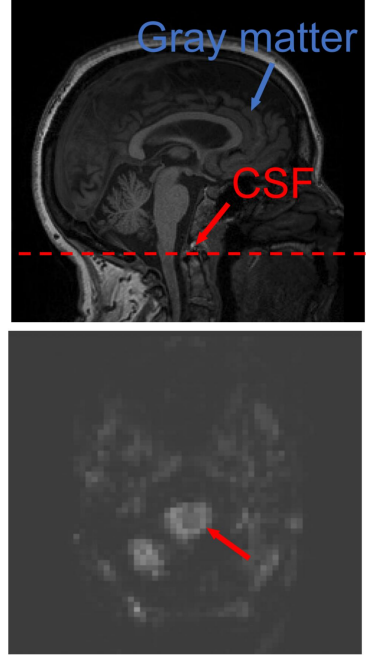
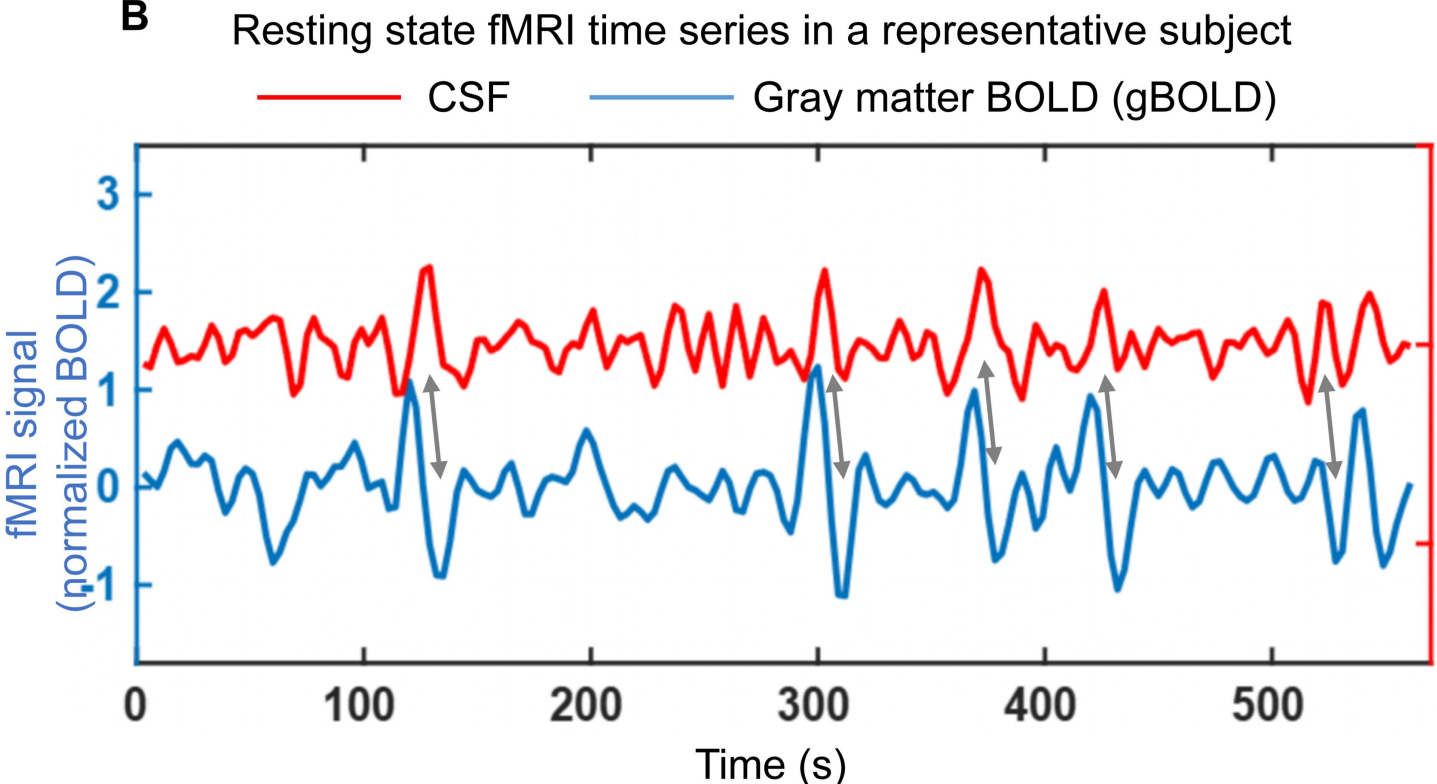
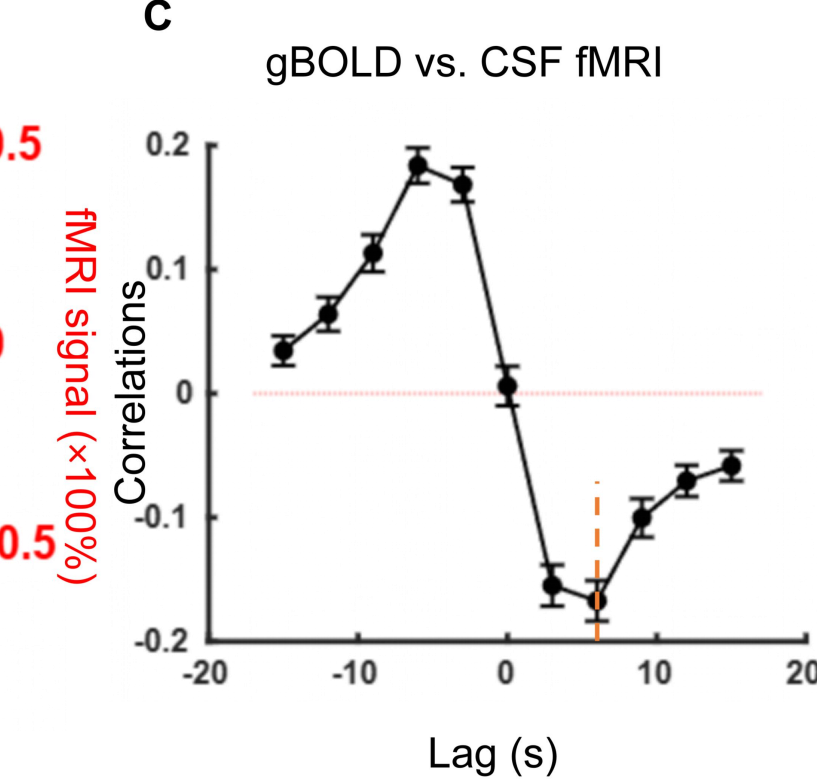
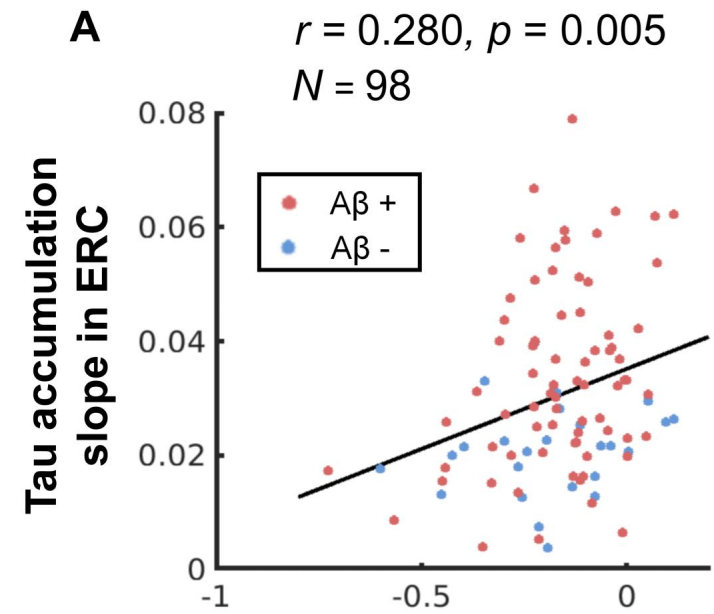
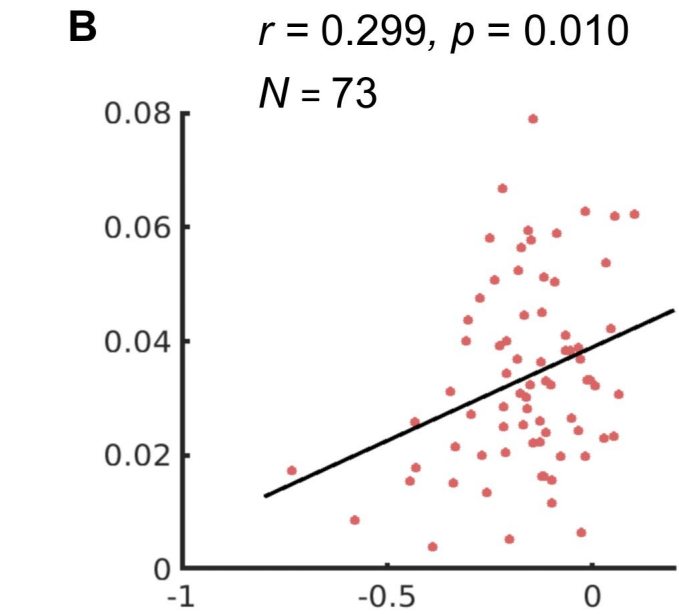
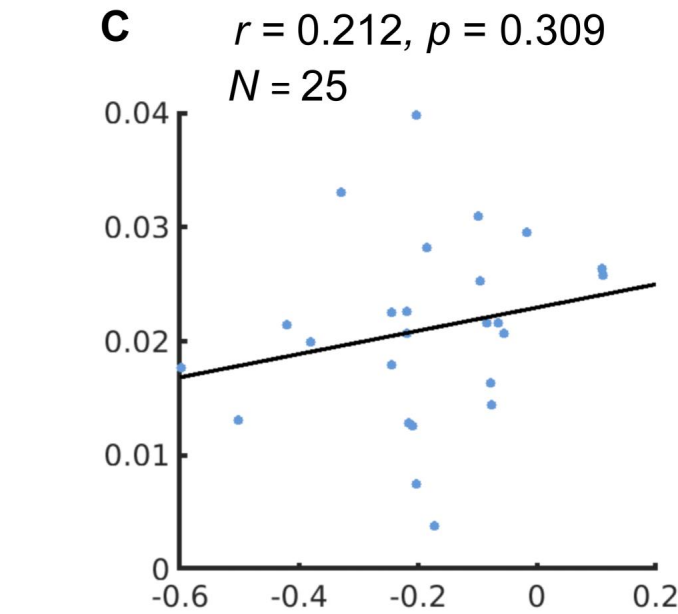
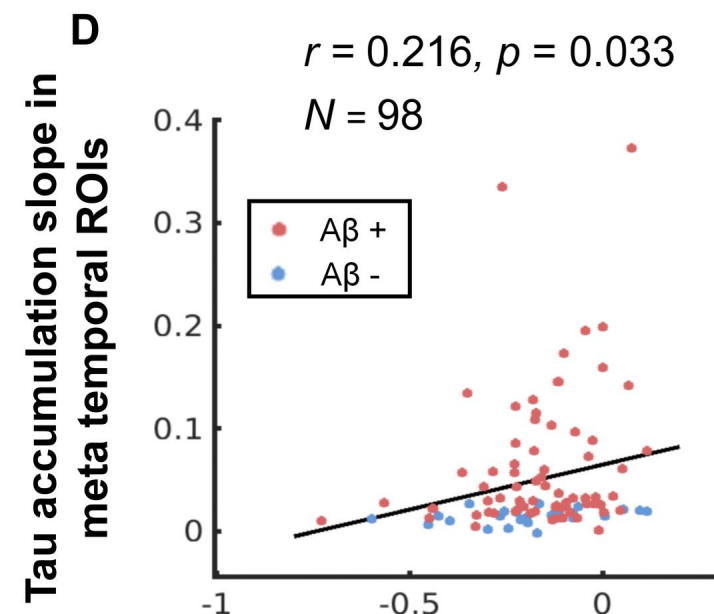
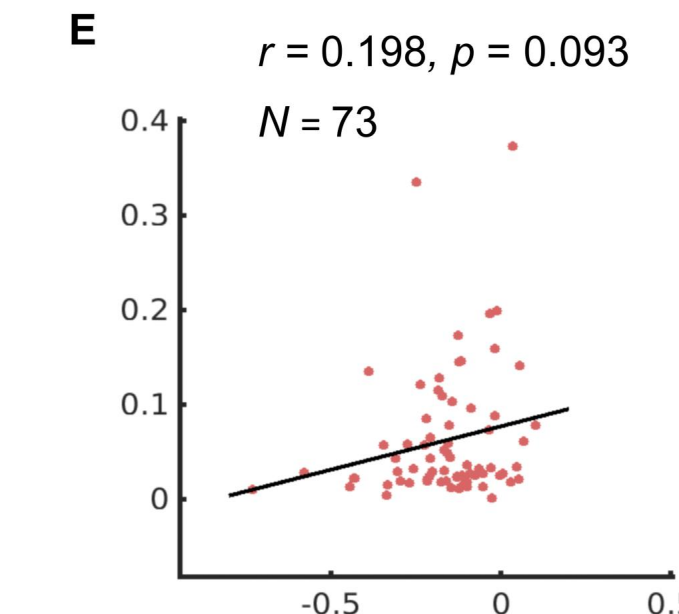
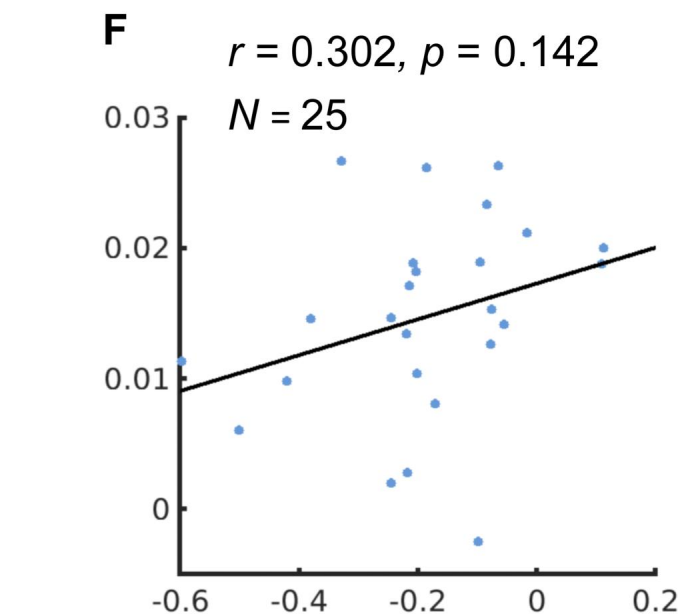
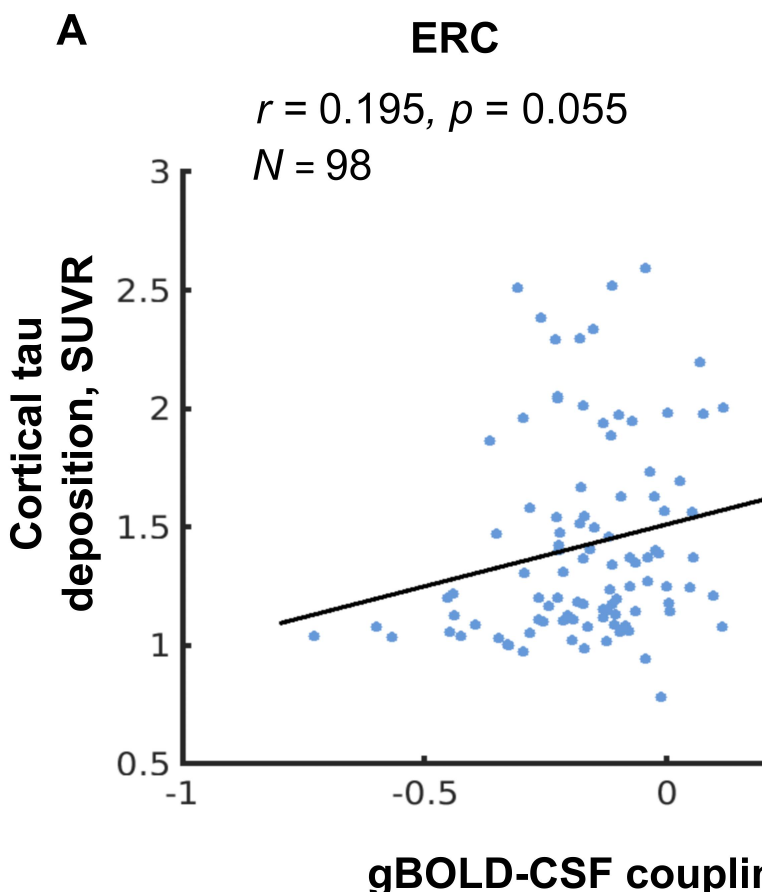
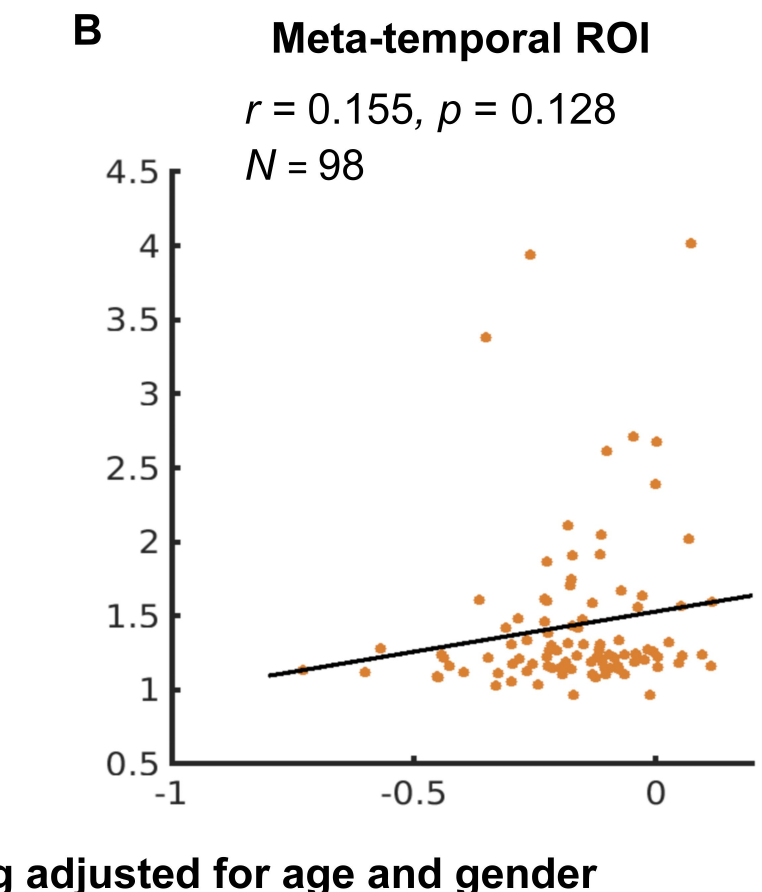


Reduced coupling between cerebrospinal fluid flow and global brain activity is related to tau accumulation rate in AD

P1-06

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INTRODUCTION	METHODS	RESULTS
Glymphatic system clears brain waste, including tau and amyloid-β ($A\beta$), through cerebrospinal fluid (CSF) movement. In Alzheimer's disease (AD), there is still no consensus on whether glymphatic impairment accelerates tau and $A\beta$ accumulation, or tau and $A\beta$ deposition impedes the clearance. Recent advances have identified the reduced coupling between resting-state functional MRI (rs-fMRI) in the global brain (gBOLD) and CSF (gBOLD-CSF coupling) as a proxy for impaired glymphatic function and cross-sectionally linked it to cortical $A\beta$ and tau deposition. We here indirectly evaluated glymphatic function with this gBOLD-CSF coupling and investigated its predictive role in longitudinal tau accumulation.	We analyzed 98 ADNI participants (72.05 ± 7.89 years; 55 females; 9 AD, 30 MCI, 59 CN) with rs-fMRI (TR=3s; within 1year around baseline tau-PET), PET-$A\beta$ (centiloid, CL; reference: whole cerebellum; $A\beta+$: > 18 CLs), and longitudinal tau PET (≥ 3 timepoints; SUVR, reference: inferior cerebellar GM). Longitudinal tau slopes were estimated using linear mixed models. CSF inflow signal was extracted from the bottom fMRI acquisition, and gBOLD was averaged from gray matter fMRI, following the previous study [1]. The gBOLD-CSF coupling (adjusting for age and sex) was correlated with cortical tau accumulation and deposition in predefined regions of interest (ROIs), including entorhinal (ERC) and meta-temporal ROIs.	CSF inflow signal was coupled with the global brain fMRI signal. For each participant, the coupling (strength) was quantified using the gBOLD-CSF cross-correlation at the negative peak (more negative, stronger). A One example for the CSF location  B Resting state fMRI time series in a representative subject  C gBOLD vs. CSF fMRI  (A)Signal extraction from gray matter and bottom-slice CSF. (B) Co-fluctuation of gBOLD and CSF signals in a representative subject. (C) Cohort-averaged cross-correlation peaking at a +6s lag ($r = -0.17$), quantifying coupling strength. Gray-matter rsfMRI (gBOLD) and CSF inflow signals are temporally coupled We found that gBOLD-CSF coupling was significantly correlated with the rate of tau accumulation. In the whole cohort, weaker coupling predicted steeper tau slopes in ERC ($r = 0.280$, $p = 0.005$) and meta-temporal ROIs ($r = 0.216$, $p = 0.033$). This association was more prominent in the $A\beta+$ subgroup, particularly in ERC region. A  B  C  D  E  F  A  B  Our cross-sectional analyses suggested that the subjects who have weaker coupling appear to have higher baseline tau load (marginally significant in ERC). The gBOLD-CSF coupling was significantly associated with the rate of tau accumulation. (A–C) ERC ROI: Weaker coupling significantly correlates with steeper tau slopes across the whole cohort (A) and the $A\beta+$ subgroup (B), with a similar non-significant trend in $A\beta-$ individuals (C). (D–F) Meta-temporal ROI: Decreased coupling predicts more rapid tau accumulation across the whole cohort (D) and shows a marginal trend in the $A\beta+$ subgroup (E) alongside a strong trend in $A\beta-$ individuals (F).
CONCLUSIONS		
Our study provides the preliminary longitudinal evidence that reduced gBOLD-CSF coupling precedes tau accumulation, particularly in ERC and meta-temporal ROI. The glymphatic decline can led to a faster tau accumulation, especially in those with elevated cortical amyloid burden.		
REFERENCES		
[1]Han F, Chen J, Belkin-Rosen A, et al. Reduced coupling between cerebrospinal fluid flow and global brain activity is linked to Alzheimer disease–related pathology[J]. PLoS biology, 2021, 19(6): e3001233.		