CORTICAL QUANTITATIVE MRI METRICS ARE SENSITIVE TO PATHOLOGY IN PRECLINICAL ALZHEIMER'S DISEASE

Aurélie Bussy[1,2], Alfie Wearn[5], Raihaan Patel[1,4], Giulia Baracchini[5,6,7], Sylvia Villeneuve[3,6], Judes Poirier[3,6], John CS Breitner[6], Gabriel A. Devenyi[1,3], R. Nathan Spreng[5,6,7] and M. Mallar Chakravarty[1,2,3,4]

[1] Computational Brain Anatomy (CoBrA) Laboratory, Douglas Mental Health University Institute, Montreal, Quebec, Canada
[2] Integrated Program in Neuroscience, McGill University, Montreal, Canada
[3] Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[4] Department of Biomedical Engineering, McGill University, Montreal, Quebec, Canada
[5] Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada
[6] Centre for the Studies on the Prevention of AD, Douglas Mental Health University Institute, Verdun, Quebec, Canada
[7] McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

Douglas Institut universitaire en santé mentale / Mental Health University Institute

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INTRODUCTION

CONTEXT

- Alzheimer's disease (AD) prevalence increases.
- Amyloid-β and p-tau are the main pathological hallmarks of AD[1].
- Multifactorial disease with microstructural changes (myelin ↓, iron ↑).
- Current tools to study AD pathology are invasive (PET, CSF, blood..).

GOAL

- Non-invasive quantitative MRI (qMRI) to estimate myelin, iron and water.
- Test if qMRI metrics sensitive of pathology in preclinical AD.

METHODS #1

PARTICIPANTS

- 94 cognitively normal older adults with parental AD-history[2]
- Ages 59-85 years; 67 females; mean/SD MoCA: 28.3/1.5

MRI IMAGES

- 3T Siemens Prisma scanner (32-channel)
- MRI Protocol : Multi-parametric : 3D FLASH acquisition (1 mm^3)[3]
- MPRAGE sequence (1 mm^3)

PET IMAGES

- [18F]NAV4694 PET scans 40–70 min for amyloid
- [18F]AV1451 scans 80–100 min post-injection for tau

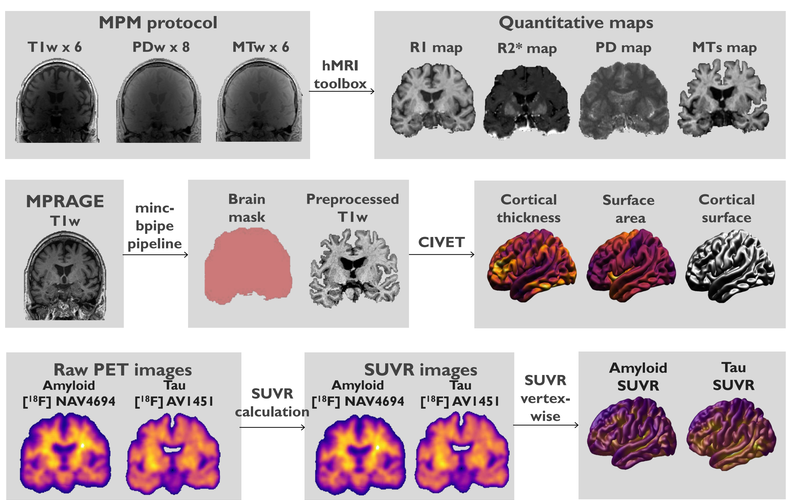
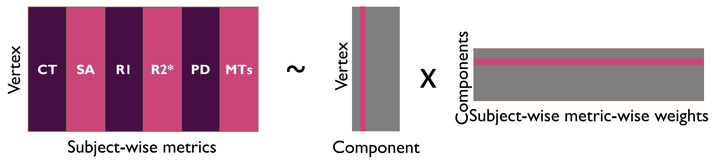


Figure 1: Main preprocessing and processing steps

METHODS #2

CORTICAL PARCELLATION

- Non-negative matrix factorization (k=2 to k=20)[4]
- Stability analyses + reconstruction error



PET GROUPS

- Amyloid SUVR threshold = 1.327 (i.e last quartile)
- Tau SUVR threshold = 1.139 (i.e last quartile)

STATISTICS

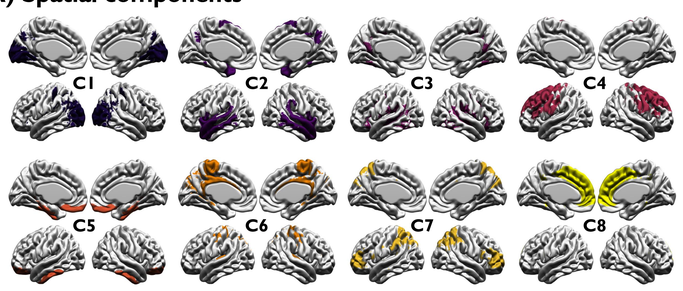
- Linear models (R 4.1.3)

NMF weights ~ Amyloid_group x Tau_group + Age + Sex

- p<0.05 corrected for FDR across 48 models (8 components x 6 metrics)

RESULTS #1

A) Spatial components



B) Subject-weights components

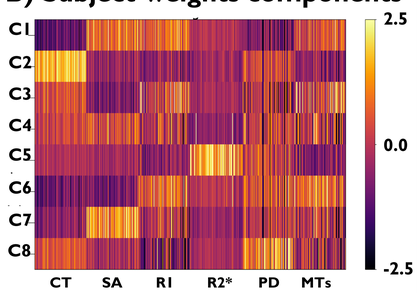
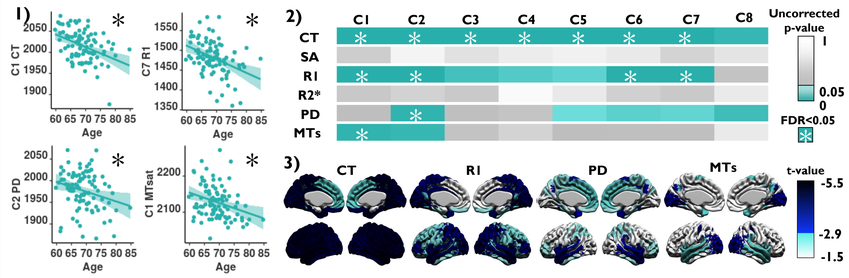


Figure 2: A) Cortical maps showing lateral and medial views of the 8 spatial patterns. Each component identifies a selection of vertices sharing a microstructural variance pattern. **B)** Matrix of the subject-specific weightings of the 8 components where each row corresponds to a specific component and the colors represent a subject-metric combination, describing the CT, SA, R1, R2*, PD and MTs patterns for each subject in each component. Each element of the matrix is z-scored, such that negative values (dark purple) indicate a below average weight for a given component and positive values (yellow) indicate an above average weight.

RESULTS #2

A) Age effect



B) Differences between low and high tau groups

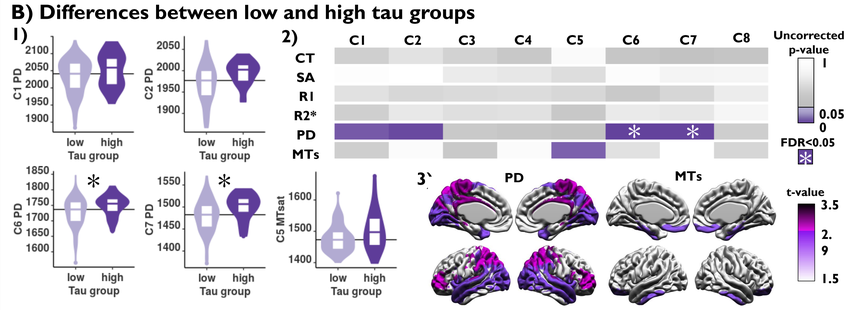


Figure 3: A) 1) Plots of age-related component-weights changes. **2)** Heatmap demonstrating uncorrected p-values corresponding to the models for each component-weight relationship with age. Cyan coloured squares represent FDR-uncorrected p-values thresholded at p<0.05, with non-significant associations in gray. Relationships that survived FDR correction at the 0.05 level are indicated with a white asterisk. **3)** Brain maps of the t-values corresponding to the significant components demonstrating age effect (cyan before FDR correction and dark blue for components who survived FDR correction). **B)** Differences between low and high tau groups. **1)** Boxplot of component-weights difference between tau groups. Horizontal lines represent the median values of the low tau group **2)** Heatmap demonstrating uncorrected p-values corresponding to the models for each component-weight relationship with tau groups. Purple coloured squares represent FDR-uncorrected p-values thresholded at p<0.05, with non-significant associations in gray. Relationships that survived FDR correction at the 0.05 level are indicated with a white asterisk. **3)** Brain maps of the t-values corresponding to the significant components for the tau group (purple before FDR correction and pink for components who survived FDR correction)

Fig 1A shows the 8 cortical components identified, while 1B shows individual level microstructural weightings for each component. Increased age was related to lower CT, R1, PD and MTs to different extent (Fig 2A). In high tau PET individuals, we found widespread higher cortical PD, while higher MTs was found in the temporal lobe (Fig 2B).

CONCLUSION

Beyond the expected age-related CT and myelin decrease, our results demonstrated that tau accumulation was strongly related to higher PD (interpreted as a sign of macromolecular content loss)[5].

1. Braak & Braak 1991, 2 Tremblay-Mercier et al. 2021, 3 Callaghan et al. 2014, 4 Patel et al. 2020, 5 Noble et al 2013

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