Glymphatic perivascular clearance and extracellular vesicles: neuroimaging & blood-based biomarkers in mild cognitive impairment

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BACKGROUND

Poor glymphatic clearance is associated with various neurodegenerative disorders[1]. Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) has been suggested as a non-invasive technique to assess glymphatic function, with lower DTI-ALPS indices having been linked to reduced glymphatic function[2]. We evaluated the relationships between the DTI-ALPS index, plasma circulating extracellular vesicles (EVs), whole brain atrophy, and executive function in mild cognitive impairment (MCI) and cognitively normal (CN) individuals.

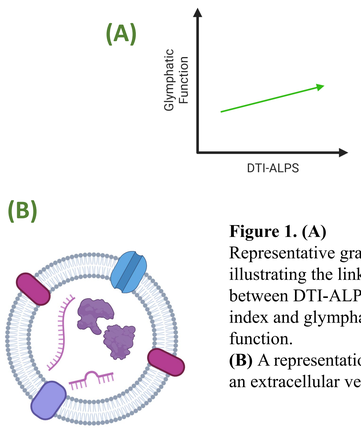


Figure 1. (A) Representative graph illustrating the link between DTI-ALPS index and glymphatic function. **(B)** A representation of an extracellular vesicle.

METHODS

- **Study participants**: a nested cohort of 35 CN and 33 MCI participants were selected from the Gait & Brain Cohort Study at Western University.
- **DTI-ALPS calculation**: each participant's DWI data, inhomogeneity corrected T1 image and T1 skull stripped mask were all converted to BIDS (Brain Imaging Structure) format. Diffusion data was cleaned (noise and Gibbs artifact removed) and FA and diffusion tensors were created. FA and diffusivity maps were registered to FMRIB58_FA_1mm template using commands from FSL's TBSS toolbox. DTI-ALPS indices were calculated by extracting diffusion data from each plane in the designated regions of interest for the right and left hemispheres.

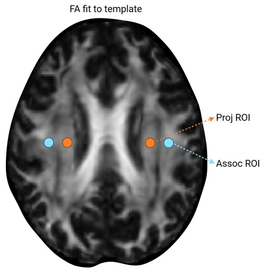
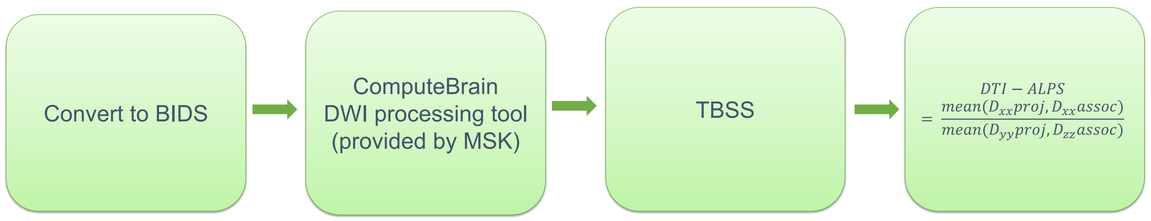


Figure 2. FA image with labelled ROI's used in DTI-ALPS index calculation.



- **EV biomarkers:** EV blood-based biomarkers were collected for each of the selected participants, including quantification of glial fibrillary acidic protein (GFAP) astrocytic EVs containing galactin-3 (GAL3) (GFAP/GAL3).
- **Structural imaging quantification**: outputs of structural MRI analysis included gray matter and white matter volumes, sulcal and ventricular CSF volumes, total intracranial volume, enlarged perivascular space (EPVS) and white matter hyperintensity (WMH) volumes, and brain parenchymal fraction (BPF).

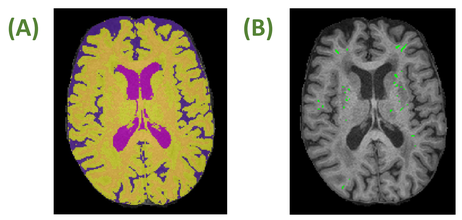


Figure 3. (A) T1 scan with tissue segmentation (WM, GM and CSF). **(B)** T1 scan with EPVS segmentation.

- **Clinical evaluation**: Trail-making-tests (TMT) A and B were administered to participants and the difference score (TMT [B-A]) was calculated to measure executive function[3].
- **Statistical analysis:** T-tests were used to compare CN vs. MCI, regression models were used to evaluate associations between DTI-ALPS, EPVS, atrophy via BPF, and executive function. Age, sex, education, body mass index, WMH, and systolic blood pressure were included as covariates.

RESULTS

(1) DTI-ALPS and MCI

The mean and left DTI-ALPS indices were found to be significantly lower in the MCI group compared to CN (mean: $p=0.05$; left: $p<0.02$).

(2) DTI-ALPS and BPF in MCI cohort

Regression models revealed that within the CN cohort, only age was negatively associated with BPF ($\beta=0.704$, $p<0.001$), however in the MCI cohort the mean DTI-ALPS index was strongly associated with BPF ($\beta=0.786$, $p<0.001$).

(3) GFAP/GAL3 and EPVS in MCI and CN

In both CN and MCI, GFAP/GAL3 was associated with a higher EPVS burden (CN: $\beta=-0.739$, $p=0.013$; MCI: $\beta=1.089$, $p=0.003$).

(4) DTI-ALPS and executive function in MCI and CN

Additional regression models revealed a negative association between left DTI-ALPS index and executive function in both the CN ($\beta=-0.395$ $p=0.025$) and MCI cohorts ($\beta=-0.447$, $p=0.02$).

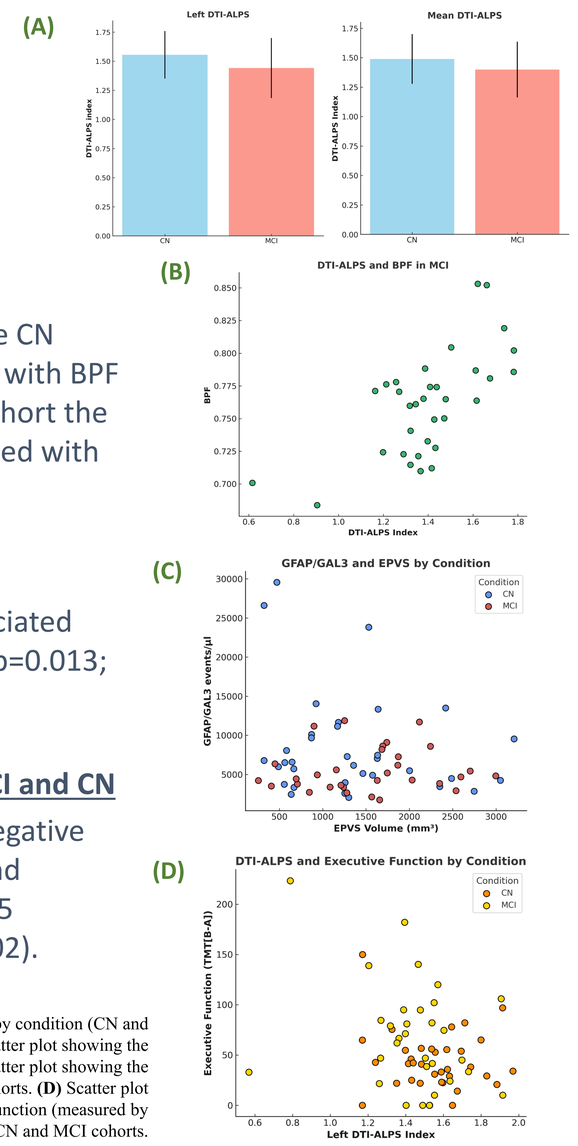


Figure 4. (A) Bar graphs showing the difference in mean DTI-ALPS index by condition (CN and MCI) for left DTI-ALPS index and mean DTI-ALPS index. **(B)** Scatter plot showing the relationship between DTI-ALPS index and BPF in the MCI cohort. **(C)** Scatter plot showing the relationship between GFAP/GAL3 and EPVS for both CN and MCI cohorts. **(D)** Scatter plot showing the relationship between left DTI-ALPS index and executive function (measured by TMT[B-A]) for both CN and MCI cohorts.

DISCUSSION

These preliminary results suggest that glymphatic dysfunction estimated by the DTI-ALPS index is associated with brain atrophy, where the left hemisphere DTI-ALPS index is associated with executive dysfunction in both CN and MCI. Additionally, GFAP/GAL3 may be a potential useful astrocytic EV biomarker to indicate dysfunction of perivascular space clearance.

Future work will examine mediation models with these imaging and EV biomarkers in neurodegenerative clinical populations.

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