

Supplementary Results

S1.1 Supplementary results for PVS indices, BOLD-CSF Coupling, and BF

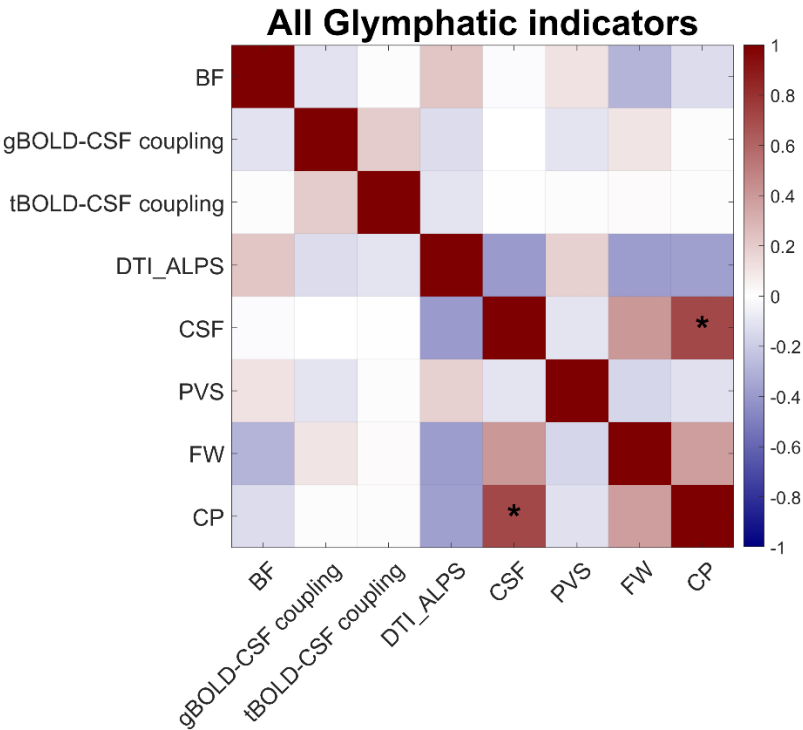
Complete age-, sex-, and scanner-adjusted ANCOVA results and post-hoc comparisons for all glymphatic structural (CSF, CP, PVS, FW, DTI-ALPS) and functional measures (gBOLD-CSF, tBOLD-CSF, fBOLD-CSF, pBOLD-CSF coupling, and BF volume) are provided in Supplementary Table S1.

Table S1. Group comparisons of glymphatic indices across the AD continuum.

Metric	<i>F</i> value (<i>p</i> value)	Comparison	<i>t</i> value (adjusted <i>p</i>)
<i>gBOLD-CSF</i> coupling	3.44 (< 0.05)	<i>AD</i> vs <i>HC</i>	2.72 (< 0.05)
<i>fBOLD-CSF</i> coupling	0.17(0.92)		
<i>tBOLD-CSF</i> coupling	2.71 (< 0.05)	<i>AD</i> vs <i>MCI</i>	2.75 (< 0.05)
<i>pBOLD-CSF</i> coupling	1.6 (< 0.05)		
<i>BF</i>	8.43 (< 0.001)	<i>HC</i> vs <i>AD</i> , <i>SCD</i> vs <i>AD</i> , <i>MCI</i> vs <i>AD</i>	3.99 (< 0.001); 5.44 (< 0.001); 3.51 (0.003)
<i>CSF</i>	18.63 (< 0.001)	<i>HC</i> vs <i>MCI</i> , <i>HC</i> vs <i>AD</i> , <i>SCD</i> vs <i>AD</i> , <i>MCI</i> vs <i>AD</i>	-2.94 (0.020); -6.49 (< 0.001); -5.04 (< 0.001); -4.08 (0.003)
<i>CP</i>	14.98 (< 0.001)	<i>HC</i> vs <i>AD</i> , <i>SCD</i> vs <i>AD</i> , <i>MCI</i> vs <i>AD</i>	-5.53 (< 0.001); -5.03 (< 0.001); -3.89 (0.003)
<i>FW</i>	30.67 (< 0.001)	<i>HC</i> vs <i>AD</i> , <i>SCD</i> vs <i>AD</i> , <i>MCI</i> vs <i>AD</i>	-8.6 (< 0.001); -7.1 (< 0.001); -8.64 (0.001)
<i>PVS</i>	2.99 (< 0.05)	<i>HC</i> vs <i>SCD</i>	-3.13 (0.011)
<i>DTI-ALPS</i>	24.52 (< 0.001)	<i>HC</i> vs <i>AD</i> , <i>SCD</i> vs <i>MCI</i> , <i>SCD</i> vs <i>AD</i> , <i>MCI</i> vs <i>AD</i>	6.97 (< 0.001); 3.01 (0.017); 7.38 (< 0.001); 5.91 (< 0.001)

At the individual level, age showed robust associations with several glymphatic-related indices: BF, CSF, DTI-ALPS, CP, and FW all correlated significantly with age ($p \leq 0.001$; $|r| \approx 0.12$ -0.56), whereas PVS and BOLD-CSF volume showed no age effect. Sex and scanner effects were evaluated using two-sample t-tests with FDR correction across metrics. After FDR correction, sex differences were significant for BF, CSF, ALPS, CP, FW, and PVS ($q < 0.05$; small-to-moderate Cohen's $d \approx 0.20$ -0.61), but not for any BOLD-CSF coupling measure. Head-motion was primarily related to CSF, ALPS, CP, and FW (all $p < 0.05$), with negligible associations for BF, PVS, and the coupling indices. Scanner effects were evaluated using two-sample t-tests performed on

covariate-adjusted residuals, in which each glymphatic metric was first regressed onto age, sex, and diagnostic group. Significant scanner effects were observed for CSF, CP, FW, DTI-ALPS, PVS, BF, and two of the BOLD-CSF coupling indices ($q < 0.05$). To ensure that subsequent cross-modal analyses were not confounded by redundancy among glymphatic metrics, we additionally quantified their inter-correlations; the resulting correlation matrix is shown in Supplementary Fig. S1, where no pair of measures approached near-collinearity ($|r| > 0.80$) and significant associations are marked with asterisks.



Supplementary Fig. S1. Pairwise correlations among glymphatic-related measures. The heatmap displays Pearson correlations across all glymphatic and perivascular indicators. Moderate correlations were observed among volumetric indices (CSF, CP, PVS) and between FW and DTI-ALPS, whereas both gBOLD-CSF and tBOLD-CSF coupling showed negligible associations with other measures. No measure pair demonstrated near-collinearity ($|r| > 0.80$). Significant correlations are marked with asterisks.

S1.2 Supplementary results for $|\chi_{\text{dia}}|$ and χ_{para} metrics

Full ANCOVA statistics (age-, sex-, and scanner-, disease stage-adjusted) and post-hoc comparisons for all ROI-wise $|\chi_{\text{dia}}|$ and χ_{para} measures are provided in Supplementary Table S2. As summarized in the main text, both diamagnetic and paramagnetic susceptibility showed widespread group differences, particularly within temporal, parietal, and limbic regions. Supplementary Table S2 reports the complete set of F values and pairwise t-tests.

Table S2. ANCOVA and post-hoc comparisons of $|\chi_{\text{dia}}|$ and χ_{para} measures across the AD continuum at the ROI and network levels.

Metric	ROI	F value (p value)	Comparison	t value (adjusted p)
$ \chi_{dia} $ (ROI)	OG	14.79 (<0.001)	AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC	-4.05 (< 0.001); -4.65 (< 0.001); 4.65 (< 0.001); 5.17 (< 0.001)
	ITG	5.78 (<0.001)	AD vs MCI, AD vs SCD	-2.78 (< 0.05); -3.54 (< 0.01)
	DN	7.37 (<0.001)	AD vs MCI, AD vs SCD, SCD vs HC	2.71 (< 0.05); 4.05 (< 0.001); -3.69 (< 0.01)
χ_{para} (ROI)	OG	9.61 (<0.001)	AD vs MCI, MCI vs HC, SCD vs HC	-3.61 (< 0.01); 3.65 (< 0.01); 4.93 (< 0.001)
	STG	8.88 (<0.001)	AD vs MCI, AD vs SCD, MCI vs HC	-5.89 (< 0.001); -3.8 (< 0.01); 3.48 (< 0.01)
	ITG	6.41 (<0.001)	AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC	-3.5 (< 0.01); -3.51 (< 0.01); 2.75 (< 0.05); 2.71 (< 0.05)
	FuG	5.67 (<0.001)	AD vs SCD, MCI vs HC, SCD vs HC	-2.76 (< 0.05); 3.08 (< 0.05); 3.33 (< 0.01)
	PhG	11.37 (<0.001)	AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC	-3.1 (< 0.05); -4.88 (< 0.01); 2.99 (< 0.05); 4.71 (< 0.01)
	Pcun	7.83 (<0.001)	AD vs MCI, MCI vs HC	7.19 (< 0.001); -3.32 (< 0.01)
$ \chi_{dia} $ (network)	LIM	13.13 (<0.001)	AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC	-3.61 (< 0.01); -4.41 (< 0.001); 4.39 (< 0.001); 4.84 (< 0.001)
	FPN	7.83 (<0.001)	AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC	-2.71 (< 0.05); -2.94 (< 0.05); 3.62 (< 0.01); 4.83 (< 0.01)
χ_{para} (network)	LIM	12.19 (<0.001)	AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC	-3.6 (< 0.01); -4.66 (< 0.001); 3.78 (< 0.01); 4.83 (< 0.001)
	DMN	10.57 (<0.001)	AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC	-4.6 (< 0.001); -2.7 (< 0.05); 4.73 (< 0.001); 3.37 (< 0.01)

At the individual level, there were no significant age or sex effects on any $|\chi_{dia}|$ or χ_{para} metrics ($p > 0.05$), consistent with the absence of systematic covariate dependencies in susceptibility measures. Scanner effects were assessed using two-sample t-tests performed on residualized susceptibility values, where each ROI-level QSM feature was first regressed onto age, sex, and diagnostic group. Multiple $|\chi_{dia}|$ and χ_{para} regions showed significant scanner-related baseline offsets ($q < 0.05$), particularly in temporal, parietal, and limbic cortices.

To determine whether regional atrophy contributed to the observed susceptibility differences, the ANCOVA was repeated with the corresponding regional GM volume included as an additional covariate. After adjustment for age, sex, scanner, and regional GM volume, significant group differences in $|\chi_{dia}|$ were observed in the MFG, OG, PL, ITG, SPL, Pcun, PoG, and DN, whereas significant χ_{para} differences were observed in the OG, STG, ITG, FuG, and PhG (FDR-corrected $p < .05$; Supplementary Table S3). Several of the principal susceptibility differences identified in

the primary analysis, including $|\chi_{dia}|$ differences in the OG, ITG, and DN and χ_{para} differences in the OG, STG, ITG, FuG, and PhG, remained significant after adjustment for regional GM volume. Additional $|\chi_{dia}|$ differences were observed in the MFG, PL, SPL, Pcun, and PoG, whereas the χ_{para} difference in the Pcun observed in the primary analysis did not remain significant.

At the network level, significant differences in $|\chi_{dia}|$ within the LIM and FPN and in χ_{para} within the LIM and DMN remained significant, while additional $|\chi_{dia}|$ differences emerged in the DAN and DMN.

Table S3. Atrophy-adjusted ANCOVA and post-hoc comparisons of $|\chi_{dia}|$ and χ_{para} measures across the AD continuum at the ROI and network levels.

Metric	ROI	F value (p value)	Comparison	t value (adjusted p)
$ \chi_{dia} $ (ROI)	MFG	6.73 (< 0.001)	SCD vs HC; SCD vs AD	3.56 (< 0.01); 3.48 (< 0.01)
	OG	14.57 (< 0.001)	SCD vs HC; MCI vs HC; SCD vs AD; MCI vs AD	5.16 (< 0.001); 4.64 (< 0.001); 4.59 (< 0.001); 4.00 (< 0.001)
	PL	6.07 (< 0.001)	SCD vs HC; MCI vs HC; SCD vs AD	3.30 (< 0.01); 3.01 (< 0.05); 2.96 (< .05)
	ITG	6.56 (< .001)	SCD vs HC; SCD vs AD; MCI vs AD	30.05 (< .05); 3.85 (< .01); 3.17 (< .05)
	SPL	6.32 (< .001)	SCD vs HC; SCD vs AD	3.95 (< .001); 3.06 (< 0.05)
	Pcun	8.52 (< 0.001)	SCD vs HC; SCD vs AD	4.22 (< 0.001); 4.08 (< 0.001)
	PoG	6.12 (< 0.001)	SCD vs HC; SCD vs AD	3.37 (< 0.01); 3.21 (< 0.05)
	DN	7.65 (< 0.001)	HC vs SCD; AD vs SCD; AD vs MCI	3.82 (< 0.01); 4.05 (< 0.001); 2.79 (< 0.05)
χ_{para} (ROI)	OG	9.82 (< 0.001)	SCD vs HC; MCI vs HC; SCD vs AD	4.97 (< 0.001); 3.67 (< 0.01); 3.67 (< 0.01)
	STG	6.31 (< 0.001)	MCI vs HC; MCI vs AD	3.36 (< 0.01); 3.74 (< 0.01)
	ITG	7.21 (< 0.001)	SCD vs HC; MCI vs HC; SCD vs AD; MCI vs AD	2.82 (< 0.05); 2.82 (< 0.05); 3.81 (< 0.01); 3.75 (< 0.01)
	FuG	6.07 (< 0.001)	AD vs SCD, MCI vs HC, SCD vs HC	3.41 (< 0.01); 3.05 (< 0.05); 2.98 (< 0.05)
	PhG	11.19 (< 0.001)	SCD vs HC; MCI vs HC; SCD vs AD	4.69 (< 0.001); 2.98 (< 0.05); 4.83 (< 0.001); 3.06 (< 0.05)
$ \chi_{dia} $ (network)	DAN	5.69 (< 0.001)	AD vs SCD, SCD vs HC	-3.18 (< 0.05); 3.46 (< 0.01)
	LIM	13.55 (< 0.001)	AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC	-4.05 (< 0.001); -4.55 (< 0.001); 4.41 (< 0.001); 4.81 (< 0.001)

	<i>FPN</i>	8.37 (<0.001)	<i>AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC</i>	-3.03 (< 0.05); -3.16 (< 0.05); 3.69(< 0.01); 3.89(< 0.01)
	<i>DMN</i>	7.71 (<0.001)	<i>AD vs SCD, MCI vs HC, SCD vs HC</i>	-3.45 (< 0.01); 2.93(< 0.05); 4.21(< 0.001)
χ_{para} (network)	<i>LIM</i>	12.77 (<0.001)	<i>AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC</i>	-3.71 (< 0.01); -4.82 (< 0.001); 3.82(< 0.01); 4.83(< 0.001)
	<i>DMN</i>	8.63 (<0.001)	<i>AD vs MCI, AD vs SCD, MCI vs HC, SCD vs HC</i>	-2.69 (< 0.05); 4.5(< 0.001); 3.61(< 0.01)

S1.3 Supplementary results for Latent Component

Table S4. Permutation significance and covariance explained by latent variables in the PLS analyses.

Model	LV	Covariance (%)	Corrected p	Model	LV	Covariance (%)	Corrected p
$ \chi_{dia} $ (ROI)	LV1	53.79	0.0003	$ \chi_{dia} $ (network)	LV1	63.28	0.0003
$ \chi_{dia} $ (ROI)	LV2	28.9	0.0003	$ \chi_{dia} $ (network)	LV2	31.78	0.0003
$ \chi_{dia} $ (ROI)	LV3	6.88	0.0003	$ \chi_{dia} $ (network)	LV3	2.99	0.045
χ_{para} (ROI)	LV1	55.55	0.0004	χ_{para} (network)	LV1	61.59	0.0003
χ_{para} (ROI)	LV2	29.72	0.0004	χ_{para} (network)	LV2	33.84	0.0003
χ_{para} (ROI)	LV3	4.13	0.4055	χ_{para} (network)	LV3	1.66	0.6876

Supplementary Methods

S2 Participants

AD, aMCI, and SCD subjects were continuously recruited from the Memory Clinic and Neurology Department of China-Japan Friendship Hospital and Nanjing Drum Tower Hospital. The diagnostic criteria for AD were based on the NINCDS-ADRDA guidelines [1], the 2011 international diagnostic criteria guidelines formulated by the National Institute on Aging and Alzheimer's Association (NIA-AA) [2] and IWG-2 criteria [3].

The criteria for aMCI subjects followed Petersen's 1999 diagnostic guidelines [4], which are: (1) the presence of memory decline complaints, confirmed by an informant; (2) cognitive decline in one (or more) domains without significant impairment in daily living activities, and not meeting the diagnostic criteria for dementia; (3) objective impairment in episodic memory (a reduction of at least 1.5 standard deviations on one or more tests); (4) a clinical dementia rating (CDR) score of 0.5.

The diagnostic criteria for SCD followed the research standards published by the SCD International Working Group in 2014 [5] and updated in 2020 [6], requiring the following: (1) a

self-perceived, persistent decline in cognitive ability compared to a previous normal state, unrelated to acute events; (2) performance within the normal range in standardized cognitive tests after adjusting for age, gender, and education level, without meeting the diagnostic criteria for MCI. Thus, the inclusion criteria for SCD in this study were: (1) clear and persistent complaints of memory and cognitive decline; (2) onset within the past five years, with an onset age of ≥ 50 years; (3) completion of a full set of neuropsychological tests, with no objective cognitive impairment.

Exclusion criteria for all subjects included: (1) a history of neurological and psychiatric diseases; (2) metabolic diseases or major illnesses; (3) alcohol or drug abuse; (4) contraindications for MRI examination; (5) abnormal findings on routine brain imaging; (6) significant head movement artifacts on MR images. (7) MR data quality does not meet analytical standards

All newly recruited AD, aMCI, and SCD subjects underwent neuropsychological test and MRI examination, , while some patients with more advanced disease were unable to complete the full neuropsychological battery. Simultaneously, age- and sex-matched healthy controls (HCs) were recruited from the local community, with their cognitive status assessed by the MMSE and MoCA.

S3 MRI Acquisition

In China-Japan Friendship Hospital site, MRI data were collected using a 3.0 Tesla MR scanner (General Electric, Discovery MR750, Milwaukee, WI, United States) with an eight-channel head coil. The scanning protocol included a 3D T1-weighted fast spoiled gradient-echo (3D-FSPGR) sequence for structural image, a 3D multi-echo gradient-echo (3D-mGRE) sequence for susceptibility mapping, a single shot gradient recalled echo-planar imaging (GRE-SS-EPI) sequence for rs-fMRI and a spin-echo echo-planar (EPI) sequence for diffusion MRI (dMRI). Detailed parameters were as follow: (1) 3D-FSPGR: repetition time (TR) = 6.7 ms, echo time (TE) = 2.9 ms, flip angle = 12° , slice thickness = 1 mm, field of view (FOV) = 256×256 mm, voxel size = $1 \times 1 \times 1$ mm³; (2) 3D-mGRE: TE1st/ Δ TE/TE8th = 3.19 ms/2.37 ms/ 19.77ms, TR = 22.9 ms, bandwidth = 62.5 Hz/pixel, slice thickness = 1.0 mm, FOV = $256 \text{ mm} \times 256 \text{ mm}$, voxel size = $1 \times 1 \times 1$ mm³; (3) GRE-SS-EPI: TR = 2000 ms, TE = 30 ms, flip angle = 90° , slice thickness = 3.5 mm, slice spacing = 0.7 mm, FOV = $224 \text{ mm} \times 224 \text{ mm}$, voxel size = $3.5 \times 3.5 \times 3.5$ mm³, with 240 time points; (4) Diffusion-weighted EPI: TR = 8028 ms, TE = 81.8 ms, flip angle = 90° , slice thickness = 2 mm, FOV = $240 \text{ mm} \times 240 \text{ mm}$, voxel size = $2 \times 2 \times 2$ mm³, with 64 diffusion-weighted directions using a b value of 1000s/mm² and five images with a b value of 0 s/mm².

In Nanjing Drum Tower Hospital site, all participants underwent scanning on a 3.0-Tesla MRI scanner (Philips Ingenia CX) with a 32-channel head coil. Structural 3D-T1w images were acquired with the following parameters: a repetition time (TR) = 8.37 ms; echo time (TE) = 3.89 ms; flip angle = 8° ; field of view (FOV) = $256 \text{ mm} \times 256 \text{ mm}$; voxel size = $1 \times 1 \times 1$ mm³. The 3D multi-echo gradient-echo (mGRE) sequence was acquired for susceptibility analysis, with the following parameters: TR= 51 ms; TE: TE1st/ Δ TE/TE6th = 7/7/42 ms; flip angle = 20° ; FOV =

288 mm×288 mm; voxel size = $0.75 \times 0.75 \times 2$ mm³. The FEEPI was acquired for rs-fMRI analysis, with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, slice thickness = 4.0 mm, slice spacing = 4 mm, voxel size = $3 \times 3 \times 4$ mm³, with 230 time points. The DTI sequence was used with the parameters: TR = 2993 ms, TE = 75.44 ms, flip angle = 90°, slice thickness = 2 mm, voxel size = $2 \times 2 \times 2$ mm³, with 128 diffusion-weighted directions using a b value of 1000 s/mm² and one image with a b value of 0 s/mm².

S4 Data processing

S4.1 MRI data preprocessing

T1-weighted images were processed using the FreeSurfer v6.0 recon-all pipeline [7], which automatically performs skull stripping, intensity normalization, tissue segmentation, and cortical and subcortical parcellation. The aseg and aparc atlases were used to generate region-of-interest (ROI) masks. Intracranial volume was derived from the aseg statistics file and used to normalize volumetric measures such as CSF, perivascular space (PVS), and choroid plexus (CP) volumes.

Diffusion-weighted images were first denoised using MP-PCA and corrected for Gibbs-ringing artifacts [8]. Eddy current distortions and head motion were corrected using a model with outlier replacement, and susceptibility-induced distortions were addressed using field-map-based adjustments. A bi-tensor model was fitted using Accelerated Microstructure Imaging via Convex Optimization (AMICO) to estimate free-water content, while diffusion tensors were reconstructed to derive fractional anisotropy and mean diffusivity maps [9]. All diffusion-derived metrics were registered to the T1 anatomical space using boundary-based registration to ensure anatomical correspondence across modalities.

Preprocessing of resting-state fMRI included slice-timing correction, rigid-body motion realignment, and two-stage nuisance regression incorporating 24 motion parameters and CSF and white-matter signals. High-motion volumes were interpolated or censored according to framewise displacement thresholds. Time series were temporally band-pass filtered between 0.01 and 0.1 Hz and spatially smoothed with a 6 mm full-width half-maximum Gaussian kernel. All fMRI volumes were co-registered to the participant's T1 image and normalized to standard space. Ventricular CSF masks were eroded to minimize partial-volume contamination before CSF time series extraction [10].

S4.2 Computation of the PVS index

The PVS index consisted of ventricular cerebrospinal fluid (CSF) compartment volume, choroid plexus (CP) volume, perivascular space (PVS) volume, free-water (FW) fraction, basal forebrain (BF), and the DTI-ALPS index. WM masks derived from FreeSurfer (see S.3.1) were used to extract WM regions. CSF compartment volume was derived from the FreeSurfer aseg segmentation by combining ventricular and CSF labels (4, 5, 14, 15, 24, 43, 44, and 72), while excluding choroid plexus labels. The resulting CSF volume was normalized by intracranial volume (TIV) to generate the CSF compartment fraction. CP volumes were obtained from T1 images using

a deep-learning segmentation model (https://github.com/hettk/chp_seg) [11]. PVS volume was computed within the white matter by applying a multi-scale Jerman vesselness filter to structural images [12], followed by percentile-based thresholding and morphological refinement to obtain binary PVS masks [13].

FW fraction maps were estimated from eddy-corrected diffusion MRI using the AMICO bi-tensor free-water model [39]. Model fitting employed the default AMICO solver parameters ($\lambda_1 = 0$, $\lambda_2 = 0.001$), a fixed isotropic diffusivity of $2.5 \times 10^{-3} \text{ mm}^2/\text{s}$, a fixed parallel diffusivity of $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$, and a perpendicular diffusivity dictionary ranging from 0.1 to $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$, without explicit spatial regularization. The final FW metric was calculated as the mean free-water fraction within white matter after excluding PVS voxels. BF were obtained from the probabilistic JuBrain cytoarchitectonic atlas implemented in the SPM Anatomy Toolbox, using the bilateral Ch4 nucleus and following previously published cholinergic imaging protocols [14].

The DTI-ALPS index was computed following the LOFT framework [8]. ROIs were placed in projection (SCR) and association (SLF) fibers, and diffusivities along x-, y-, and z-axes were extracted. The ALPS index was calculated as:

$$DTI - ALPS \text{ index} = |(D_{x_{proj}} + D_{x_{assoc}}) / (D_{y_{proj}} + D_{z_{assoc}})|$$

S4.3 BOLD-CSF Coupling Analysis

BOLD-CSF coupling was computed following established glymphatic fMRI protocols [15, 16]. After preprocessing, the global BOLD (gBOLD) signal was extracted from gray-matter voxels defined by the BNA246 atlas. Regional BOLD signals were obtained by averaging across frontal (fBOLD), temporal (tBOLD), and parietal (pBOLD) parcels, respectively. To obtain the CSF inflow signal, an eroded inferior-ventricle mask was applied to the lower slices of each subject's fMRI, ensuring consistent cerebellar coverage and minimizing partial-volume effects. Non-zero voxels within these slices were averaged to form the CSF time series. Both BOLD and CSF signals were normalized to unit variance across subjects.

Coupling strength was quantified by computing the cross-correlation function between the CSF signal and the negative temporal derivative of each BOLD signal. Cross-correlation was calculated over time lags ranging from -9 s to $+9 \text{ s}$, and the lag corresponding to the most negative correlation was taken as each subject's coupling value; for gBOLD, the peak typically occurred at $+3 \text{ s}$. This procedure was repeated for regional BOLD signals to obtain fBOLD-CSF, tBOLD-CSF, and pBOLD-CSF coupling.

Statistical significance of coupling values was assessed using a permutation framework in which BOLD and CSF time series were randomly reassigned across subjects for 1,000 iterations. The empirical p-value was defined as the proportion of permutations in which the randomized correlation exceeded the true negative coupling. Subjects with more than 20% motion-censored volumes were excluded from coupling analyses.

S4.4 Reconstruction of sub-voxel QSM maps and spatial normalization

The susceptibility maps were generated from 3D-mGRE data through the standard pipeline in the STISuite (<http://people.eecs.berkeley.edu/~chunlei.liu/software.html>) and APART-QSM toolboxes (<https://github.com/AMRI-Lab/APART-QSM>) [17]. In short, the multi-echo raw phase images were firstly unwrapped through Laplacian-based method [18, 19], and brain mask was extracted from the averaged magnitude image across echoes using brain extraction tool (BET) in FSL version 6.0.0 [20]. Then, the local field map was calculated with brain mask using varying spherical kernel filtering algorithm (LBV) [21]. QSM image was reconstructed from tissue field map through STAR-QSM method [22]. Next, the R_2 map was calculated using a mono-exponential function in STISuite. Lastly, the QSM, tissue phase, multi-echo magnitude and R_2 data were combined into the APART-QSM [17] to generate paramagnetic (χ_{para}) and diamagnetic susceptibility (χ_{dia}) maps. To avoid complications of explanations in signal source, the absolute diamagnetic susceptibility maps ($|\chi_{\text{dia}}|$) were used for subsequential analyses. Higher χ_{para} and $|\chi_{\text{dia}}|$ values indicate greater amount of paramagnetic and diamagnetic content in brain tissue, respectively.

Firstly, individual T1 images were normalized to MNI (Montreal Neurological Institute) standard space using the deformable b-spline co-registration routine in ANTs (Advanced Normalization Tools) [23]. The first-echo of magnitude images with radio-frequency bias-correction were rigidly co-registered to their corresponding T1 images by affine approach in ANTs. Then, paramagnetic (χ_{para}) and absolute diamagnetic susceptibility ($|\chi_{\text{dia}}|$) maps were warped to MNI space using the combined deformation matrixes above through “antsApplyTransforms” algorithm.

In addition, T1 structural images were segmented into gray matter and white matter probabilistic maps using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>). The probabilistic maps were also transformed into the MNI space through above individual T1 normalization deformations, and the final binary brain masks excluding nonparenchymal voxels were generated with a 0.6 threshold on tissue probability. The final binary brain mask was used to restrict the parenchymal boundary in the normalized paramagnetic and absolute diamagnetic susceptibility maps, which more accurately masked out CSF regions.

S5 Partial Least Squares (PLS) Analysis

To identify multivariate glymphatic-susceptibility relationships beyond their shared associations with disease stage, Partial Least Squares Correlation (PLS-C) analysis was performed at both ROI and network levels. Subject availability was first harmonized across modalities by aligning glymphatic measures to participants with valid QSM data, ensuring one-to-one correspondence between glymphatic and susceptibility measures.

Prior to PLS analysis, both glymphatic-related and susceptibility measures were residualized for diagnostic stage, age, sex, and scanner using linear regression. The residualized variables were

then z-score normalized across participants. Separate PLS models were constructed for paramagnetic (χ_{para}) and diamagnetic ($|\chi_{\text{dia}}|$) susceptibility components at both at the ROI and network levels. The glymphatic feature matrix comprised eight complementary measures: global BOLD–CSF coupling, temporal BOLD–CSF coupling, FW, CSF, PVS, DTI-ALPS, BF, and CP. These glymphatic-related measures were global or anatomically defined indices and were not averaged within the susceptibility ROIs or networks. The QSM feature matrix comprised χ_{para} or $|\chi_{\text{dia}}|$ values from the 28 anatomically defined ROIs for ROI-level analyses or from the seven Yeo cortical networks for network-level analyses.

Cross-covariance matrices were decomposed using singular value decomposition (SVD), yielding latent variables (LVs) that maximally capture shared variance between X and Y. The significance of each LV was assessed using permutation testing (3,000 permutations), and feature stability was evaluated using bootstrap resampling (3,000 bootstraps). Bootstrap ratios were used to quantify the reliability of feature saliences, with $|BR| \geq 5$ considered a stable contribution.

For significant LVs, we extracted (i) salience weights for glymphatic and susceptibility features, (ii) subject-level LV scores, and (iii) the proportion of cross-modal covariance explained by each LV. This multivariate framework was used to identify coordinated glymphatic–susceptibility covariance patterns that persisted after accounting for their shared associations with diagnostic stage and other covariates.

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