

The Mediating Effect of Glymphatic Efficiency on the Relationship Between Choroid Plexus Volume and Cognition in Alzheimer’s Disease



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In Alzheimer’s disease, **enlarged choroid plexus** is associated with **poorer glymphatic clearance** and **worse cognition**. Glymphatic dysfunction may partially mediate this relationship, highlighting both as promising biomarkers for dementia detection.

Introduction

The choroid plexus (CP) supports the glymphatic system by secreting CSF which facilitates the clearance of neurotoxins, including amyloid-β and Tau implicated in Alzheimer’s disease (AD). Although enlarged CP and impaired glymphatic function has been associated with cognitive impairment and decline, the mediators of the association are not yet fully understood in mild cognitive impairment (MCI) and AD. Here, we investigated the associations between CP and glymphatic efficiency and its effect on cognition.

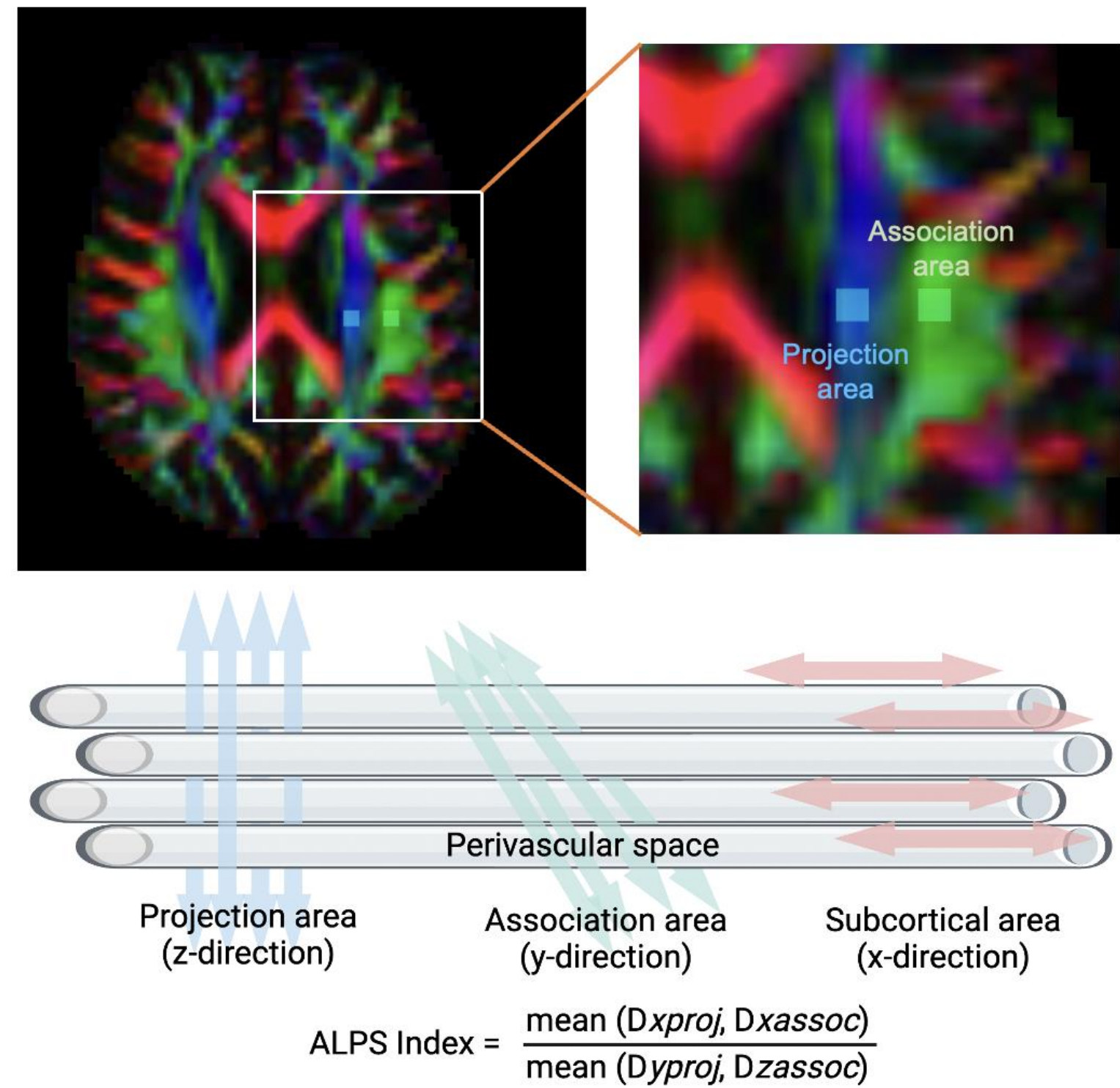


Figure 1. ROIs were marked on an axial slice at the level of the body of the lateral ventricle. Each ROI comprised 4 voxels placed in a square, constituting 12.17mm³. Two ROIs were drawn per hemisphere in the projection and association area.

Methods

100 patients were recruited from the memory clinics at the National Neuroscience Institute, Singapore, and grouped into AD (n=46) and non-AD (n=54) according to published Plasma pTau217 cut-offs. pTau217 was measured using SIMOA AlzAPath. 3-Tesla DTI-MRI data, color FA map was generated and used to mark regions of interest for Diffusion Tensor Image Analysis ALong the Perivascular Space (DTI-ALPS) index calculation (**Fig. 1**). CP volume normalised to estimated Total Intracranial Volume was derived from T1-weighted images processed through Fastsurfer (**Fig. 2**).

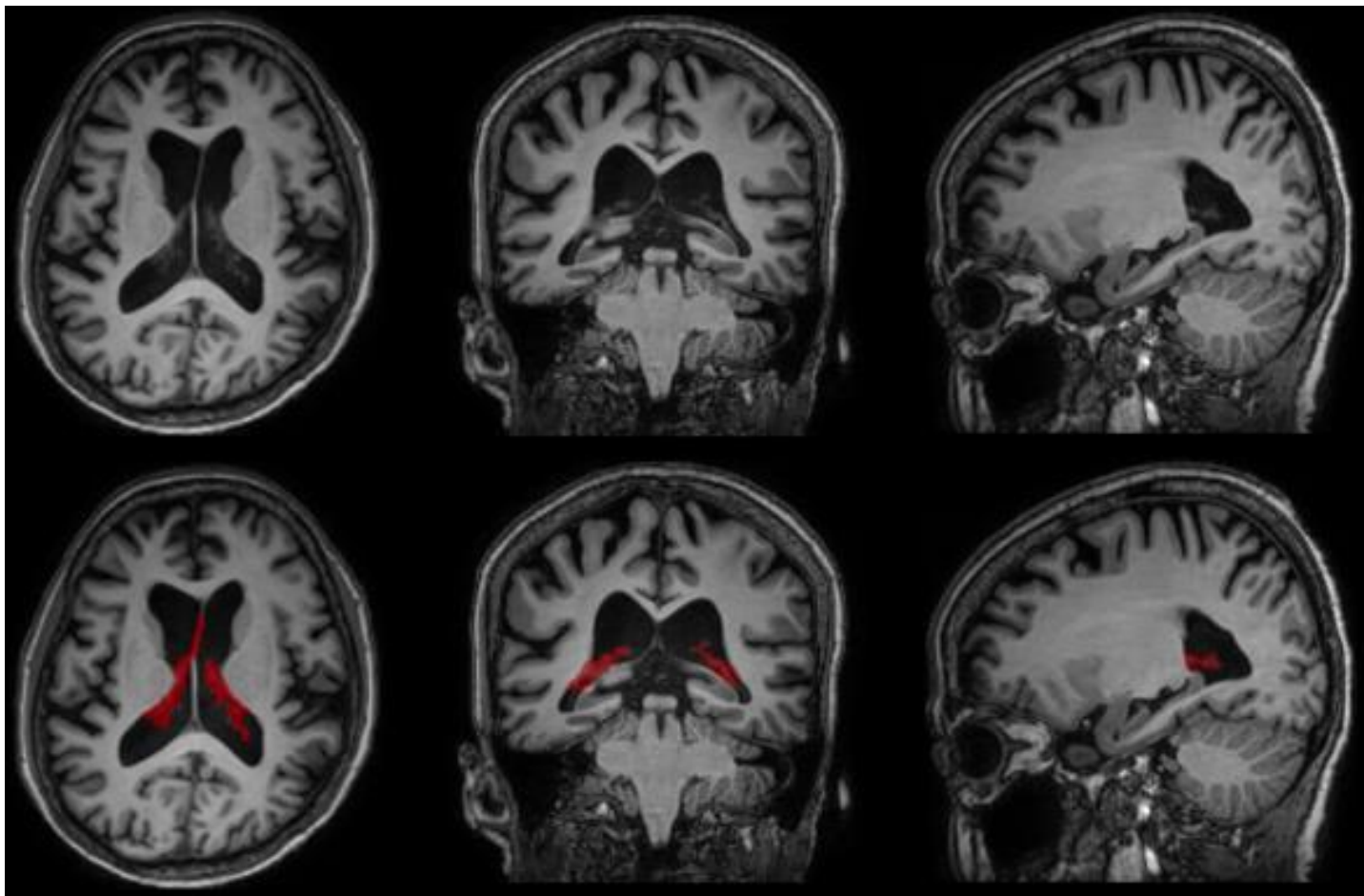


Figure 2. Representative images showing choroid plexus segmentation (red) overlaid on three-dimensional T1-weighted magnetic resonance images in the axial (left), coronal (center), and sagittal (right) planes.

All participants underwent neuropsychological assessment. Linear regression was performed to determine associations between CP volume, ALPS index and global cognition, adjusting for age and education. Mediation analysis was performed to examine the effect of glymphatic efficiency on the relationship between CP and cognition.

Results

Demographic characteristics of the study population are reported in Table 1. Regression analyses revealed that lower ALPS index (reflecting poorer glymphatic clearance) was significantly associated with enlarged CP in AD ($\beta = -.454$, $p < .001$) but not in non-AD (**Fig.3(a)**). Enlarged CP was significantly associated with poorer MMSE ($\beta = -.014$, $p = .032$) in AD but not in non-AD shown in (Fig.1(b)). No significant association was found between ALPS and cognition. Mediation analysis showed DTI-ALPS index partially mediated the relationship between CP and MMSE ($\beta = 1.755$, 95%CI[0.307, 4.076]) and MoCA ($\beta = 1.647$, 95%CI[0.154, 3.726]) (**Fig. 4**).

Table 1. Clinical characteristics

	nAD (N = 54)	AD (N = 46)	p-value
Sex (male)	26 (47.3%)	25 (54.3%)	0.484
Age	67.33 ± 8.68	68.79 ± 6.78	0.347
Education	13.11 ± 4.47	13.08 ± 3.27	0.962
CPV 10 ³	1.19 ± 0.25	1.28 ± 0.26	0.077
DTI-ALPS	1.45 ± 0.25	1.43 ± 0.29	0.680
pTau217	0.25 ± 0.08	1.18 ± 0.82	<.001
MMSE	27.47 ± 2.39	24.59 ± 5.71	0.004
MoCA	26.28 ± 2.90	22.55 ± 6.11	<.001

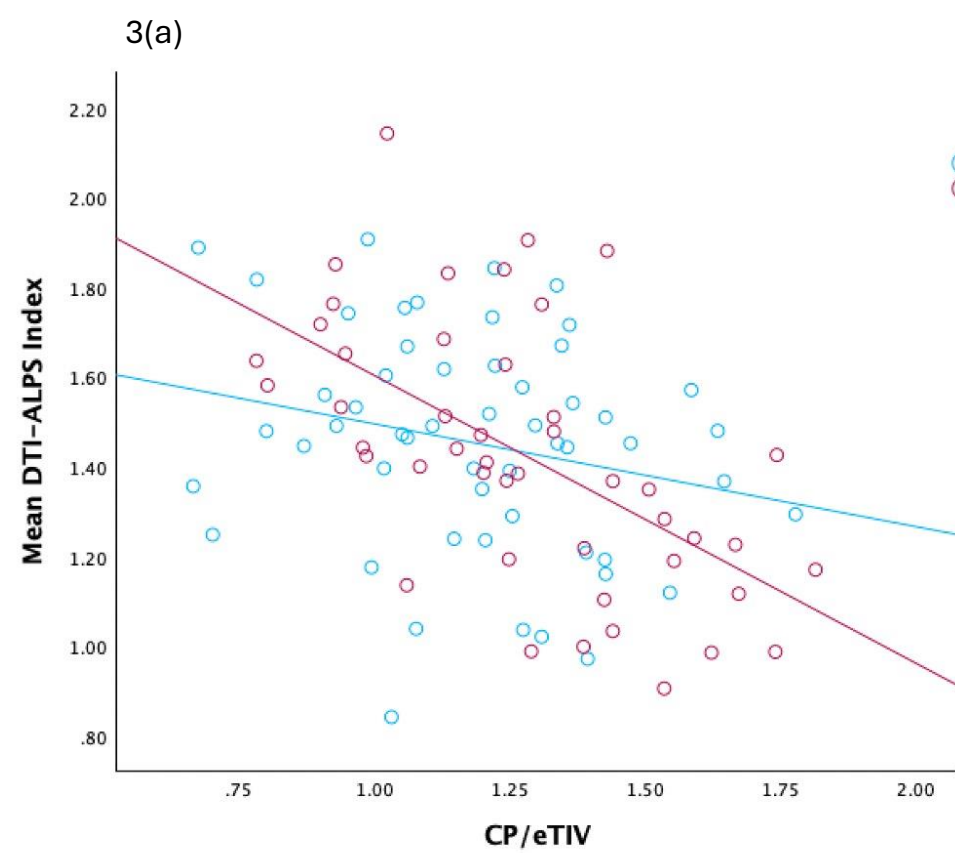


Figure 4. The mediating effect of DTI-ALPS in the relationship between (a) CP volume and MMSE and (b) CP volume and MoCA

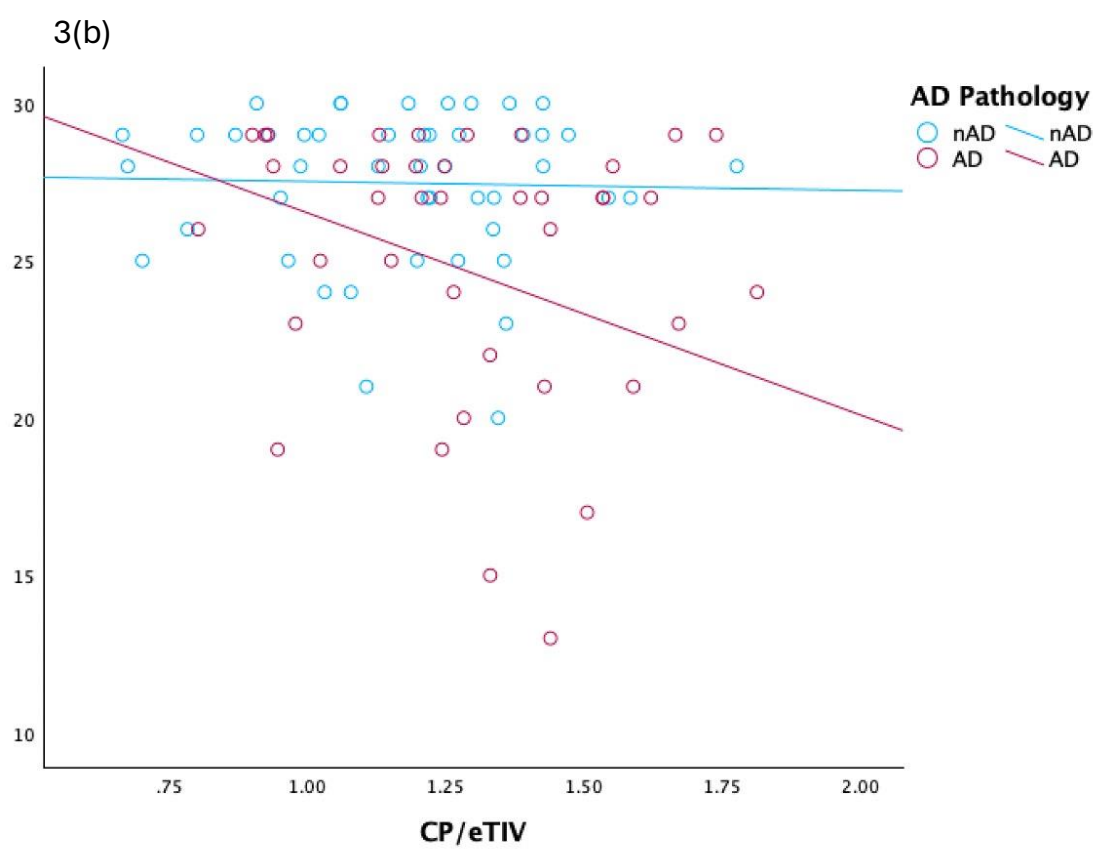
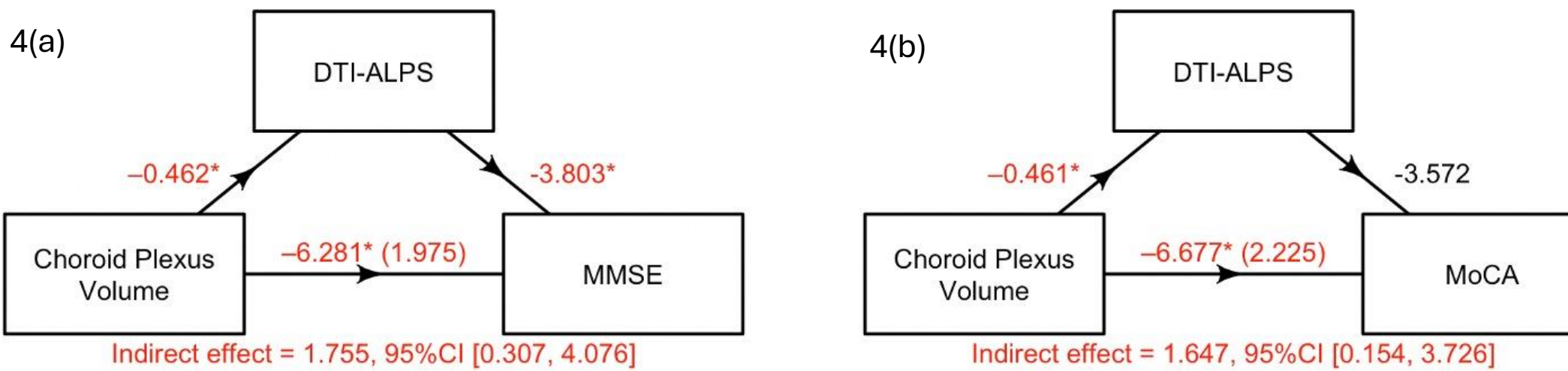


Figure 3. Linear regression analysis showing the relationship between (a) CP/eTIV and Mean DTI-ALPS Index and (b) CP/eTIV and MMSE

References

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