Glymphatic function decline as a mediator of core memory-related brain structures atrophy in aging

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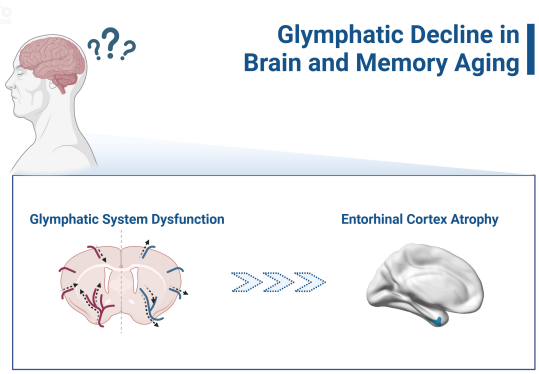
ABSTRACT

Background and Objectives: This study aimed to elucidate the role of the glymphatic system—a crucial pathway for clearing waste in the brain—in the aging process and its contribution to cognitive decline. We specifically focused on the diffusion tensor imaging analysis along the perivascular space (ALPS) index as a noninvasive biomarker of glymphatic function. **Methods:** Data were drawn from the Alzheimers Disease Neuroimaging Initiative (ADNI) database and a separate validation cohort to analyze the ALPS index in cognitively normal older adults. The relationships among the ALPS index, brain morphometry, and memory performance were examined. **Results:** As a biomarker of glymphatic function, the ALPS index appeared to decline with age in both cohorts. According to the brain morphology analysis, the ALPS index was positively correlated with the thickness of the left entorhinal cortex (r = 0.258, $P_{\text{false discovery rate (FDR)}} = 2.96 \times 10^{-4}$), and it played a mediating role between aging and left entorhinal cortex thinning. The independent cohort further validated the correlation between the ALPS index and the left entorhinal cortex thickness (r = 0.414, P_{FDR} = 0.042). Additionally, in both the primary and validation cohorts, the ALPS index played a significant mediating role in the relationship between age and durable or delayed memory decline. **Conclusion:** This study highlights the ALPS index as a promising biomarker for glymphatic function and links it to atrophy of the core memory brain regions during aging. Furthermore, these results suggest that targeting glymphatic dysfunction could represent a novel therapeutic approach to mitigate age-related memory decline.

Graphical Abstract



Key words: aging, cognitive function, glymphatic system, entorhinal cortex, memory

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INTRODUCTION

Aging is commonly associated with cognitive decline, which has significant implications for individuals' quality of life and public health. Studies have suggested that memory deterioration in normal aging can often be traced to structural and functional changes in the brain, particularly in the medial temporal lobe (MTL), including the hippocampus, the entorhinal cortex (EC), the perirhinal cortex, the presubiculum, and the parahippocampal gyrus (PHG).[1] While traditional approaches to understanding memory decline have focused on neuronal loss or impairments in synaptic plasticity, one critical yet often overlooked aspect of this process is the role of the glymphatic system. This waste clearance pathway removes the metabolic by-products, including the amyloid-beta and tau proteins, associated with neurodegenerative conditions.[2,3] Research has indicated that the efficiency of the glymphatic system decreases with age and leads to the accumulation of neurotoxic substances that may contribute to cognitive decline, thereby increasing the risk of neurodegenerative diseases.[4,5] Understanding the implications of glymphatic function in aging is essential for developing potential therapeutic strategies to preserve cognitive function and mitigate age-related neurological disorders.[6]

In a study by Taoka *et al.*, analysis along the perivascular space (ALPS) index was first introduced as a noninvasive method to assess glymphatic system function *via* diffusion tensor imaging (DTI) and as a potential biomarker of cognitive performance in patients with Alzheimers disease (AD).[7] Accumulating evidence highlights the importance of monitoring the ALPS index in pathological aging. In particular, the ALPS index is associated with cognitive dysfunction in patients with AD and Parkinson's disease (PD), and it can sensitively predict subsequent pathological development and disease progression in the early stages.[8,9] The ALPS index, which also decreases with age during normal aging, is associated with memory and executive function decline as well as a reduction in gray matter volume in key brain regions critical to cognitive function.[10] These findings underscore the importance of monitoring glymphatic function *via* the ALPS index during the normal aging process in humans.

However, current research has utilized voxel-based morphometry (VBM) methods to analyze the relationship between the ALPS index and brain atrophy. Nevertheless, surface-based morphometry (SBM) analysis can capture subtle variations in cortical thickness and gray matter morphology, thereby demonstrating that age-related structural changes are more sensitive.[11,12] To explore the impact of glymphatic function on brain atrophy during normal aging, in this study, we utilized data from the publicly available Alzheimers Disease Neuroimaging Initiative (ADNI) database to analyze the relationship between the ALPS index and brain morphology in 313 cognitively normal (CN) older adults *via* SBM methods. To further enhance the reliability of our results, we recruited an independent validation cohort of 61 elderly individuals to confirm our findings.

METHODS

Participants and study design

This study involved the ADNI and an independent validation cohort that were recruited at Peking University Sixth Hospital. Primary analyses were conducted using data from the ADNI cohort, with a focus on the associations between the ALPS index and aging, brain morphometry, and memory performance in older CN adults. The findings of the validation cohort were replicated, and the role of the ALPS index in brain atrophy was assessed.

The data used in the primary analysis were obtained from the ADNI website (http://adni.loni.usc.edu/) in October 2024. Launched in 2003, the ADNI has collected a wealth of data, including clinical assessments, neuroimaging, and biomarker information, and serves as a critical resource for researchers investigating the progression of aging. The ADNI received approval from the institutional review boards of each participating center, and all participants provided written, informed consent. The detailed inclusion and exclusion criteria can be found in previous publications.[13]

We initially selected CN ADNI participants without neuropsychiatric disorders who had DTI data for the ALPS index analysis. CN was defined as a cognitive level of an mini-mental state examination (MMSE) score 24, a sum - of - boxes clinical dementia rating (CDR) score 0.5, and no evidence of objective memory impairment, as determined by delayed recall performance on the Wechsler Memory Scale Logical Memory II. Participants with a score greater than 6 on the Geriatric Depression Scale were excluded. Moreover, because head motion can reduce the reliability of the ALPS index, potential participants with severe head motion on DTI were excluded.[14,15] Finally, 313 participants were included in the ADNI cohort. To further investigate the association between the ALPS index and distinct memory abilities, we used digital cognitive biomarkers (DCBs), which are comprehensive analyses derived from the Alzheimers Disease Assessment Scale-Cognitive Subscale Wordlist Memory assessments that utilize a hierarchical Bayesian cognitive processing model.[16] In our study, 217 participants in the ADNI cohort had memory indices with DCBs.

The validation cohort included right-handed CN individuals over 60 years of age who had an MMSE score 24, a CDR score 0.5, and delayed recall on the auditory verbal learning test-Huashan (AVLT-H) -1.5 standard deviations (SDs) of the age-matched control subjects.[17,18] Participants were excluded if they had metal implants in the head, implanted electronic devices, a history of neurological problems, head injury, organic brain diseases, or claustrophobia. Additionally, those with current use of psychoactive medication, hypertension, diabetes, chronic kidney disease, a Beck Depression Inventory score > 13, a Generalized Anxiety Disorder 7 test score > 5, or a Pittsburgh Sleep Quality Index (PSQI) score > 5 were not eligible for the study. This study was a secondary analysis of a clinical trial that was conducted at Peking University Sixth Hospital, the original research protocol of which was approved by the ethics committee of Peking University Sixth Hospital (Peking USH20231027) and adhered to the provisions of the Declaration of Helsinki. All participants provided written, informed consent and were recruited voluntarily. Sixty-five elderly individuals were initially recruited, but four participants were excluded from further analyses because of abnormal magnetic resonance T1-weighted magnetic resonance imaging (MRI) lesions.

MRI data acquisition

In the ADNI cohort, participants underwent 3.0T MRI scans *via* General Electric Company (GE), Philips, and Siemens equipment. The ADNI has established standardized scanning parameters for each type of scanner to ensure the comparability of images generated by different devices. Each series in each scan underwent quality control at the Mayo Advanced Digital Imaging Research (ADIR) Lab. The ADNI website can access comprehensive details regarding the MRI acquisition protocols (https://adni.loni.usc.edu/data-samples/adni-data/neuroimaging/mri/).

The scanning session for each subject in the validation cohort included high-resolution structural MRI and DTI *via* a research-dedicated 3.0T GE Excite High Definition (HD) scanner (GE Medical Systems, Milwaukee, WI, USA) at the MRI Research Center, Peking University Sixth Hospital. Structural images were acquired *via* three-dimensional sagittal T1-weighted magnetization-prepared rapid gradient echo (6700 ms repetition time [TR], 192 slices, 1 mm slice thickness, 1 mm × 1 mm × 1 mm voxel size, 12 flip angles, 450 ms inversion time, and 256 mm × 256 mm field of view [FOV]). DTI acquisition was aligned with the anterior commissure posterior commissure plane. The TR = 8980 ms, echo time (TE) = 92 ms, slice thickness = 2 mm, flip angle = 90°, voxel resolution = 2 mm × 2 mm × 2 mm, FOV = 240 mm^2 × 240 mm^2, and the number of gradient directions = 64. The sequence's b value was 1000 s/mm^2, with 8 acquisitions at b = 0 s/mm^2.

Brain morphometry analysis

We analyzed T1-weighted MR data from the two cohorts using the FreeSurfer software and an automated recon-all processing stream (version 7.2.0), which performs standard normalization procedures.[19] This pipeline facilitated cortical surface reconstruction and tissue class segmentation without manual editing to maintain consistency and automation in our analysis. The Desikan-Killiany atlas was utilized for cortical parcellation and yielded measurements of the cortical subregion thickness and surface area.[20] Surface annotations of the volumetric atlas cortical labels were created *via* the FreeSurfer tool aparc. annot for each hemisphere. Subcortical structures were segmented *via* the subcortical segmentation protocol of FreeSurfer aseg.mgz. Quality control was implemented through visual inspection of the segmentation results to identify and correct any anomalies, thereby ensuring the integrity of the data analysis.

The ALPS index calculation

The evaluation of the ALPS index aligned with findings from previous studies and was processed *via* DSI Studio (https://dsi-studio.labsolver.org/).[7,21,22] First, the original 4D DTI digital imaging and communications in medicine (DICOM) files were converted into source (SRC) format. The images were subsequently reconstructed *via* the q-space diffeomorphic reconstruction method, which applies generalized q-sampling imaging in Montreal Neurological Institute (MNI) space and normalizes them to the ICBM152 adult templates. After automatic processing, diffusivity maps along the x-axis (right-left), y-axis (anterior-posterior), and z-axis (inferior-superior), along with colored fractional anisotropy (FA) maps, were selected. Regions of interest (ROIs) with a diameter of 5 mm were placed on the bilateral projection and association fibers within the FA map template (Figure S1a). The ROIs were initially placed at the following coordinates: left projection fiber (53, 47, 40), left association fiber (59, 47, 40), right projection fiber (25, 47, 40), and right association fiber (19, 47, 40). Manual corrections were then performed to ensure the accuracy of both the registration and the placement of the ROIs for each participant. We recorded diffusivity values along the x-axis (Dx), y-axis (Dy), and z-axis (Dz) for the ROIs on the projection and association fibers, denoted as Dxproj, Dyproj, Dzproj, Dxassoc, Dyassoc, and Dzassoc, respectively (Figure S1b-d). The ALPS index was then calculated using the formula $\frac{Dxproj + Dxassoc}{Dyproj + Dzassoc}$. To minimize discrepancies arising from the selection of ROIs on different sides (left and right), we averaged the ALPS indexes from the bilateral ROIs to derive a mean ALPS index for further analyses.[22]

Memory performance assessment

In the ADNI cohort, seven base DCBs represented the probability of information processing through different

Table 1: Demographic and clinical characteristics of participants in the ANDI cohort and the validation cohort

Characteristic		ADNI Cohort (*N* = 313)	Validation Cohort (*N* = 61)
ADNI Phase, *n* (%)	ANDI2	15 (4.792)	
	ANDI3	272 (86.900)	
	ADNI4	26 (8.307)	
Age, *n* (%)	50～59 years	33 (10.543)	-
	60～69 years	118 (37.700)	50 (81.967)
	70～79 years	124 (39.617)	11 (18.033)
	80～89 years	33 (10.543)	-
	90～99 years	5 (1.597)	-
Sex, *n* (%)	Male	108 (34.505)	19 (31.148)
	Female	205 (65.495)	42 (68.852)
Handedness, *n* (%)	Right-handed	287 (91.693)	61 (100.00)
	Left-handed	26 (8.307)	-
Years of Education, years		16.437 ± 2.264	12.475 ± 2.328
MMSE Score		29.051 ± 1.196	30[28,30]
ALPS index		1.434 ± 0.144	1.510 ± 0.150

ADNI: Alzheimer's Disease Neuroimaging Initiative; MMSE: Mini-Mental State Examination; ALPS: analysis along the perivascular space.

encoding (N_1, N_2, N_3, N_4) or retrieval (R_1, R_2, R_3) pathways to and from three distinct storage states: pre-task, transient, or durable storage states. Additionally, three measures (M_1, M_2, and M_3) were employed to quantify a person's probability of recall (Table S1). N_2, R_1, and M_1 reflected transient memory encoding, retrieval, and recall capabilities, respectively. N_1 and N_3 indicated the direct and consolidated encoding abilities for durable storage. R_2 and R_3 reflected the immediate and delayed retrieval abilities for durable memory, whereas M_2 and M_3 demonstrated the immediate and delayed recall abilities. In addition, N_4 was correlated with the effect of practice on the transition of transient storage to durable memory. Memory performance was indexed by the probability of recalling details from learned material.

In our independently recruited cohort, we employed the AVLT-H for each subject. The AVLT consists of 12 words read aloud by the examiner, after which the participant is asked to immediately recall as many words as possible. This immediate recall task was repeated three times. Following this, 5-min-short and 20-min-long delayed recall tasks were performed after the initial presentation.

Statistical analyses

All analyses were performed using the R software (version 4.1.1). Demographic data were summarized using means and SDs or percentages (%), whereas medians and interquartile ranges were employed for nonnormally distributed variables. After assessing the normality of the data, we conducted partial correlation analyses to examine the relationships among age, the ALPS index, and brain morphology. False discovery rate (FDR) correction was applied to multiple comparisons separately among the brain regions in the left hemisphere (LH) and right hemisphere (RH). Simple and chain mediation analyses were used to examine the mediating effect of the ALPS index on the relationships among aging, thinning of the LH EC, and memory decline. Bootstrap resampling was performed 5000 times to validate the reliability of the mediation effects in all the models. Statistical significance was determined at a threshold of $P < 0.05$ or when the 95% confidence interval (CI) did not encompass 0.

RESULTS

Demographic characteristics

The demographic characteristics of the participants in both the ADNI and the validation cohorts are detailed in Table 1. The ADNI cohort consisted of 313 CN older adults, with a mean age of 70.310 years (SD = 7.592), including 108 males (34.504%) and 205 females (65.495%). Most participants were right-handed (91.693%), with an average of 16.437 years of education (SD = 2.264) and a mean MMSE score of 29.051 (SD = 1.196), indicating generally preserved cognitive function. The validation cohort included 61 older adults with a mean age of 65.984 years (SD = 3.897) and a mean education level of 12.475 years (SD = 2.328), and all participants were right-handed. Like the ADNI cohort, the validation cohort included 19 males (31.148%) and 42 females (68.852%), with a median MMSE score of 30.

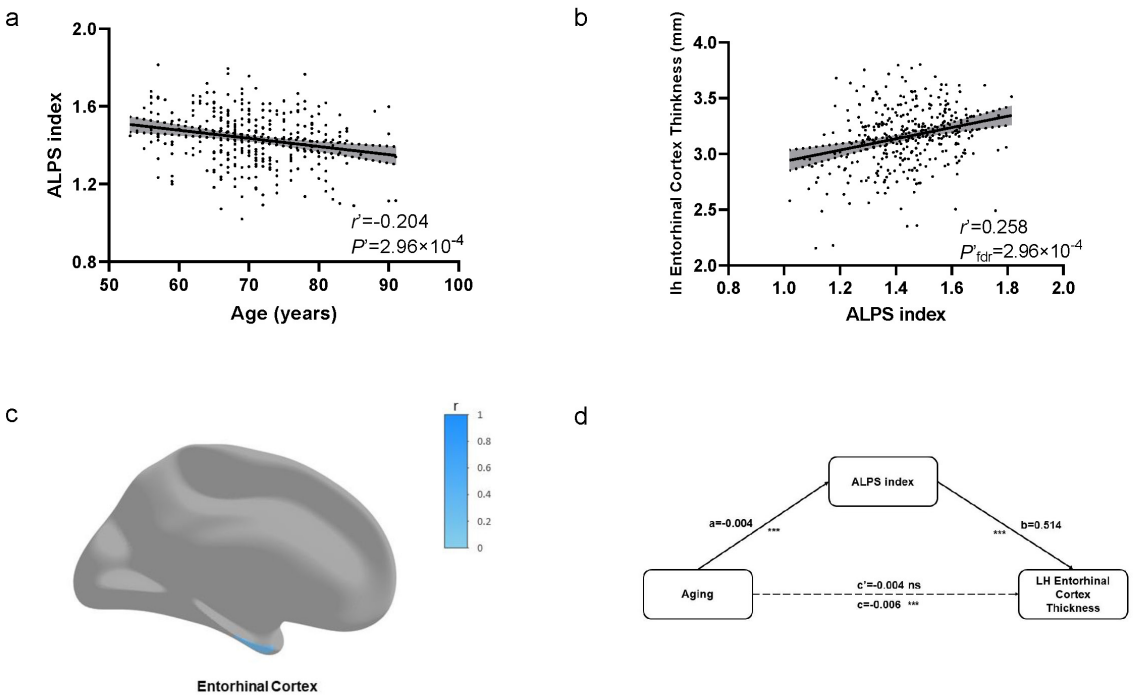

Figure 1: The associations among aging, the ALPS index, and entorhinal cortex thinning. (a) The ALPS index decreases with age. (b) The ALPS index is positively correlated with the thickness of the LH entorhinal cortex. (c) The ALPS index position of the LH entorhinal cortex in the Desikan-Killiany atlas. (d) ALPS index mediates the role of the ALPS index in the relationship between age and LH entorhinal cortex thinning. ALPS: analysis along the perivascular space; LH: left hemisphere. ***$P < 0.001$.

Exploring the associations between the ALPS index and aging and brain morphometry in the ADNI cohort

The mean ALPS index in the ADNI cohort was 1.434 (SD = 0.144). Figure 1a shows a significant negative correlation between the ALPS index and age (r = -0.204, $P = 2.96 \times 10^{-4}$). As shown in Figure 1b and c, further analysis revealed a significant positive correlation between the ALPS index and the cortical thickness of the LH EC (r = 0.258, $P_{FDR} = 2.96\ 10^{-4}$), with no other brain regions showing statistically significant correlations after correction (Table 2). Additionally, neither the cortical region surface area (Table S2) nor the subcortical region volume (Table S3) was associated with the ALPS index in older CN adults in the ADNI cohort.

In the ADNI cohort, the thickness of the LH EC was negatively correlated with age (r = -0.156, P = 0.006). We further explored the potential mediating role of the ALPS index in the relationship between age and LH EC thinning (Figure 1d). The results indicated that age-related decreases in the ALPS index (a = -0.004, $P = 2.96 \times 10^{-4}$) significantly mediated the thinning of the LH EC (b = 0.514, $P = 4.36 \times 10^{-6}$). In contrast, the direct effect of age on LH EC thickness was not statistically significant (c' = -0.004, P = 0.067) after adjusting for confounding variables. Bootstrap analysis (5000 resamples) revealed a significant indirect effect of age on LH EC thickness through the ALPS index (95% CI = [-3.67×10^{-3}, -7.38×10^{-4}]), suggesting that the decline in the ALPS index fully mediated the effect of age on LH EC thinning. The detailed results of the mediation model are provided in Table 3.

Validating the association between the ALPS index and brain morphometry in an independent sample

To verify the replicability of our results, we examined the relationship between the ALPS index and aging. As shown in Figure S2, the ALPS index was negatively correlated with age (r = -0.313, P = 0.016). The thickness of the LH EC was significantly associated with the ALPS index (r = 0.414, P_{FDR} = 0.042), as shown in Figure 2a and b. Additionally, as shown in Figure 2c and d, the ALPS index was significantly correlated with the thickness of another MTL region, the PHG (r = 0.494, P_{FDR} = 0.003). Multiple comparison corrections indicated that the ALPS index was not associated with cortical thickness in any other brain region (Table 2) or with the cortical surface area of any region (Table S2). Moreover, none of the volumes of the subcortical regions correlated with the ALPS index (Table S3). However, in the validation cohort, no statistically significant correlation was detected between age and the

Table 2: Correlations between the ALPS index and cortical thickness in the ANDI cohort and the validation cohort

Region	ADNI Cohort (N = 313)		Validation Cohort (N = 61)	
	r	P_{FDR}	r	P_{FDR}
LH Banks superior temporal sulcus	-0.024	0.897	0.049	0.785
LH Caudal anterior-cingulate cortex	0.081	0.628	0.162	0.451
LH Caudal middle frontal gyrus	-0.082	0.628	0.103	0.607
LH Cuneus cortex	-0.092	0.556	0.146	0.490
LH Entorhinal cortex	0.258	$2.96 \times 10^{-4***}$	0.414	0.042*
LH Frontal pole	-0.059	0.653	0.004	0.977
LH Fusiform gyrus	0.064	0.653	0.352	0.114
LH Inferior parietal cortex	-0.061	0.653	0.179	0.451
LH Inferior temporal gyrus	0.013	0.927	-0.030	0.877
LH Insula	0.064	0.653	0.180	0.451
LH Isthmus-cingulate cortex	0.029	0.897	0.130	0.538
LH Lateral occipital cortex	-0.055	0.653	0.172	0.451
LH Lateral orbital frontal cortex	-0.005	0.972	0.142	0.490
LH Lingual gyrus	-0.037	0.885	0.163	0.451
LH Medial orbital frontal cortex	0.027	0.897	0.188	0.451
LH Middle temporal gyrus	0.055	0.653	0.083	0.607
LH Parahippocampal gyrus	-0.022	0.897	0.308	0.211
LH Paracentral lobule	0.101	0.473	0.178	0.451
LH Pars opercularis	-0.042	0.828	-0.019	0.912
LH Pars orbitalis	-0.076	0.644	0.247	0.348
LH Pars triangularis	-0.011	0.927	0.093	0.607
LH Pericalcarine cortex	-0.106	0.473	-0.266	0.297
LH Postcentral gyrus	-0.040	0.844	0.217	0.387
LH Posterior-cingulate cortex	0.063	0.653	0.095	0.607
LH Precentral gyrus	-0.012	0.927	0.153	0.474
LH Precuneus cortex	-0.074	0.653	0.271	0.297
LH Rostral anterior cingulate cortex	0.024	0.897	0.236	0.363
LH Rostral middle frontal gyrus	-0.025	0.897	0.101	0.607
LH Superior frontal gyrus	-0.002	0.983	0.090	0.607
LH Superior parietal cortex	-0.131	0.425	0.224	0.387
LH Superior temporal gyrus	0.063	0.653	0.118	0.568
LH Supramarginal gyrus	-0.001	0.983	0.116	0.568
LH Temporal pole	0.071	0.653	0.167	0.451
LH Transverse temporal cortex	0.099	0.473	0.083	0.607
RH Banks superior temporal sulcus	0.025	0.897	-0.109	0.546
RH Caudal anterior-cingulate cortex	0.117	0.425	0.150	0.520
RH Caudal middle frontal gyrus	-0.010	0.927	0.133	0.520
RH Cuneus cortex	-0.063	0.653	0.149	0.520
RH Entorhinal cortex	0.085	0.612	0.278	0.258
RH Frontal pole	-0.043	0.828	-0.047	0.816
RH Fusiform gyrus	0.035	0.885	0.273	0.258

(To be continued)

(Continued)

RH Inferior parietal cortex	-0.011	0.927	0.124	0.546
RH Inferior temporal gyrus	-0.016	0.925	0.200	0.498
RH Insula	0.103	0.473	0.139	0.520
RH Isthmus-cingulate cortex	-0.044	0.828	0.133	0.520
RH Lateral occipital cortex	-0.089	0.576	0.227	0.371
RH Lateral orbital frontal cortex	0.120	0.425	0.160	0.520
RH Lingual gyrus	-0.060	0.653	0.172	0.520
RH Medial orbital frontal cortex	-0.055	0.653	0.009	0.978
RH Middle temporal gyrus	0.022	0.897	-0.001	0.997
RH Parahippocampal gyrus	-0.027	0.897	0.494	0.003**
RH Paracentral lobule	0.062	0.653	0.106	0.546
RH Pars opercularis	0.063	0.653	-0.135	0.520
RH Pars orbitalis	0.032	0.897	0.057	0.787
RH Pars triangularis	-0.012	0.927	-0.014	0.977
RH Pericalcarine cortex	-0.136	0.425	-0.136	0.520
RH Postcentral gyrus	-0.077	0.644	0.105	0.546
RH Posterior-cingulate cortex	0.115	0.425	0.144	0.520
RH Precentral gyrus	0.008	0.945	0.138	0.520
RH Precuneus cortex	-0.004	0.972	0.331	0.189
RH Rostral anterior cingulate cortex	0.021	0.897	-0.044	0.816
RH Rostral middle frontal gyrus	-0.034	0.885	0.111	0.546
RH Superior frontal gyrus	0.020	0.897	0.115	0.546
RH Superior parietal cortex	-0.124	0.425	0.242	0.358
RH Superior temporal gyrus	0.028	0.897	0.181	0.520
RH Supramarginal gyrus	0.018	0.918	0.293	0.258
RH Temporal pole	0.101	0.473	0.237	0.358
RH Transverse temporal cortex	0.056	0.653	0.090	0.612

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. ADNI: Alzheimer's Disease Neuroimaging Initiative; FDR: false discovery rate; LH: left hemisphere; RH: right hemisphere.

thickness of the LH EC (r = -0.156, P = 0.238) or the thinning of the RH PHG (r = -0.001, P = 0.999).

Exploring the associations among the ALPS index, LH EC thinning, and aging-related memory decline in the ADNI cohort

We explored the memory decline characteristics associated with aging in the ADNI cohort, and, after adjusting for confounding variables, age was significantly associated with indicators including N_3, R_3, M_2, and M_3, which all reflected levels of durable memory storage (Figure S3a, d-f). In addition, N_4 and R_1 also decreased with aging (Figure S3b and c). We subsequently analyzed the relationship between the ALPS index and aging-related durable memory decline. As shown in Figure S4a, partial correlation analysis indicated that the ALPS index was significantly and robustly correlated with the memory indices M_3 (r = 0.151, P = 0.028). Moreover, the correlation analysis suggested that the ALPS index might also be associated with the memory indices N_3 (r = 0.220, P = 0.001), R_3 (r = 0.175, P = 0.010), and M_2 (r = 0.231, P = 0.001, Figure S4b-d). Additionally, our analyses revealed that the thickness of the LH EC was significantly correlated with N_3 (r = 0.146, P = 0.033), R_3 (r = 0.139, P = 0.042), M_2 (r = 0.162, P = 0.018), and M_3 (r = 0.188, P = 0.006), collectively representing all indices associated with durable memory storage (Figure S5a-d).

We conducted chain mediation analyses adjusted for confounding variables to further understand the relationships among age, the ALPS index, LH EC thickness, and durable memory ability. As shown in Figure 3, the direct effects of age on M_2 (c' = -1.03 × 1 0^{-3}, P = 0.100) and M_3 (c' = -1.34 × 10^{-3}, P = 0.060) were not statistically significant. In contrast, the indirect effects, as mediated

Table 3: Bootstrap mediating effects of the ALPS index on age, LH EC thickness, and memory decline in the ADNI cohort

Characteristic	Pathway	Effect	Bootstrap 95% CI	
			LLCI	ULCI
LH EC thickness				
Total effect	Aging→LH EC thickness	-5.81×10^{-3}	-9.96×10^{-3}	-1.67×10^{-3}
Direct effect	Aging→LH EC thickness	-3.83×10^{-3}	-7.92×10^{-3}	2.66×10^{-4}
Indirect effect	Aging→the ALPS index→LH EC thickness	-1.99×10^{-3}	-3.67×10^{-3}	-7.38×10^{-4}
M_2				
Total effect	Aging→M_2	-1.66×10^{-3}	-2.82×10^{-3}	-4.92×10^{-4}
Direct effect	Aging→M_2	-1.03×10^{-3}	-2.27×10^{-3}	2.00×10^{-4}
Total indirect effect		-6.21×10^{-4}	-1.10×10^{-3}	-2.43×10^{-4}
Indirect effect 1	Aging→the ALPS index→M_2	-2.04×10^{-4}	-5.54×10^{-4}	6.88×10^{-5}
Indirect effect 2	Aging→LH EC thickness→M2	-3.37×10^{-4}	-7.59×10^{-4}	-4.64×10^{-5}
Indirect effect 3	Aging→the ALPS index→LH EC thickness→M_2	-7.98×10^{-5}	-1.97×10^{-4}	-1.09×10^{-5}
M_3				
Total Effect	Aging→M_3	-2.17×10^{-3}	-3.50×10^{-3}	-8.42×10^{-4}
Direct Effect	Aging→M_3	-1.34×10^{-3}	-2.74×10^{-3}	5.86×10^{-4}
Total indirect effect		-8.29×10^{-4}	-1.39×10^{-3}	-3.77×10^{-4}
Indirect effect	Aging→the ALPS index→M_3	-2.81×10^{-4}	-6.76×10^{-4}	4.74×10^{-5}
	Aging→LH EC thickness→M_3	-4.46×10^{-4}	-9.32×10^{-4}	-1.03×10^{-4}
	Aging→the ALPS index→LH EC thickness→M_3	-1.05×10^{-4}	-2.31×10^{-4}	-2.09×10^{-5}

ALPS: analysis along the perivascular space; LH: left hemisphere; EC: entorhinal cortex; CI: confidence interval; LLCI: lower level of confidence interval; ULCI: upper level of confidence interval.

by the ALPS index and LH EC thickness, were found to be significant for age and M_2 (indirect effect [IE] = -6.21×10^{-4}, 95% CI = [-1.10×10^{-3},-2.43×10^{-4}]) and M_3 (IE = -8.29×10^{-4}, 95% CI = [-1.39×10^{-3},-3.77×10^{-4}]). Importantly, the ALPS index did not directly impact M_2 (b_1 = 0.040, P = 0.196) or M_3 (b_1 = 0.055, P = 0.117); instead, it was mediated by the influence on LH EC thickness (M_2, b_2 = 0.030, P = 0.049; M_3, b_2 = 0.040, P = 0.006). The specific bootstrap analyses of the chain mediation models are summarized in Table 3.

In addition, as shown in Figure S6a and b, the mediation models indicated that the ALPS index and LH EC thickness also partially mediated the impact of aging on N_3 (37.410%) and R_3 (38.203%). The detailed results of the mediation models are presented in Table S4. These findings highlighted the significant mediating effects of the ALPS index and LH EC thickness on aging and durable memory decline.

Validating the association between the ALPS index and aging-related memory decline in an independent sample

In our independently recruited cohort of CN older adults, the 5-min (r = -0.303, P = 0.020) and 20-min (r = -0.266, P = 0.042) delayed recall scores on the AVLT-H decreased with age (Figure S7a and b), which also represented long-term memory ability. Moreover, immediate recall performance was not significantly associated with age, as shown in Table S5. Additionally, the ALPS index was also positively correlated with the 5-min (r = 0.491, P = 9.271×10^{-5}) and 20-min (r = 0.564, P = 3.959×10^{-6}) delayed recall performances, as shown in Figure S8a and b.

We subsequently examined the mediating role of the ALPS index and aging-related memory decline. As shown in Figure 4, the ALPS index indirectly mediated the effects of the 5-min delayed recall (c' = -0.080, P = 0.213) and 20-min delayed recall (c' = -0.051, P = 0.452) tasks. The mediating role of the ALPS index in aging and memory decline was also validated; the chain models are summarized in detail in Table 4.

DISCUSSION

In this study, we leveraged the ALPS index and SBM methods to investigate the relationship between glymphatic function and brain morphometry in aging. Our findings suggest that the ALPS index mediated core memory-related brain structure atrophy during normal aging.

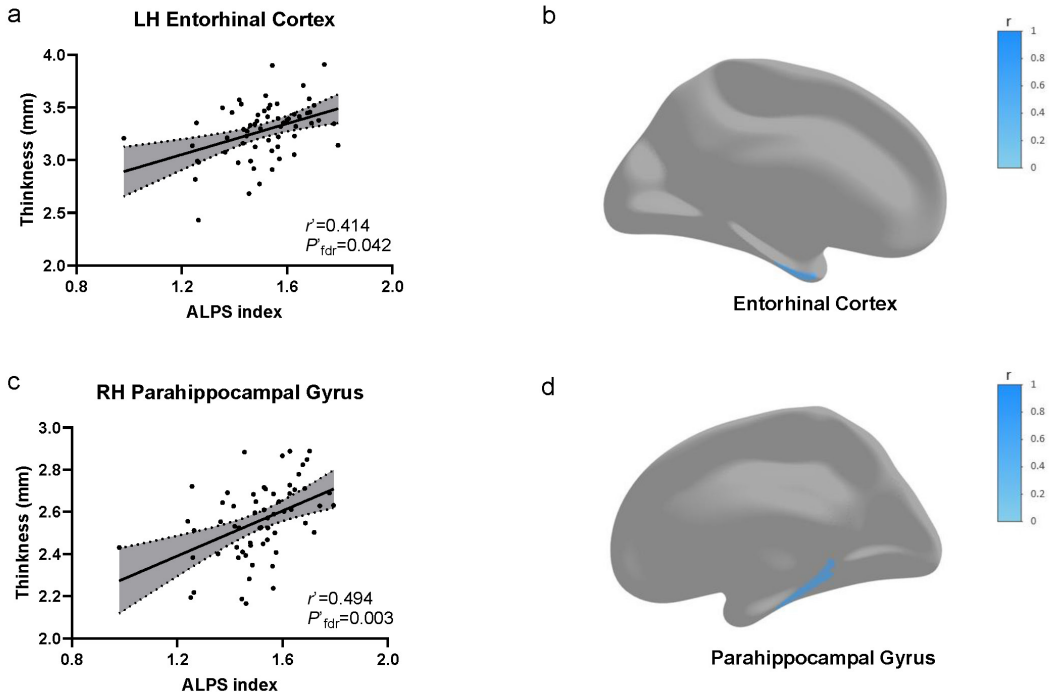

Figure 2: Validation of the association between the ALPS index and entorhinal cortex thickness in older people in our recruited cohort. (a-b) The analysis along the perivascular space (ALPS) index is positively correlated with the thickness of the left hemisphere (LH) entorhinal cortex. (c-d) The ALPS index is positively correlated with the thickness of the right hemisphere (RH) parahippocampal gyrus.

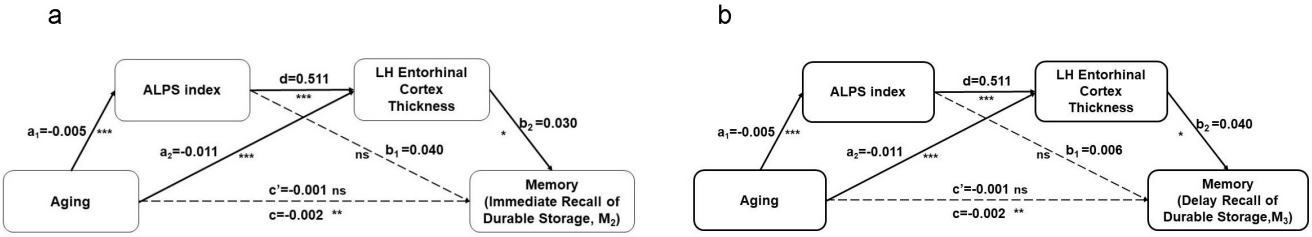

Figure 3: The role of the ALPS index and entorhinal cortex thickness in mediating memory decline and aging. (a-b) The mediating effects of analysis of the perivascular space (ALPS) index and left hemisphere (LH) entorhinal cortex thickness were significant for age and M_2 and M_3. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

The DTI-ALPS method has overcome the limitations of invasive approaches, thereby enabling widespread use of the ALPS index to study age-related changes in glymphatic function. Negative correlations between the ALPS index and age have been reported in an increasing number of studies involving nondementia elderly populations.[10,23-25] These findings align with the broader understanding of glymphatic dysfunction during aging, which is characterized by a reduction in the vessel wall pulsatility of the intracortical arterioles, widespread loss of perivascular aquaporin-4 polarization along the penetrating arteries, and a significant decline in cerebrospinal fluid (CSF) lymphatic outflow.[4,5] At the same time, older adults generally experience decreased sleep quality and reduced slow-wave sleep recorded *via* polysomnography,[26] which severely hinders the efficiency of interstitial fluid (ISF)-CSF exchange and waste clearing during sleep.[27]

The gradual glymphatic system degeneration in aging leads to waste accumulation, synaptic dysfunction, and neuronal damage, which might be drivers of brain atrophy and cognitive decline.[6] Similar to our findings, the ALPS index has been shown to be correlated with subjective cognitive complaints as well as overall cognitive function in nondementia populations.[28] Furthermore, a longitudinal study in cognitively normal aging populations revealed that a higher ALPS index was a protective factor against global cognitive decline in normal aging.[24] Several studies have

Table 4: Bootstrap mediating effects of the ALPS index on aging and memory decline in the validation cohort

Characteristic	Pathway	Effect	Bootstrap 95% CI	
			LLCI	ULCI
AVLT-H				
5-min delayed recall				
Total effect	Aging→5-min delayed recall	-0.156	-0.287	-0.026
Direct effect	Aging→5-min delayed recall	-0.076	-0.197	0.045
Indirect effect	Aging→the ALPS index→5-min delayed recall	-0.080	-0.175	-0.015
20-min delayed recall				
Total effect	Aging→20-min delayed recall	-0.160	-0.314	-0.006
Direct effect	Aging→20-min delayed recall	-0.051	-0.186	0.084
Indirect effect	Aging→the ALPS index→20-min delayed recall	-0.109	-0.224	-0.026

AVLT-H: auditory verbal learning test-Huashan; ALPS: analysis along the perivascular space; CI: confidence interval; LLCI: lower level of confidence interval; ULCI: upper level of confidence interval.

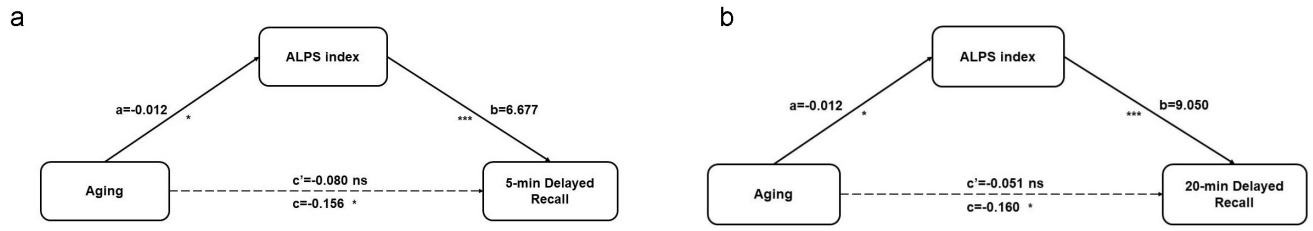

Figure 4: Validation of the role of the ALPS index in mediating memory decline and aging. The mediating effect of the ALPS index was significant for age and performance on the AVLT-H 5-min and 20-min delayed recall tests. ALPS: analysis along the perivascular space; AVLT-H: auditory verbal learning test-Huashan. *$P < 0.05$; ***$P < 0.001$.

investigated the neuroimaging mechanisms underlying the relationship between the ALPS index and cognitive aging, both in terms of overall and subjective cognitive function. For example, Siow *et al.* reported that a higher ALPS index is associated with greater gray matter volume in regions such as the hippocampus and thalamus, although gray matter atrophy was only linked to subjective cognitive complaints.[10] Similarly, Chang *et al.* reported correlations between the ALPS index and gray matter volumes in the amygdala-hippocampus complex and cerebellum, with the amygdala volume specifically associated with mental manipulation function.[29] More recently, a study highlighted that the ALPS index is linked to functional and structural connectivity involving the PHG and middle temporal gyrus, with connectivity coupling also tied to subjective cognitive function.[30] Our study further explored the mechanisms by which the ALPS index mediates core memory region atrophy during aging, which results in objective durable and delayed memory decline.

According to studies by Eide's team, using dynamic contrast-enhanced MRI, they observed that gadolinium-based contrast agents, after entering the brain *via* large arteries, preferentially accumulated in deep brain regions (such as the mediobasal frontal cortex, cingulate cortex, insular cortex, and limbic structures including the MTL) and exhibited significantly prolonged retention.[31,32] This dynamic distribution pattern of the contrast agents suggests that the clearance efficiency of the glymphatic system in deep brain regions may be limited, consequently, metabolic waste may become trapped in the tortuous extracellular spaces of these regions, leading to localized neurotoxic reactions.[6] The human MTL, which involves the parahippocampal cortices and hippocampus, is critically involved in episodic memory.[33] The perirhinal cortex receives object information and transfers it to the lateral EC, while the PHG receives spatial information and transfers it to the medial EC. Meanwhile, the EC is recognized as a critical hub in the MTL; it connects the hippocampus with the neocortex and transfers and integrates information between these regions.[34] As has been shown, the LH EC is significantly activated during verbal memory tasks, whereas the RH PHG is more involved in nonverbal memory tasks.[35] This functional specificity of the MTL may be accompanied by excessive regional metabolic productions,

thereby leading to the vulnerablility to the glymphatic dysfunction. Notably, the thinning process of the EC appears to be faster in the RH compared to the LH during normal aging.[36,37] The preservation of the LH MTL might be a protective and compensatory rather than a destructive process in maintaining cognitive homeostasis under genetic control.[38,39] However, our research findings indicated that subjects with a lower ALPS index score exhibited thinner LH EC thickness and poorer objective memory performance. This suggests that glymphatic dysfunction may adversely impact the preservation of cognitive function. Fortunately, emerging evidence highlights the potential for interventions that enhance glymphatic function, thereby offering promising avenues to mitigate cognitive decline.[40] In addition, the ALPS index seemed to have no correlation with transient memory performance, which is predominantly governed by the prefrontal cortex rather than the MTL.[41] As pointed out in previous studies, the degeneration of the glymphatic system occurs to a relatively limited extent during normal aging,[42,43] and this level of degeneration might be insufficient to induce broad cortex changes and significant transient memory decline.

Nevertheless, we should note that our current results should be interpreted with caution, as the FreeSurfer estimation of cortical thickness in the parahippocampal regions is often considered suboptimal.[44] According to a study of older (mean age 68.1 years) subjects with posttraumatic stress disorder, the ALPS index was found to have a statistically significant association with cortical thickness in the LH EC, PHG, and fusiform gyrus, but it was significantly correlated with the cortical mean diffusivity (a novel and more sensitive biomarker to cortical structure) in the bilateral parahippocampal cortices.[45] Thus, the impact of glymphatic system degeneration on cortical microstructure might be overlooked in the older adults. Second, the MRI data within the ADNI dataset originated from multiple centers and scanners, which could give rise to variations. In an effort to alleviate the influence of scanner variability, we incorporated a validation cohort that was scanned using a single scanner and consistent imaging parameters. However, in our smaller, independent validation cohort, we found no association between age and the thickness of the LH EC and RH PHG. A plausible explanation is that the cortical thickness of both the EC and PHG displays significant interindividual variability.[44] The limited sample size and narrow age range of our validation cohort might also have compromised our statistical power to identify age-related associations in these specific regions. We look forward to future studies with larger sample sizes to verify these findings. Additionally, further research is required to elucidate the mechanisms underlying the heightened susceptibility of the parahippocampal cortices to glymphatic system dysfunction.

CONCLUSION

This study highlights the ALPS index as a promising biomarker for glymphatic function by demonstrating its connection to core memory-related brain structure atrophy in aging. Additionally, the research points to glymphatic dysfunction as a potential therapeutic target for mitigating age-related memory impairments and offers new avenues for both future investigations and clinical strategies aimed at preserving cognitive health in aging populations.

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Author Contributions

Lin Lu: Conceptualization. Xiao Lin: Conceptualization. Peng Li: Conceptualization. Shan Chong: Writing – Original draft, Data curation, Validation, Formal analysis. Sanwang Wang: Data curation, Validation, Formal analysis. Yong Han: Formal analysis. Teng Gao: Resources. Kai Yuan: Resources. Le Shi: Resources. Alzheimer's Disease Neuroimaging Initiative collected and shared clinical and neuroimaging data of older adults. All authors have seen and approved the final version of the manuscript being submitted.

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Ethical Approval

The ADNI received approval from the institutional review boards from each participating center and complied with the provisions. The validation cohort was a secondary analysis of a clinical trail conducted in the Peking University Sixth Hospital, the original research protocol of which was approved by the Ethics Committee of the Peking University Sixth Hospital (PekingUSH20231027). Informed consent statement for tha ADNI cohort has been described in the original articles.

Informed Consent

All participants of the validation cohort were recruited

voluntarily and provided written informed consents.

Conflict of Interest

The authors report no biomedical financial interests or potential conflicts of interest.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

The ADNI cohort data are available to researchers who apply with a ADNI data request (https://adni.loni.usc.edu/data-samples/adni-data/#AccessData). The depersonalized data of the validation cohort are available from the corresponding author Lin Lu (linlu@bjmu.edu.cn) upon reasonable request.

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