Project title: Human Brain Clearance Imaging (HBCI)
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EU Joint Programme – Neurodegenerative Disease Research

Human brain clearance imaging in healthy subjects & in patients with cerebral amyloid angiopathy

BACKGROUND

The increasing interest in brain waste clearance has led to great insights into the way cerebrospinal fluid (CSF) acts as a lymphatic-like system[1,2]. Current knowledge on brain clearance mechanisms is mostly based on invasive experimental studies performed in rodents using microscopy, which is a technique that cannot be applied in humans. MRI, however, is an excellent candidate to provide information on brain clearance dynamics in humans as CSF, the waste carrier, has different magnetic properties compared to blood and tissue.

AIMS & WORKING HYPOTHESIS

Develop a clinically applicable brain clearance imaging **biomarker**.

Investigate if CSF-STREAM can detect changes in CSF-mobility in a suspected brain clearance disease (cerebral amyloid angiopathy (CAA))[5,6].

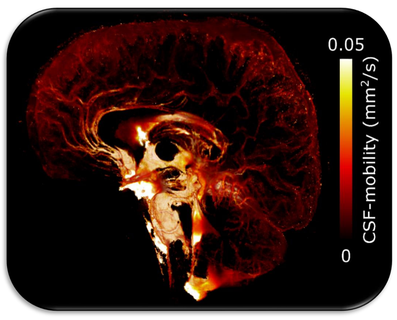

Figure 1: CSF-mobility map example

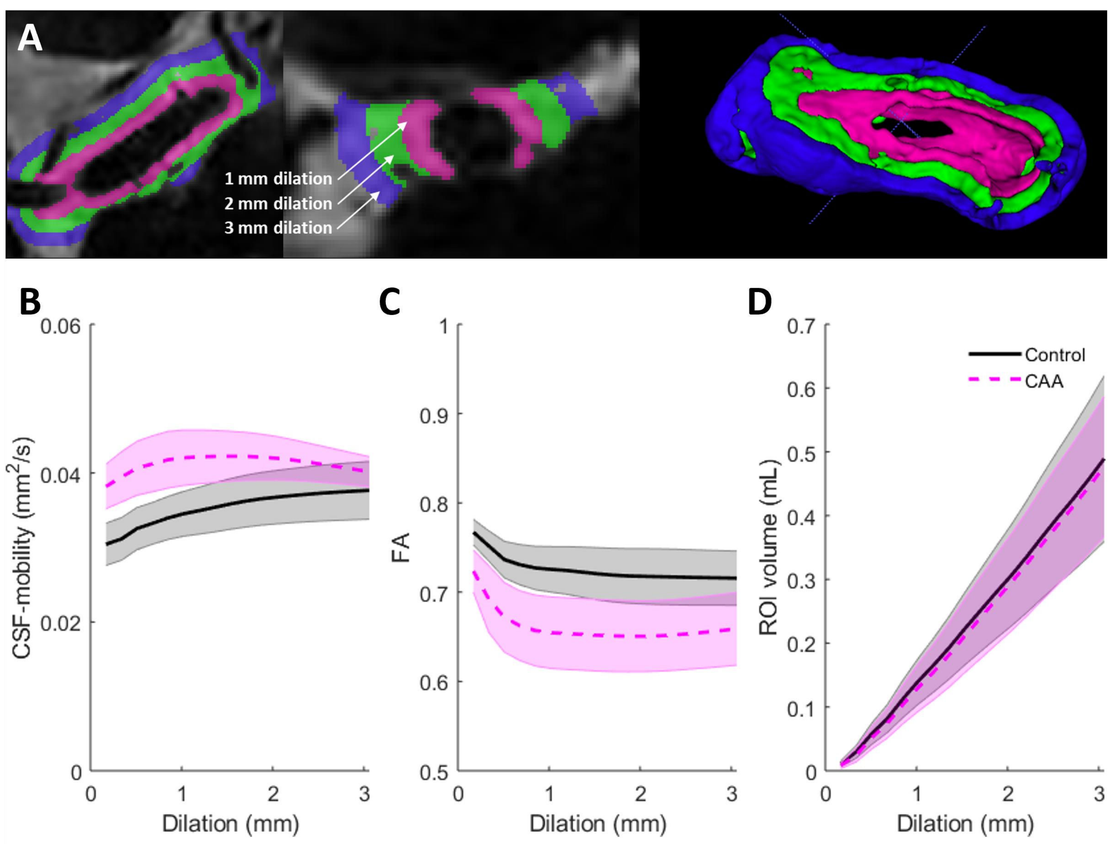

Figure 3: CSF-mobility, FA and ROI volume as a function of the distance to the middle cerebral artery (MCA). (A) Example of dilations around the middle cerebral artery of 1 mm (magenta), 2 mm (green) and 3 mm (blue) containing CSF. (B) CSF-mobility, (C) FA and (D) ROI volume across dilation width in CAA patients (pink, dashed line) and healthy controls (black, full line). Each line represents the mean over individuals and the shaded error areas represent confidence intervals of SD×1.96/√n (n=8 per group).

SIGNIFICANCE & IMPACT

This study provides first evidence that CSF-STREAM might be a suitable MRI-technique to assess changes related to brain clearance pathology.

The development of biomarkers to study the clearance system in humans creates new opportunities to explore this system in both healthy individuals and those with neurodegenerative diseases, potentially shedding light on how impaired clearance contributes to pathology.

METHODS IMPLEMENTED BY THE CONSORTIUM

1. **Share & implement** the CSF-STREAM package[3] (sequence, reconstruction and post-processing tools) developed in Leiden (Philips scanner) with Bonn (Siemens scanner).

2. **Scan** 8 patients with cerebral amyloid angiopathy and 8 healthy elderly controls.

3. **Meet & discuss** intermediate findings with the whole consortium (in-person meetings every 6-months for hands-on sessions & tri-weekly online meetings)

Non-invasive imaging strategy: CSF-STREAM[3]
T_2-prepared turbo-spin-echo (TSE) sequence: 0.45 mm isotropic resolution, 17x accelerated compressed sense readout[7], TSE-factor=146, TE=497ms, TR=3486ms, VENC=3.5mm/s, 6 directions, acquisition time = 30 min.

Reconstructions – Every scan was reconstructed using the BART toolbox[8].

Post-processing – Registration using Elastix, CSF-mobility and fractional anisotropy (FA) computation in Matlab, ROI delineations (MCA, PVS).

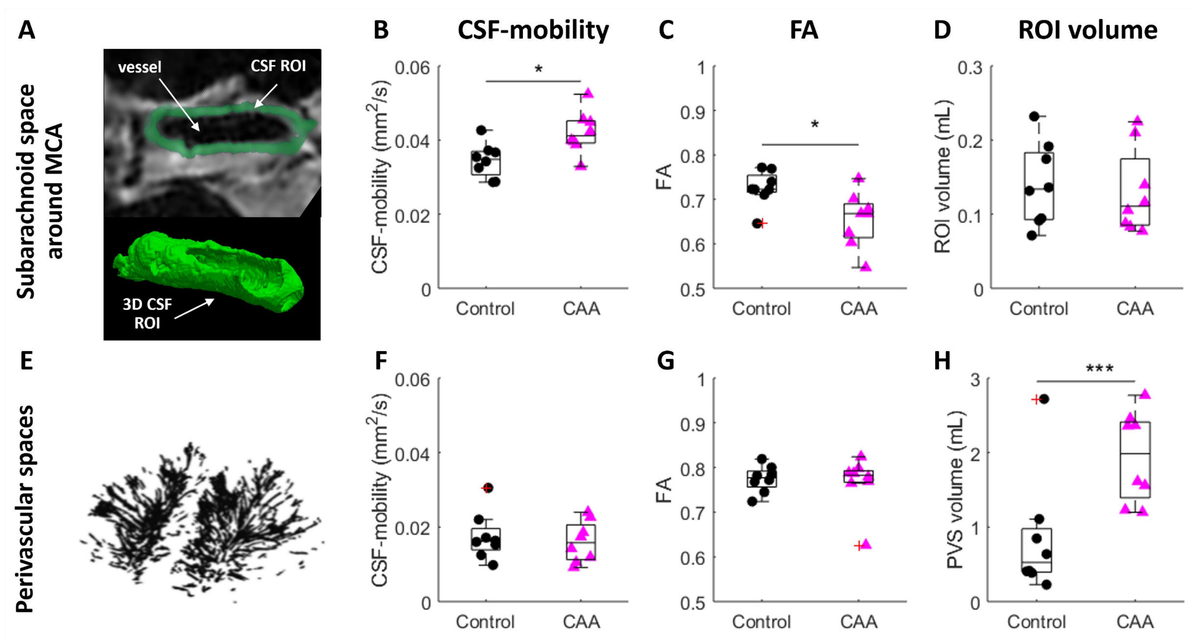

Figure 2: CSF-STREAM in CAA patients versus healthy controls. (A) Example of a 1-mm CSF-rim in the subarachnoid space (SAS) around the middle cerebral artery (MCA). (B) CSF-mobility is significantly increased (p=0.01, Mann-Whitney U-test) and (C) FA is significantly decreased (p=0.02, Mann-Whitney U-test) in the 1 mm-thick SAS around the MCA of CAA patients (pink) versus healthy controls (black). (D) ROI volume around the MCA in controls and CAA patients. (E) Example of perivascular space (PVS) segmentation around penetrating vessels in the centrum semi-ovale (CSO). No significant change in (F) CSF-mobility nor (G) FA was found in PVS. (H) The PVS volume was significantly increased (p = 0.007, Mann-Whitney U-test) in CAA patients. Each datapoint represents the value per individual in a region of interest (ROI).

OUTCOMES OF THE PROJECT

Achieved milestones
- Measure CSF-mobility non-invasively in detail, down to the level of perivascular spaces.
- Assess changes in CSF-mobility in CAA, a neurodegenerative patient cohort.

Key results
- CSF-mobility can be measured in patients down to the level of perivascular spaces surrounding penetrating vessels using CSF-STREAM
- A significant 20% increase in CSF-mobility and 10% decrease in FA was observed in patients with cerebral amyloid angiopathy compared to controls. No change was found in PVS. This aligns with previous findings in rodents[6].

- Findings were presented at conferences (ISMRM 2022, ISMRM 2024)
- Manuscript under revision[4]

NEXT STEPS

Investigate CSF-mobility and FA in perivascular spaces more in detail (regional analysis, dependence on PVS size), and in brain regions more affected by the disease (occipital lobe).

References

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