Cerebrospinal fluid and PET measures of *tau* pathology reflect different states of AD pathophysiological progression

Pierre-François Meyer, MSc,[1,2] Alexa Pichet-Binette, MSc,[1,2] John C.S. Breitner, M.D, MPH[1,2] and Sylvia Villeneuve[1,2] for the Alzheimer's Disease Neuroimaging Initiative

[1]McGill University Faculty of Medicine, Montréal, Québec, Canada [2]Centre for Studies on the Prevention of Alzheimer's Disease, Douglas Mental Health University Institute, Montréal, Québec, Canada

Background

Alzheimer's disease (AD) is characterized by a decades-long period of pathological changes leading to the onset of dementia. At the dementia stage, the brain is likely to be too seriously affected for any intervention to meaningfully alter the disease process. As a result, some in the research field have suggested to shift from a cognitive-based to a biology-based definition of the disease.[1] Criteria for disease definition include measures of pathological hallmarks (amyloid-β [Aβ] and *tau*) and neurodegeneration.

Owing to the availability of cerebrospinal fluid (CSF) and imaging markers, either magnetic resonance imaging (MRI) or positron emission tomography (PET), of disease processes, modalities are often used interchangeably. However, investigations of CSF and PET measures of Aβ pathology suggest that these two modalities provide both overlapping and complementary information.[2,3] Some investigators have suggested that CSF Aβ abnormality may occur earlier than PET.[4]

With the availability of novel PET tracers we can now investigate whether CSF (P-*tau*) and PET (Flortaucipir; FTP) measures of *tau* pathology are indicative of different pathophysiological stages.

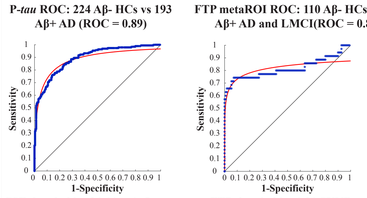
Participants and Methods

248 ADNI participants with at least:
- One FTP-PET scan
- One elecsys assay of CSF AD biomarkers

→ **117 ADNI participants** (62 healthy, 55 with MCI) with a FTP PET- scan and a CSF biomarker assessment within a 24-month period

Tau quantification:
- FTP-PET SUVRs in AD metaROI[5]
  - non-PVE corrected
  - Cerebellum grey normalized
- CSF P-*tau* levels

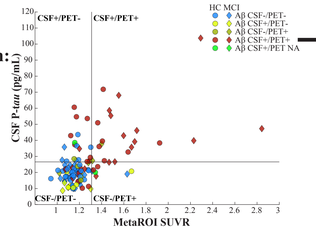
Threshold derivation: ROC analyses



CSF threshold = 26.64 pg/mL

FTP threshold = 1.31 SUVR

CSF/PET classification:



Cross-sectional analysis:

Group comparison of
- Key demographic variables
- Global PET amyloid (AV45, cerebellum normalized)
- FTP PET Braak stage
- Cognition (Executive function and memory)

Retrospective analysis:

Group comparison of
- P-*tau* rate of change
- Cognitive rate of change

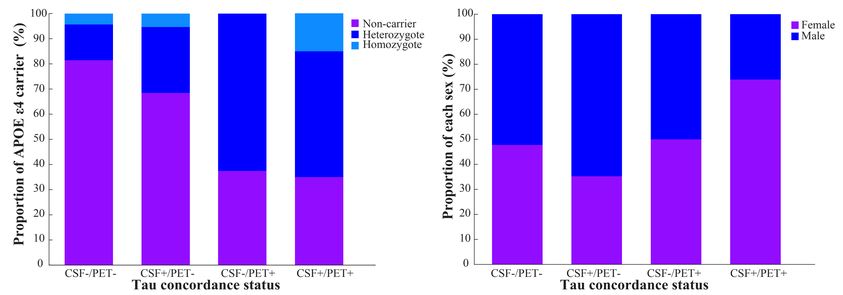
Sample characteristics

Group	CSF-/PET-	CSF+/PET-	CSF-/PET+	CSF+/PET+	P
Sample Size	70	19	8	20	
Age (Years)	76.59 (7.04)	79.94 (7.94)	77.50 (6.00)	77.50 (5.32)	0.50
Sex F (%)	33 (47%)	8 (42%)	4 (50%)	15 (75%)	0.13[c,e]
MCI (%)	34(48%)	4 (21%)	4 (50%)	13 (65%)	0.05[a,e]
Education (years)	16.42 (2.55)	16.05 (3.00)	18.00 (2.07)	15.70 (2.66)	0.2[f]
APOE ε4 carriers (%)	13 (19%)	6 (32%)	5 (63%)	13 (65%)	<0.001[b,c]
Memory composite	0.93 (0.67)	1.05 (0.65)	0.37 (0.93)	-0.18 (1.18)	<0.001[b,c,d,e]
Executive function composite	0.99 (0.86)	0.73 (0.97)	0.88 (0.80)	0.10 (1.02)	<0.005[c,e,f]
Global AV45 SUVR	1.06 (0.11)	1.22 (0.24)	1.33 (0.30)	1.47 (0.18)	<0.001[a,b,c,e]

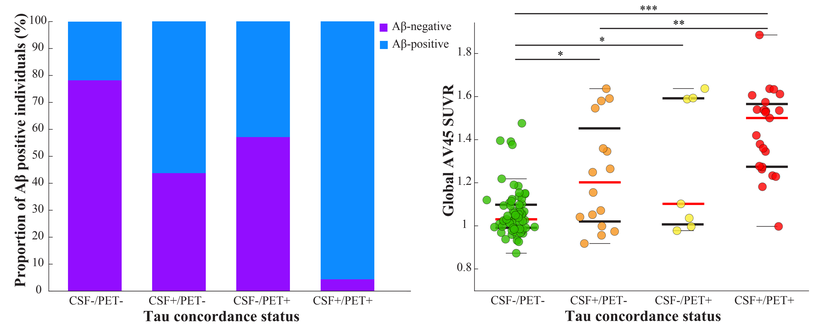
[a] $P_{CSF-/PET- vs CSF+/PET-} < 0.05$; [b] $P_{CSF-/PET- vs CSF+/PET+} < 0.05$; [c] $P_{CSF-/PET- vs CSF+/PET+} < 0.05$; [d] $P_{CSF+/PET- vs CSF+/PET+} < 0.05$; [e] $P_{CSF+/PET- vs CSF+/PET+} < 0.05$; [f] $P_{CSF-/PET+ vs CSF+/PET+} < 0.05$

Cross-sectional Results

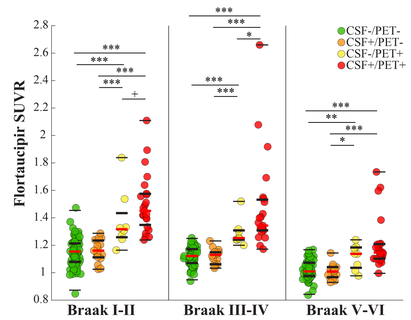
Demographics: Increased proportion of at risk individuals with *tau* positivity



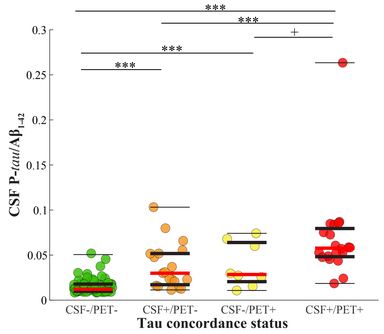
Imaging: Higher AV45 (Aβ) binding in *tau* positive groups



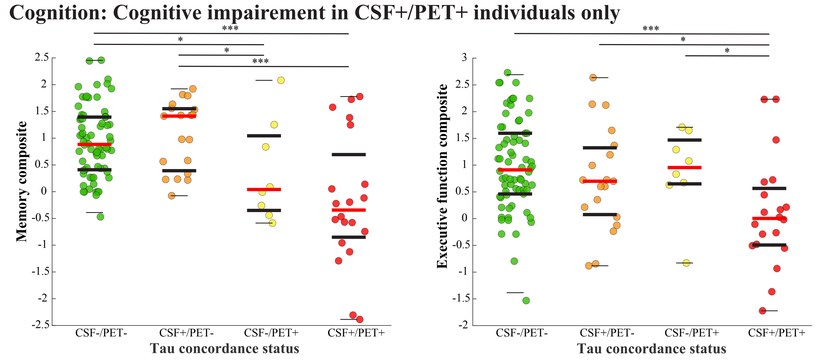
Imaging: Advanced Braak spreading in PET+



CSF: Comparable P-*tau*/Aβ in *tau*+



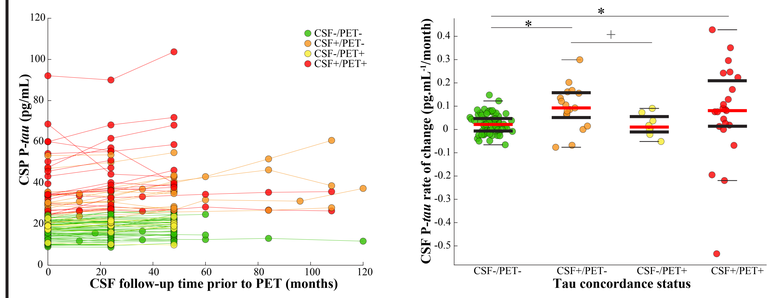
Cognition: Cognitive impairement in CSF+/PET+ individuals only



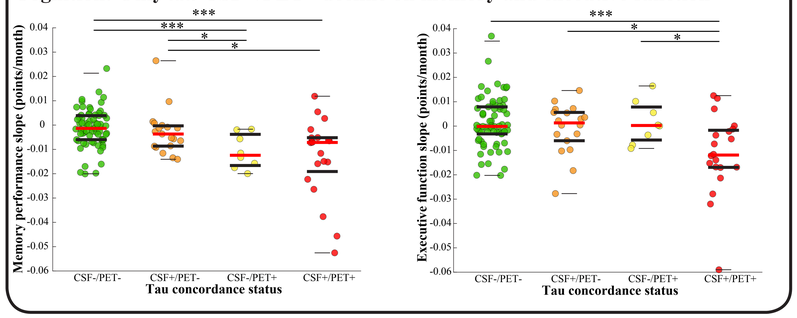
*P <0.1; *P<0.05; **P<0.001; ***P<0.005

Retrospective analysis

CSF: CSF *tau*+ persons have increased retrospective CSF P-*tau* accrual



Cognition: Only *tau* CSF+/PET+ decline on memory and executive function



Conclusions

Among 117 ADNI participants categorized according to their levels of *tau* pathology as measured by PET and CSF we found that:

- CSF-/PET+ occured less frequently than CSF+/PET-, CSF-/PET- or CSF+PET+
- Participants with at least one positive *tau* biomarker had increased Aβ pathology
- Only CSF+ showed retrospective change in CSF *tau* levels
- CSF+/PET+ participants were more likely to have worse cognitive performance
- CSF+/PET+ participants had consistent retrospective cognitive decline

Results are consistent with the notion that CSF P-*tau* is an early indicator of AD pathophysiological changes. Given the reduced inference from the CSF-/PET+ group, it is unclear whether this stage is artifactual or represents an alternate pathogenetic route. Longitudinal CSF/PET studies will improve our understanding of this phenomenon.

References

[1]Jack *et al. Alzh. & Dem.* (2018);14:535-562

[2]Mattsson *et al. Brain* (2015);138:772-783

[3]Palmqvist *et al. Brain* (2016);139:1226-1236

[4]Palmqvist *et al. Nat. Commun* (2018);8:1214

[5]Ossenkoppele *et al. JAMA* (2018);320:1151-1162

Contact

: pierre-francois.meyer@mail.mcgill.ca

: @pf_meyer

An online version of this poster is available at :

Acknowledgments

ADNI

Douglas

Villeneuve Lab
www.villeneuvelab.com