

Glymphatic dysfunction shapes non-memory cognitive impairment in Alzheimer's disease

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Introduction

- Glymphatic dysfunction has been increasingly implicated in Alzheimer's disease (AD), but its association with regional amyloid burden and cognitive dysfunction remains unclear.

Materials & Methods

- We analyzed 149 patients with amyloid-positive AD. The ALPS index derived from diffusion MRI and lobar amyloid burden measured by FBB PET were examined in relation to cognitive domains. General linear models were used to investigate the effects of ALPS and parietal FBB uptake on cognitive scores after controlling for age, sex, education, APOE4 carrier status, and intracranial volume.

Results

Table 1. Demographic and clinical features of participants

	AD ^{SCD} (N=31)	AD ^{MCI} (N=58)	AD ^{Dementia} (N=60)	P
Age	71.7 ± 7.3	71.8 ± 7.2	74.3 ± 7.4	0.115
Female, N (%)	26 (83.9%)	42 (72.4%)	41 (68.3%)	0.281
Education	10.7 ± 5.7	11.7 ± 4.9	9.8 ± 4.9	0.138
APOE4, N (%)	20 (64.5%)	34 (58.6%)	18 (30%)	0.435
MMSE	28.0 ± 1.9 ^{a,b}	25.8 ± 2.3 ^{a,c}	19.5 ± 4.3 ^{b,c}	<0.001
ALPS	1.4 ± 0.2	1.4 ± 0.2 ^c	1.3 ± 0.2 ^c	0.005
Global FBB uptake	1.5 ± 0.2 ^b	1.6 ± 0.2 ^c	1.8 ± 0.3 ^{b,c}	<0.001
Frontal FBB uptake	1.5 ± 0.2 ^b	1.7 ± 0.3 ^c	1.8 ± 0.3 ^{b,c}	<0.001
Parietal FBB uptake	1.5 ± 0.2 ^b	1.7 ± 0.2 ^c	1.8 ± 0.3 ^{b,c}	<0.001
Occipital FBB uptake	1.4 ± 0.2 ^b	1.5 ± 0.2	1.6 ± 0.3 ^b	0.002
Temporal FBB uptake	1.4 ± 0.2 ^b	1.6 ± 0.2 ^c	1.7 ± 0.3 ^{b,c}	<0.001

Data are expressed as means ± standard deviations for continuous variables and as numbers (%) for categorical variables. Three-group comparisons were performed using ANOVA or chi-square tests, as appropriate. Superscripts indicate significant pairwise differences: a, AD^{SCD} vs. AD^{MCI}; b, AD^{SCD} vs. AD^{Dementia}; c, AD^{MCI} vs. AD^{Dementia}. Abbreviations: AD, Alzheimer's disease; ALPS, Diffusion tensor imaging-based analysis along the perivascular space; FBB, florbetaben

Table 2. Factors associated with ALPS

Predictors	Frontal lobe		Parietal lobe		Occipital lobe		Temporal lobe	
	β	P	β	P	β	P	β	P
Age	-0.39	<0.001	-0.39	<0.001	-0.40	<0.001	-0.39	<0.001
Sex	-0.20	0.017	-0.19	0.022	-0.19	0.022	-0.19	0.024
Education	0.18	0.012	0.17	0.013	0.17	0.017	0.18	0.012
APOE4	0.08	0.225	0.07	0.325	0.05	0.490	0.06	0.362
FBB uptake	-0.15	0.026	-0.18	0.007	-0.12	0.093	-0.12	0.084

Results are based on general linear regression models of ALPS, adjusted for age, sex, education, APOE4 carrier status, intracranial volume, and lobar FBB uptake. False discovery rate correction was applied for multiple comparisons across four lobar analyses.

Table 3. Effect of ALPS and parietal FBB on cognition

	Model 1 (Univariable analyses)				Model 2 (Multivariable analyses)			
	ALPS		Parietal FBB		ALPS		Parietal FBB	
	β	P	β	P	β	P	β	P
Attention								
Digit span backward	0.15	0.161	-0.23	0.007	0.10	0.375	-0.19	0.035
Language								
K-BNT	0.16	0.151	-0.13	0.118	0.13	0.255	-0.10	0.266
Visuospatial								
RCFT copy	0.42	<0.001	-0.24	0.003	0.37	<0.001	-0.16	0.043
Memory								
SVLT delayed recall	0.14	0.202	-0.30	<0.001	0.06	0.566	-0.26	0.003
RCFT delayed recall	0.20	0.061	-0.34	<0.001	0.12	0.273	-0.30	0.001
Executive								
COWAT supermarket	0.24	0.027	-0.35	<0.001	0.14	0.163	-0.31	<0.001
COWAT phonemic	0.30	0.005	-0.19	0.020	0.26	0.018	-0.13	0.127
TMT part A	0.34	0.001	-0.18	0.027	0.30	0.004	-0.12	0.157

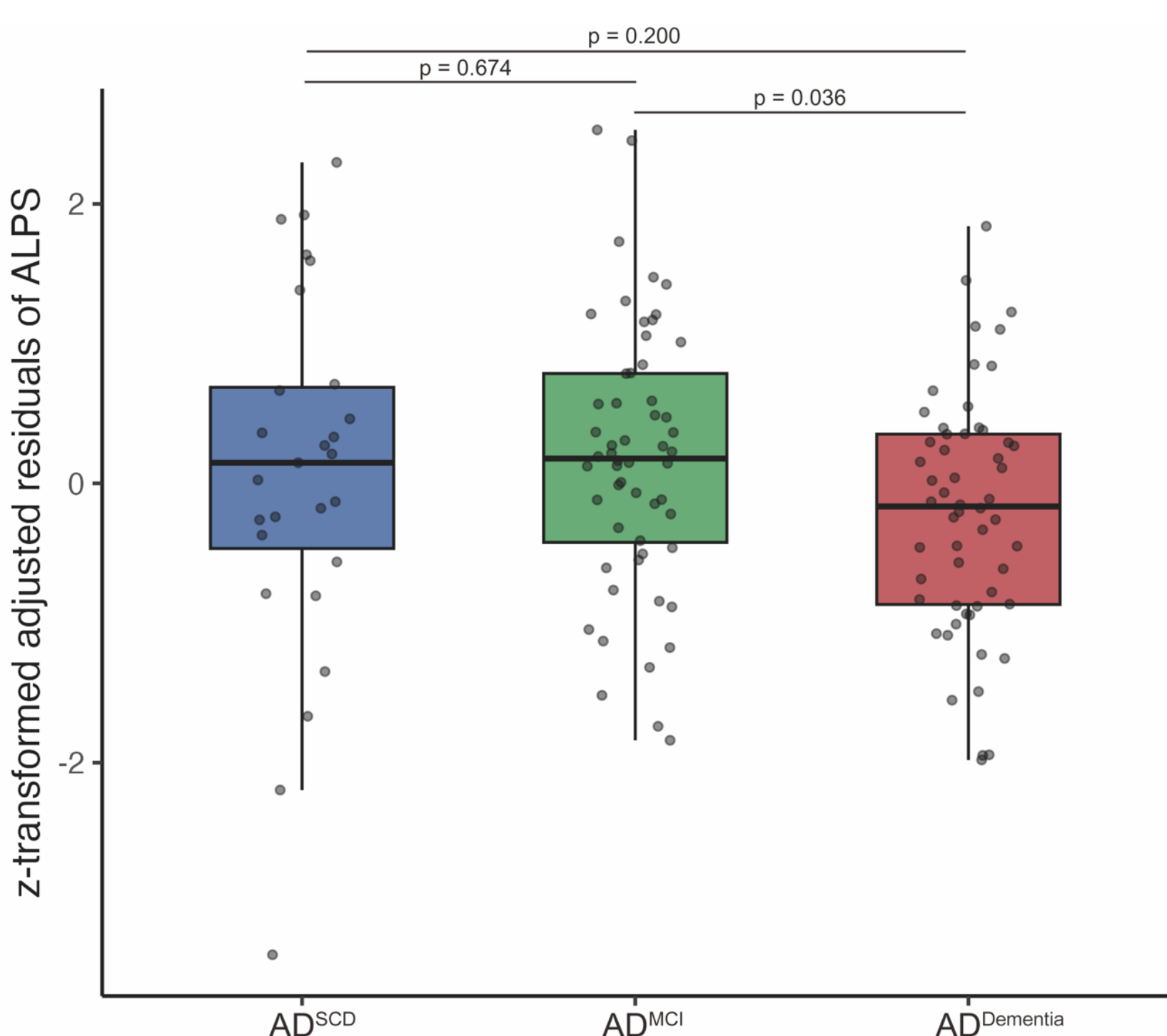
Results are based on general linear regression models of cognitive outcomes using ALPS and parietal FBB uptake as predictors, adjusted for age, sex, education, APOE4 carrier status, and intracranial volume. In Model 1, ALPS and parietal FBB uptake were entered separately. In Model 2, both predictors were included simultaneously to assess their independent effects. False discovery rate (FDR) correction was applied for multiple comparisons across eight cognitive tests.

Table 4. Interaction effects of APOE4 with ALPS and parietal FBB uptake on cognition

	Model 1								Model 2							
	ALPS		Parietal FBB		APOE4		APOE4×ALPS		ALPS		Parietal FBB		APOE4		APOE4×Parietal FBB	
	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P
Attention																
Digit span backward	-0.22	0.169	-0.14	0.101	-1.75	0.009	1.84	0.008	0.09	0.403	-0.08	0.582	0.60	0.288	-0.58	0.314
Language																
K-BNT	0.06	0.720	-0.09	0.322	-0.31	0.647	0.39	0.577	0.12	0.292	0.10	0.462	1.08	0.052	-1.05	0.065
Visuospatial																
RCFT copy	0.27	0.076	-0.15	0.067	-0.54	0.384	0.57	0.368	0.36	<0.001	-0.05	0.690	0.59	0.250	-0.60	0.256
Memory																
SVLT delayed recall	-0.08	0.610	-0.24	0.006	-0.85	0.204	0.82	0.225	0.05	0.647	0.00	0.980	1.30	0.016	-1.39	0.012
RCFT delayed recall	0.11	0.493	-0.30	0.001	-0.11	0.872	0.06	0.930	0.11	0.299	-0.16	0.220	0.62	0.244	-0.70	0.203
Executive																
COWAT supermarket	0.04	0.796	-0.30	<0.001	-0.50	0.426	0.60	0.352	0.14	0.183	-0.18	0.154	0.72	0.167	-0.66	0.213
COWAT phonemic	0.13	0.416	-0.12	0.191	-0.59	0.382	0.74	0.279	0.26	0.019	-0.10	0.482	0.31	0.569	-0.19	0.742
TMT part A	0.17	0.263	-0.10	0.233	-0.72	0.262	0.73	0.263	0.29	0.005	0.08	0.518	1.01	0.052	-1.06	0.053

Results are based on general linear regression models of cognitive outcomes using ALPS and parietal FBB uptake as predictors, adjusted for age, sex, education, APOE4 carrier status, and intracranial volume. In Model 1, an interaction term between ALPS and APOE4 status (ALPS × APOE4) was included. In Model 2, an interaction term between parietal FBB uptake and APOE4 status (FBB × APOE4) was included. Standardized regression coefficients (β) and corresponding p-values are presented.

Figure 1. Group comparison of ALPS



Boxplots with individual data points show z-transformed residuals of ALPS after adjusting for age, sex, education, intracranial volume, and APOE4 status. Residuals were derived from a linear regression model excluding disease stage.

Figure 3. Mediation analysis

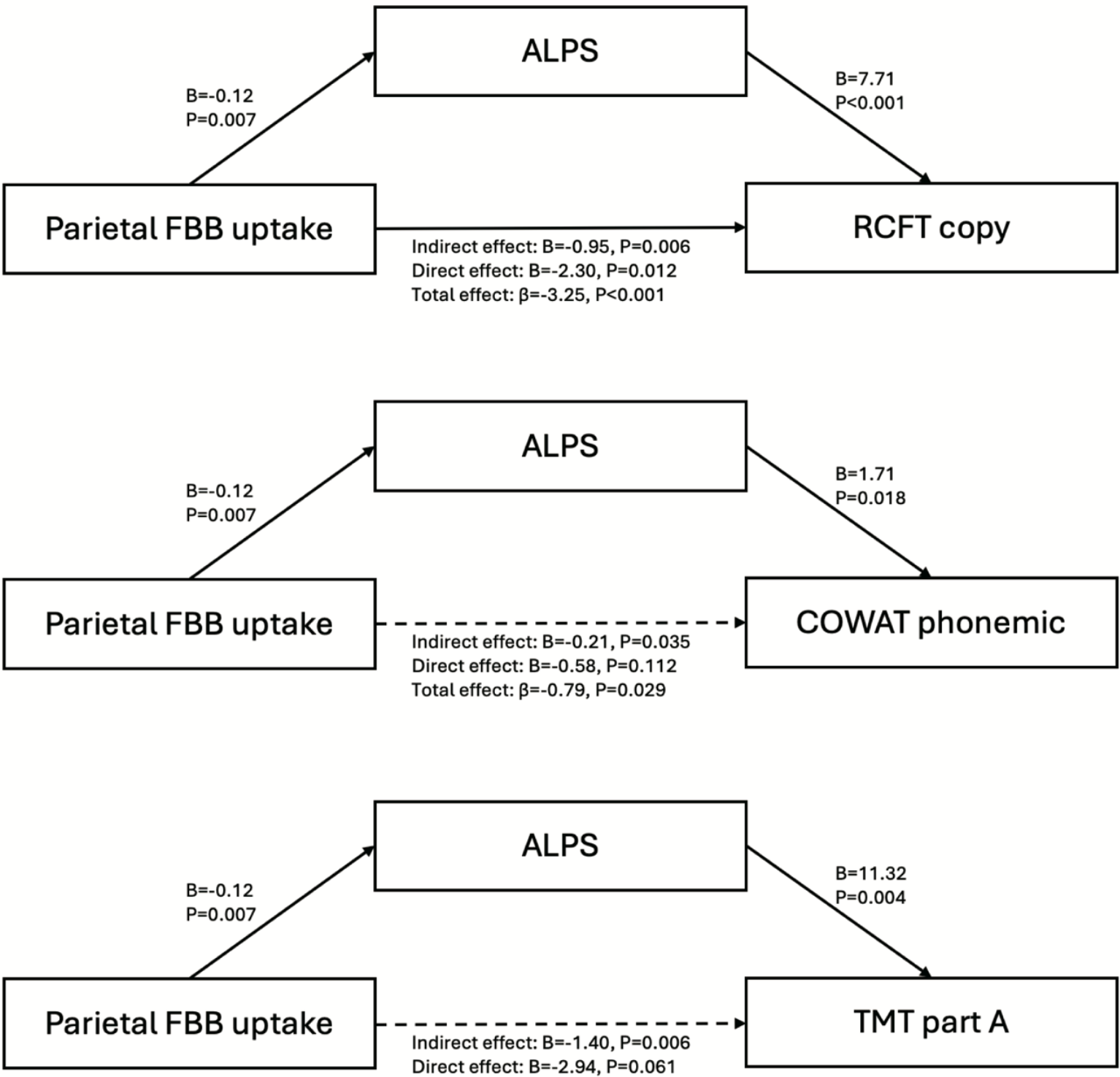
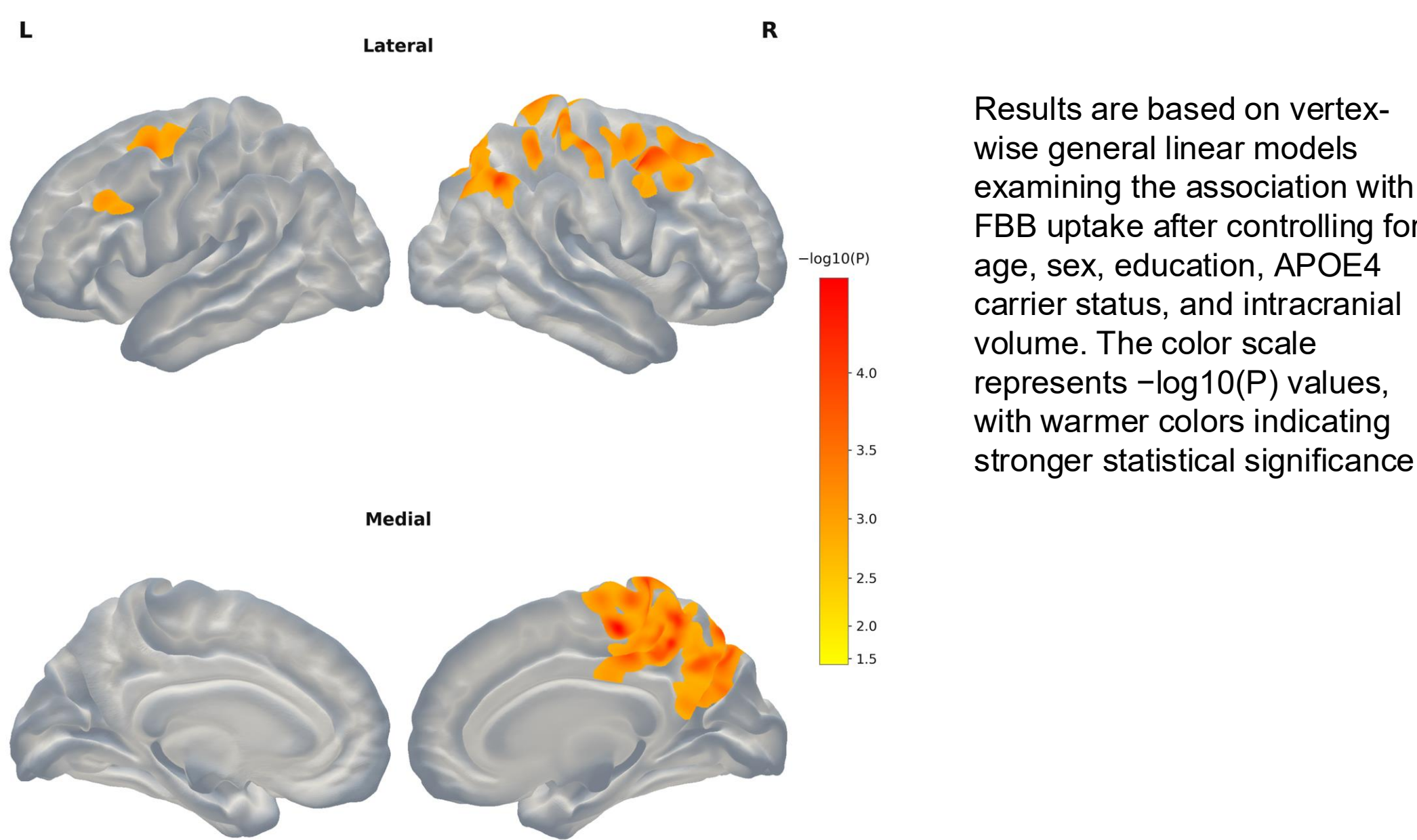


Figure 2. Association between ALPS and amyloid uptake

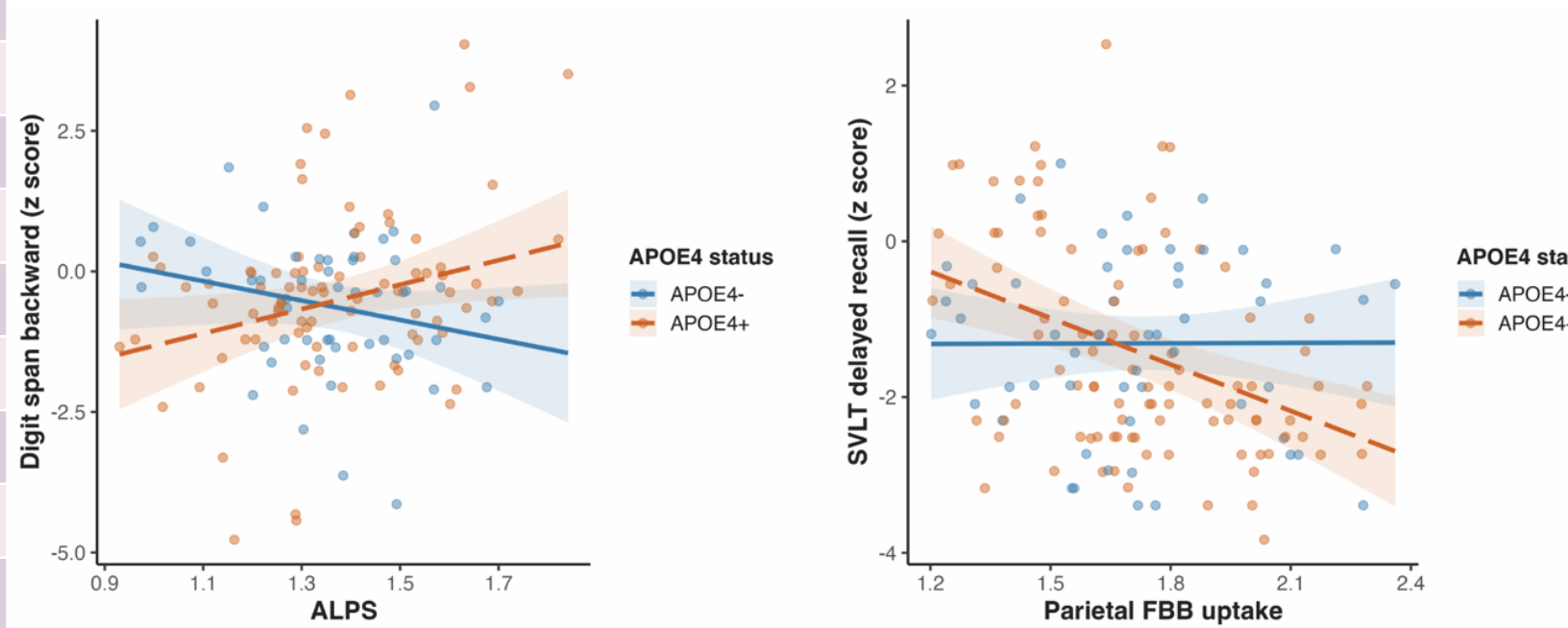


Main findings

- Table 2 & Figure 2** → lower ALPS index was specifically associated with higher parietal FBB uptake
- Table 3** → ALPS was independently associated with visuospatial and frontal/executive functions, while parietal FBB uptake was independently associated with memory and semantic fluency.
- Figure 3** → ALPS mediated the effect of parietal FBB uptake on visuospatial and frontal/executive functions
- Table 4 & Figure 4** → APOE4 status and ALPS synergistically influenced attention, whereas APOE4 and parietal FBB uptake synergistically affected verbal memory.

Conclusion: Glymphatic dysfunction, as reflected by the ALPS index, contributes to non-amnestic cognitive impairment in AD by mediating the impact of parietal amyloid burden on visuospatial and executive functions, while synergistically interacting with APOE4 status to influence attentional performance.

Figure 4. Interaction of APOE4 with ALPS and parietal FBB uptake on cognition



Interaction plots showing the associations of ALPS (left) and parietal FBB uptake (right) with cognitive performance, stratified by APOE4 carrier status. Lines represent fitted regression slopes from linear models adjusted for age, sex, education, and intracranial volume, with shaded areas indicating 95% confidence intervals.