Hippocampal T1-weighted and FLAIR contrast is associated with CSF biomarkers in asymptomatic individuals with parental history of Alzheimer's disease

Christine L Tardif, Robert S C Amaral, Gabriel A Devenyi, Pedro Rosa-Neta, Judes Poirier, John Breitner, M Mallar Chakravarty and The PREVENT-AD Research Group

Douglas Mental Health University Institute, Montreal, Canada
McGill University, Montreal Canada

christine.tardif@mail.mcgill.ca
mallar.chakravarty@douglas.mcgill.ca

Introduction

- CSF biomarkers and hippocampal (HC) subfield morphometry have consistently been used as biomarkers of preclinical Alzheimer's disease (AD).
- We have recently shown that the bilateral subiculum volumes are related to the interplay of CSF tau and Aβ in cognitively healthy subjects with a parental history of AD[1].
- Here we investigate the relationship between the CSF biomarkers and the microstructure of the HC circuit, including the subfields[2] and extra-hippocampal WM structures[3], using the T1-weighted/FLAIR signal ratio in the same cohort.

Methods

Data

Data were obtained from the PREVENT-AD program[4] (data release 3.0, November 30, 2016). 88 cognitively healthy individuals with a family history of AD were scanned on a Siemens Trio 3T with a 12-ch head coil.

- 1mm^3 T1-weighted MPRAGE: TI=900ms, TE=5ms, α=9°, TR=2300ms, ~9mins.
- 1mm^3 T2-weighted FLAIR: TI=1800ms, TE=389ms, α=120°, TR=5000ms, ~6mins

The subjects underwent a lumbar puncture to assay CSF Aβ and total tau levels using Innotests ELISA, and were genotyped for Apolipoprotein E4 (ApoE4) status.

Table 1. Cohort demographics

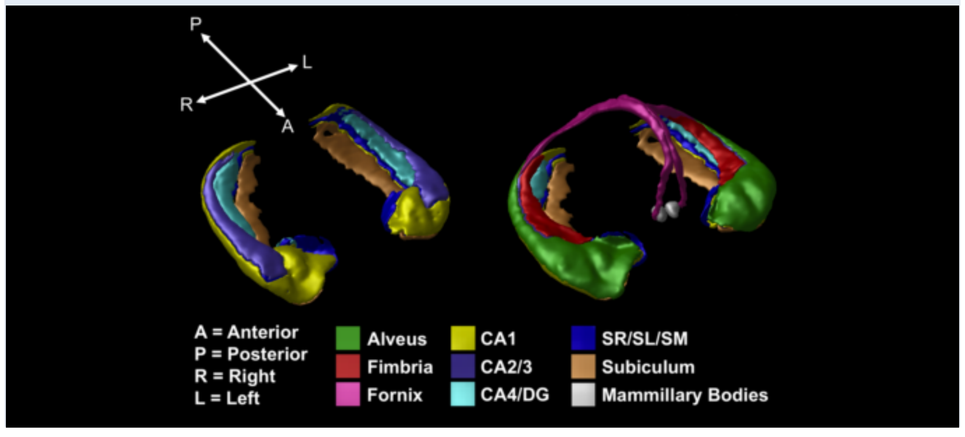
Sex	27 men, 61 women
Age (sd)	62.8 (5.6) years
Age until parental onset of AD (sd)	12.4 (6.9) years
Education (sd)	14.9 (3.0) years
ApoE4	30 carriers, 58 non-carriers

Processing

Preprocessed[5] T1-weighted images were segmented using MAGeT[6,7] to label the HC subfields[2] and HC white matter[3]. We calculated the T1-weighted and FLAIR signal intensities within each structure, as well as the T1w/FLAIR signal ratio. Statistical analysis was performed in R using the following linear model. FDR was used to correct for multiple comparisons.

$$\text{T1w/FLAIR} = \beta_{intercept} + \beta_{gender}(\text{Gender}) + \beta_{age}(\text{Age}) + \beta_{age2parental}(\text{Age2ParentalOnset}) + \beta_{education}(\text{Education}) + \beta_{ApoE4}(\text{ApoE4 status}) + \beta_{tau}(\text{CSF tau}) + \beta_{A\beta}(\text{CSF A}\beta) + \beta_{tau:A\beta}(\text{CSF tau} \times \text{CSF A}\beta) + \text{error}$$

Fig. 1: 3D reconstruction of hippocampal subfield[2] and extra-hippocampal white matter[3] atlases.



Results

The T1w/FLAIR signal ratio was associated with the interaction of tau and Aβ in the left fornix, right fimbria and total right and left extra-hippocampal WM (q<0.05). No significant association with the CSF biomarkers was detected for the T1w/FLAIR ratio of the HC subfields.

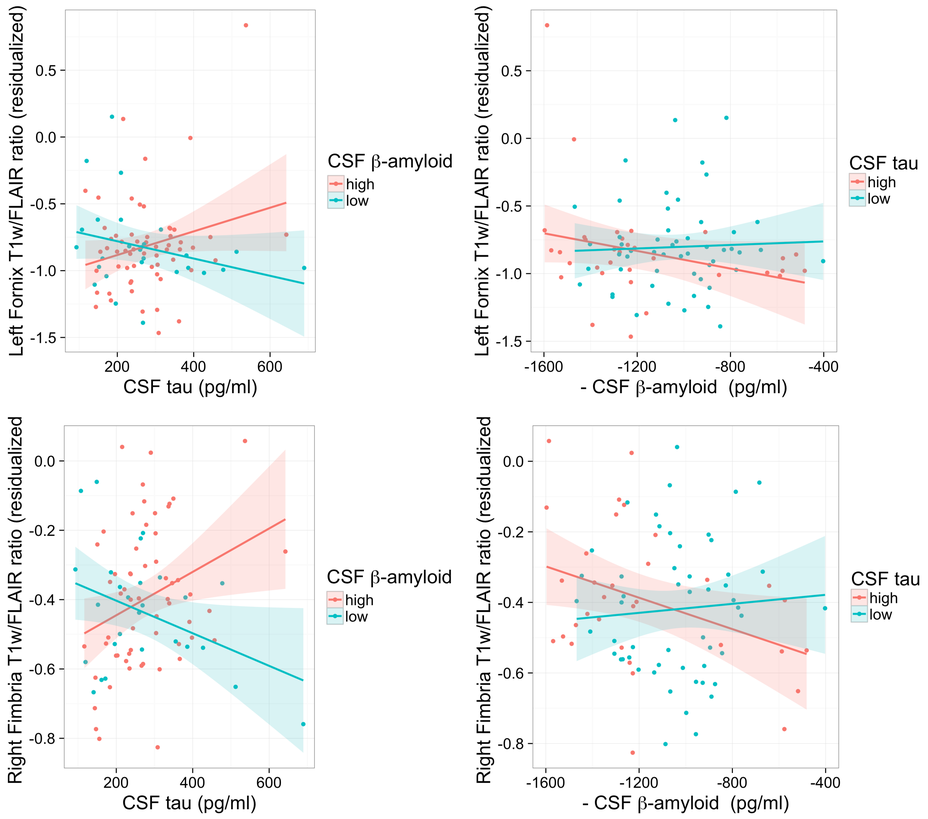


Fig. 2 Linear models of the T1w/FLAIR ratio of the left fornix (top) and right fimbria (bottom) as a function of tau and Aβ. Cutoffs of tau = 290 pg/ml and Aβ = 950 pg/ml were used to categorize the subjects into high/low groups. The T1w/FLAIR ratios were residualized against the following covariates: sex, age, age until parental onset, education and ApoE4 status.

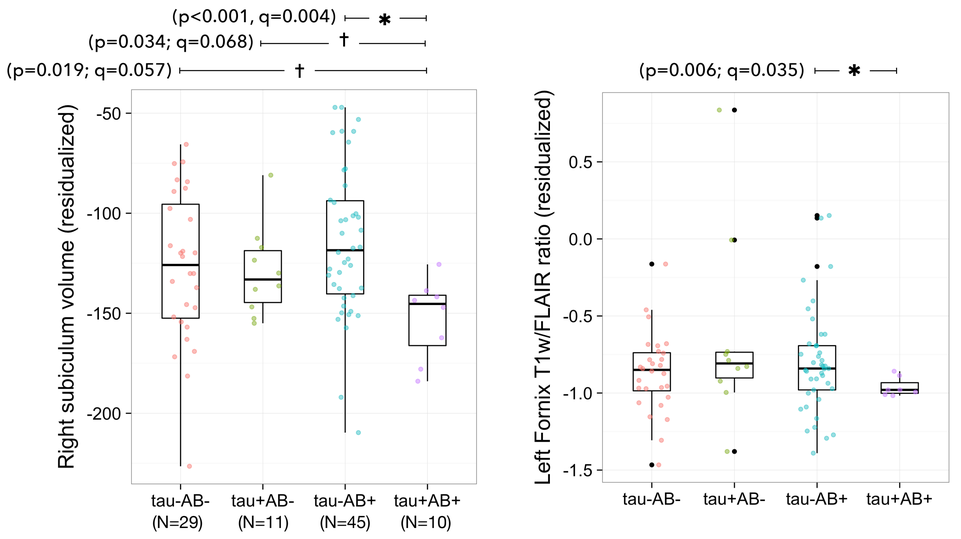


Fig. 3 Structural characterization of four CSF subgroups. The cohort was divided into four subgroups, eg. tau-Aβ- refers to the subgroup of individuals with low CSF tau and high CSF Aβ concentrations. Left: The residualized subiculum volume is smaller in the tau+Aβ+ subgroup than the three others. Right: The residualized T1w/FLAIR ratio of the left fornix is lower in the tau+Aβ+ subgroup than the tau-Aβ+.

Discussion

- **The accumulation of both tau and Aβ pathology is associated with a lower T1w/FLAIR signal ratio in the left fornix and right fimbria in asymptomatic individuals.**
- **The accumulation of tau or Aβ in the absence of the other is associated with an increase in T1w/FLAIR ratio.**
- These differences in T1w/FLAIR ratio may be caused by a combination of astrogliosis and the partial loss of myelin sheaths, axons, and oligodendrocytes, previously observed in the white matter of AD patients[8].
- Early biomarkers of HC circuit structural integrity should be included in models of preclinical AD. The T1w/FLAIR ratio is a widely available marker, which we have shown to be sensitive to AD-related pathology in the extra-hippocampal WM.

References

[1] Tardif et al. SfN Proceedings 2016
[2] Winterburn et al, NeuroImage 74, 254-265 (2013)
[3] Amaral et al, NeuroImage (in press)
[4] http://www.prevent-alzheimer.ca
[5] https://github.com/CobraLab/minc-bpipe-library
[6] Chakravarty et al. Human Brain Mapping 34(10), 2635-2654 (2013)
[7] Pipitone et al. NeuroImage 101, 494-512 (2014)
[8] Englund and Brun, Histopathology 16(5), 433-439 (1990)