteinopathies remain uncharacterized^[2, 3].
- Objective:** To non-invasively characterize **ventricular CSF behavior** across the human lifespan using **intravoxel incoherent motion (IVIM) MRI** and evaluate its association with **amyloid/tau pathology**.

Results



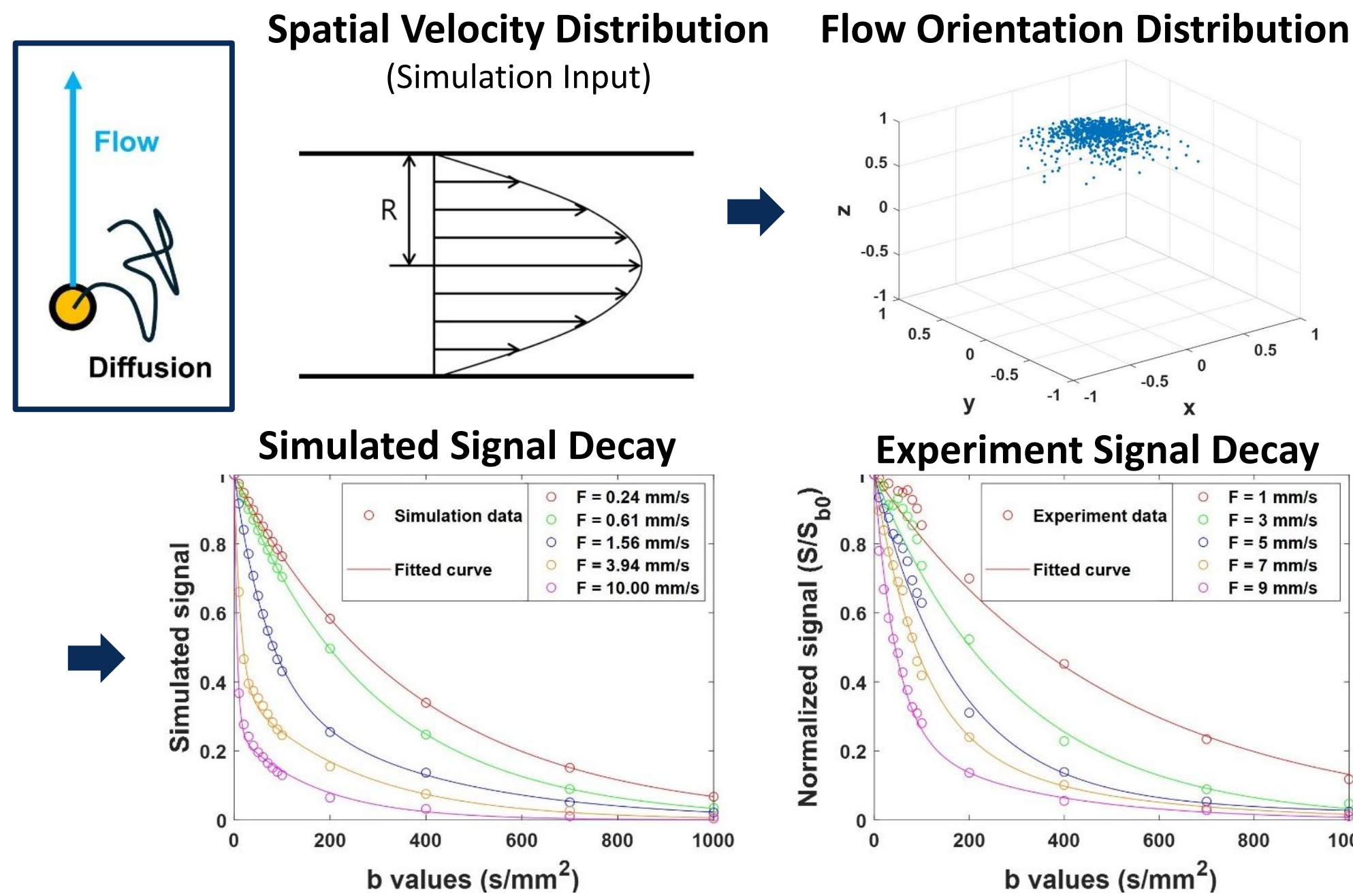
▲ **Figure 1. Directional dependence of IVIM signal decay across ventricular regions and groups.**
IVIM signal attenuation curves (S/S_0) are plotted against b-values along three orthogonal directions, x (left-right), y (anterior-posterior), and z (head-foot), for four distinct ventricular regions: (A) lateral ventricles, (B) dorsal 3rd-ventricle, (C) ventral 3rd-ventricle, and (D) 4th ventricle. Group-wise patterns are color-coded for children, young adults, CNE, MCI patients, and dementia patients. In all regions, the most pronounced direction-dependent decay was observed in the z-direction, particularly in the ventral 3rd-ventricle, indicating directionally biased CSF-flow. Notably, the dementia group showed relatively reduced signal attenuation, suggesting impaired CSF-dynamics. The lateral ventricles exhibited the slowest decay across directions, consistent with their larger, more stagnant CSF space.

Methods

- Lifespan & Cognitive Continuum Cohort (total N=201)**
Children (7-17 aged, N=40), Young Adults (20-49 aged, N=37), CNE (65-85 aged, N=39), MCI (65-85 aged, N=41), Dementia (65-85 aged, N=44)
*Abb. CNE = Cognitively Normal Elderly, MCI = Mild Cognitive Impairment
- Assessment Protocols**
 - Young Cohorts**
 - Inclusion Criteria** (no brain injury, psychiatric history)
 - 3.0T MRI scan** (IVIM, T1-weighted MPRAGE)
 - Elderly Cohorts**
 - Clinical evaluation**
 - 3.0T MRI scan** (IVIM, T1-weighted MPRAGE)
 - PET scan & SNSB-II** (18F-MK-6240, 18F-FLUTE)

Validating IVIM for CSF Flow Dynamics with 7.0T MRI

Using a biexponential model, IVIM detects flow-attributable signal decay at **low b-values**. It requires **no contrast agents**, **no cardiac gating**, and **captures intravoxel velocity heterogeneity**^[4].



▲ **Figure 2. Group-wise comparisons of the z-directional flow-related fraction (f_z) across ventricular regions.**
Box plots show f_z values across the five groups (children, young adults, CNE, MCI patients, and dementia patients) for four ventricular regions: (A) lateral ventricles, (B) dorsal 3rd and (C) ventral 3rd-ventricles, and (D) 4th ventricle. Group differences were assessed using one-way ANOVA, with follow-up pairwise comparisons. Significant group differences were observed across all regions, particularly in the lateral and ventral 3rd-ventricles. Asterisks indicate the statistical significance levels: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 3. Representative ventricular morphology and IVIM-derived parameter maps across the elderly groups.

Sagittal brain volume rendered images from representative participants in the CNE, MCI, and dementia groups illustrate (A) the ventricular structure alongside IVIM-derived parameters. Maps of (B) z-directional flow-related fraction (f_z), (C) pseudo-diffusion coefficient (D_z^*), and (D) their product ($f_z \times D_z^*$) are overlaid on ventricular masks, showing progressive reductions in f_z and D_z^* values with advancing cognitive decline. Note the trend of increasing ventricular size (A) and decreasing f_z -related metrics (B-D) from CNE to dementia, consistent with impaired CSF-dynamics.

Metrics	CNE	MCI	Dementia
CSF volume	21.35	29.44	32.51
Ventral 3 rd f_z	0.3839	0.3703	0.2560
MMSE score	28.67	25.20	17.18
Global MK-6240 SUVR (Tau)	0.99	1.21	2.17

Comparison of key CSF, pathological, and cognitive metrics across the elderly cohorts.

Reference

- Nedergaard M, Goldman SA (2020): Glymphatic failure as a final common pathway to dementia. Science 370: 50-56.
- Kamagata K et al. (2022): Association of MRI indices of glymphatic system with amyloid deposition and cognition in mild cognitive impairment and Alzheimer disease. Neurology 99: e2648-e2660.
- Huang S-Y et al. (2024): Glymphatic system dysfunction predicts amyloid deposition, neurodegeneration, and clinical progression in Alzheimer's disease. Alzheimers Dement 20: 3251-3269.
- Yamada S et al. (2023): Usefulness of intravoxel incoherent motion MRI for visualizing slow cerebrospinal fluid motion. Fluids Barriers CNS 20: 16.

Mathematical Modeling (Levenberg-Marquardt algorithm)

$$\frac{S}{S_0} = f \cdot e^{-b(D^*+D)} + (1-f) \cdot e^{-bD}$$

- f : Flow-Related Fraction**
: Represents the proportion of signal attenuation caused by fluid movement.
- D* : Pseudo-Diffusion Coefficient**
: Represents intravoxel fluid flow velocity heterogeneity.
- D : True Diffusion Coefficient**
: Background thermal water motion.

z-directional flow-related fraction (f_z) is a **robust, non-invasive, contrast-free index** of regional convective CSF motion.

f_z in the ventral 3rd ventricle

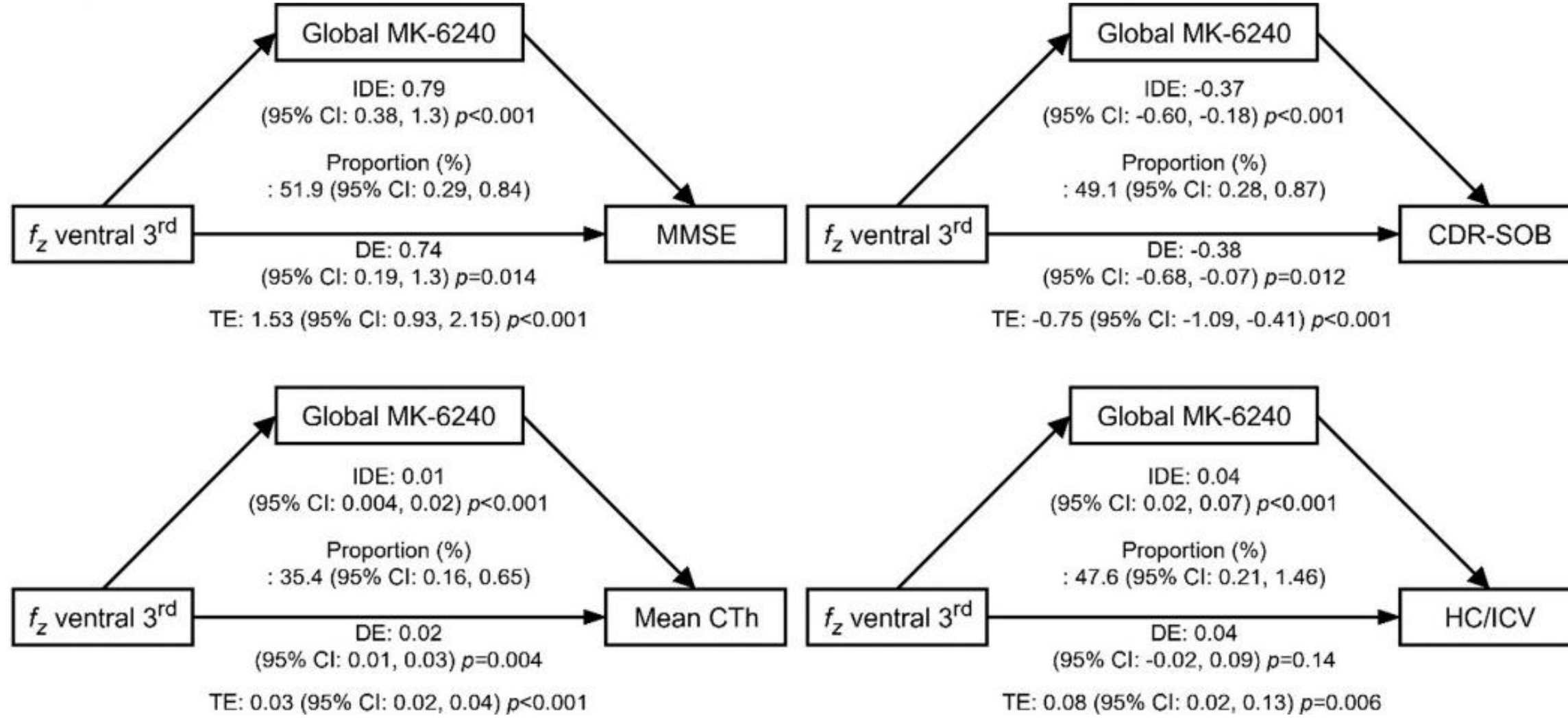
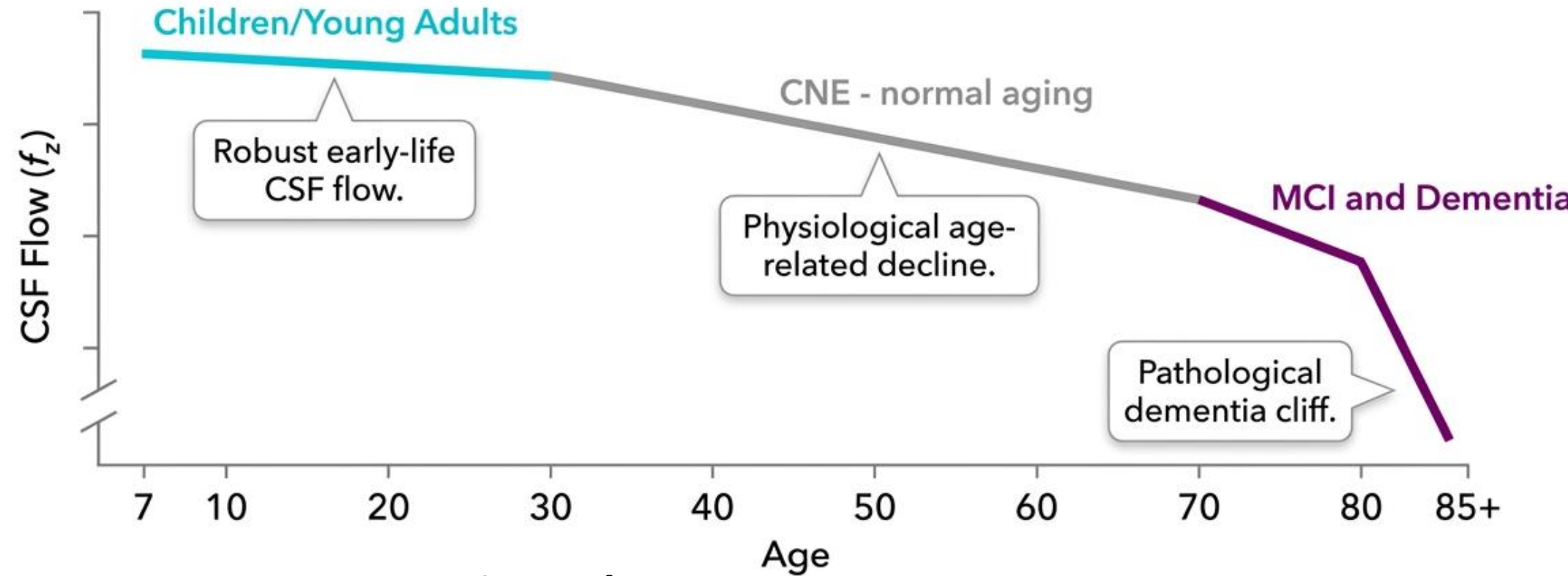


Figure 4. Mediation effects of tau burden (global MK-6240 SUVR) on the association between f_z and cognitive function and neurodegeneration.
Significant indirect effects indicate that higher tau burden explains a substantial portion of the relationship between reduced CSF-flow and worse cognitive performance or greater structural degeneration, with these indirect effects observed for the ventral 3rd ($p < 0.001$) ventricles across all outcomes.

Conclusion

Continuum of Decline in 3rd ventricular f_z across the lifespan



IVIM as a Next-Gen Biomarker

Early Risk Stratification	Disease Staging	Therapeutic Monitoring
Identifies preclinical states of impaired clearance (abnormally low f_z) before severe cognitive drop or irreversible atrophy occurs.	Successfully differentiates MCI from overt Dementia based purely on fluid flow metrics, providing complementary data to structural MRIs.	Offers a fast, contrast-free, non-invasive method to monitor the efficacy of emerging disease-modifying therapies targeting glymphatic clearance.