

Hippocampus and subfield volumes are associated with CSF  
β-amyloid and p-tau and their interaction in asymptomatic  
individuals with familial history of Alzheimer's disease

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SfN Annual Meeting, San Diego, 2016



>CoBrA Lab  
computational brain anatomy



# Biomarkers in the early stages of Alzheimer's disease (AD)

## CSF measures of tau and $\beta$ -amyloid:

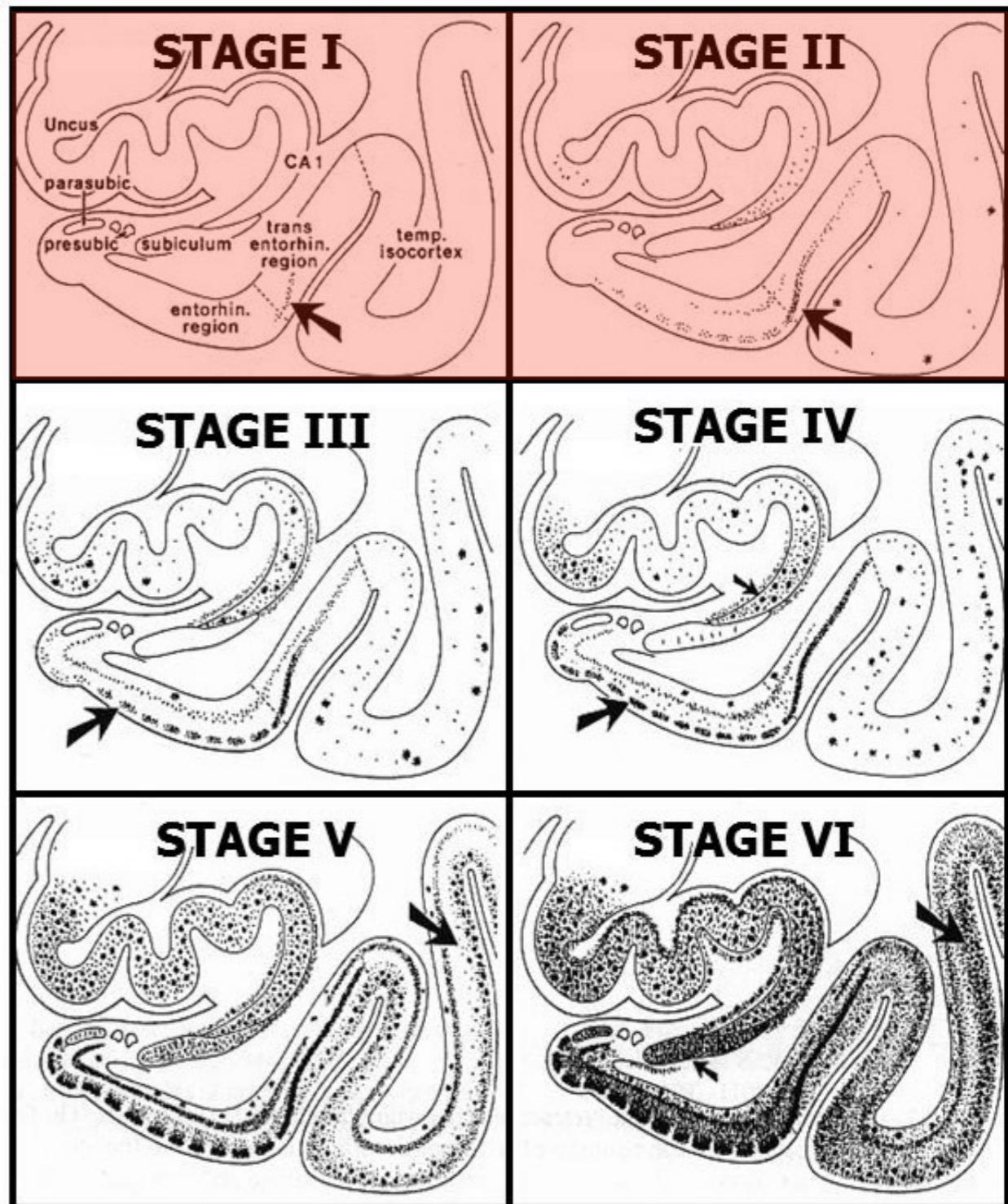
- sensitive to the pathological status in preclinical AD
- good predictors of cognitive performance

(Brier et al, Sci Transl Med 2016, Dowling et al. NeuroImage 2015)

## MRI-based neuroanatomical biomarkers of preclinical AD:

- Hippocampus - focal atrophy of the CA1 and subiculum subfields

(La Joie et al, NeuroImage Clin 2013  
Perrotin et al, J Alzheimers Dis 2015  
Carlesimo et al, Alzheimers Dement 2015  
Review: De Flores et al, Neuroscience 2015)



Braak stages of AD neuropathology base on the pattern of neurofibrillary change  
(Luna-Muñoz et al. 2013)



## Individuals with a familial history of AD that are asymptomatic

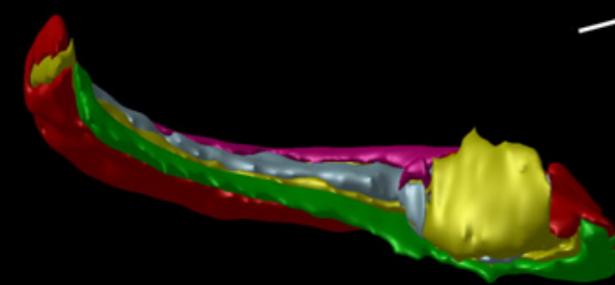
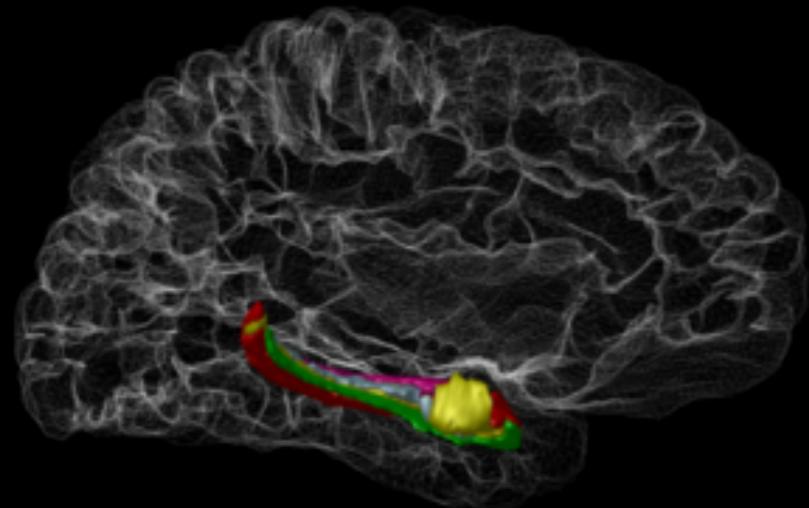
- 95 subjects (29 males)
- **62.8** (5.5) years of age

### Biomakers:

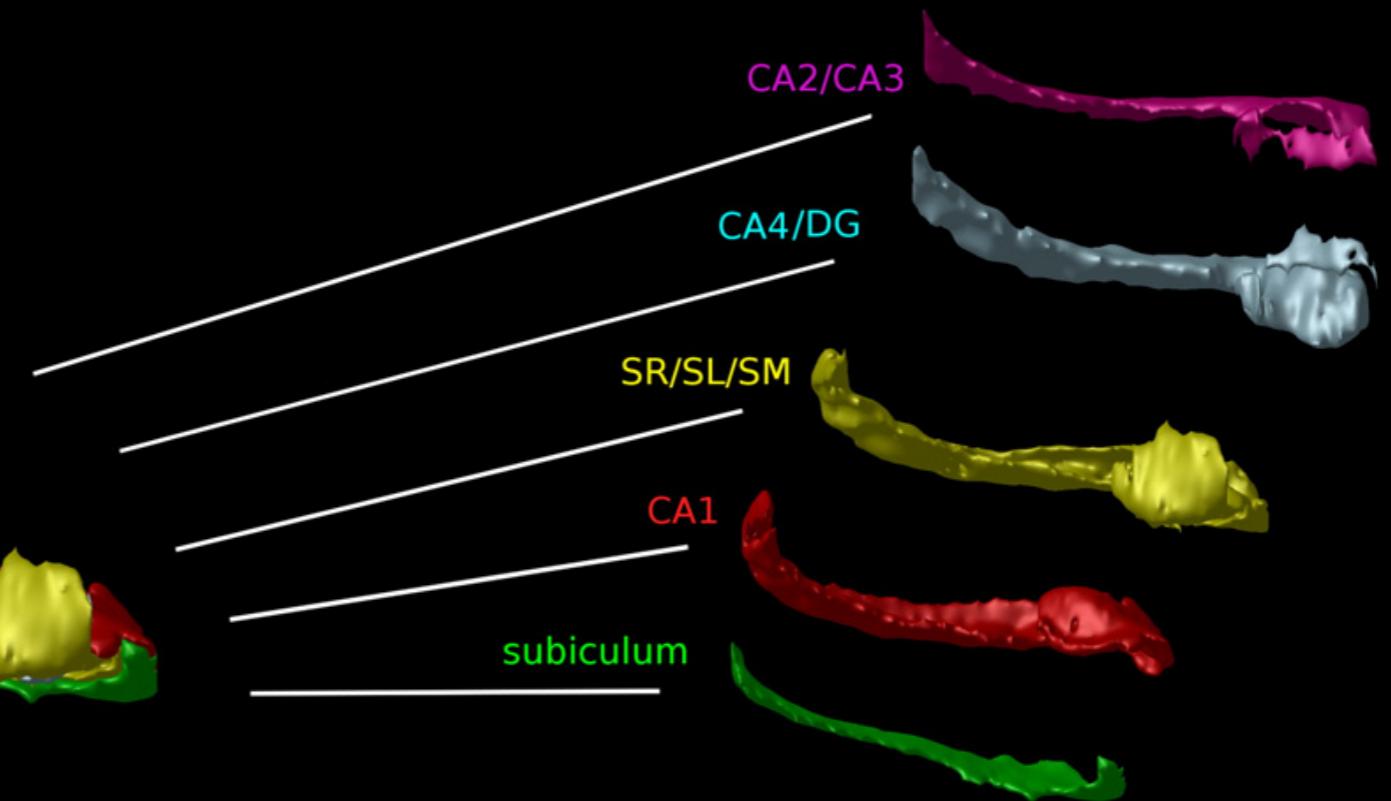
- CSF biomarkers using Innotests ELISA:
  - $\beta$ -amyloid<sub>1-42</sub>
  - phosphorylated-tau 181p (p-tau)
  - total tau (tau)
- Apolipoprotein E4 (ApoE4) genotype
  - (34/95 carriers)
- 1mm<sup>3</sup> T1-weighted MRI at 3T (ADNI MPRAGE protocol)
  - total brain volume
  - HC and subfield volumetry

# Hippocampal subfield MRI atlases (N=5)

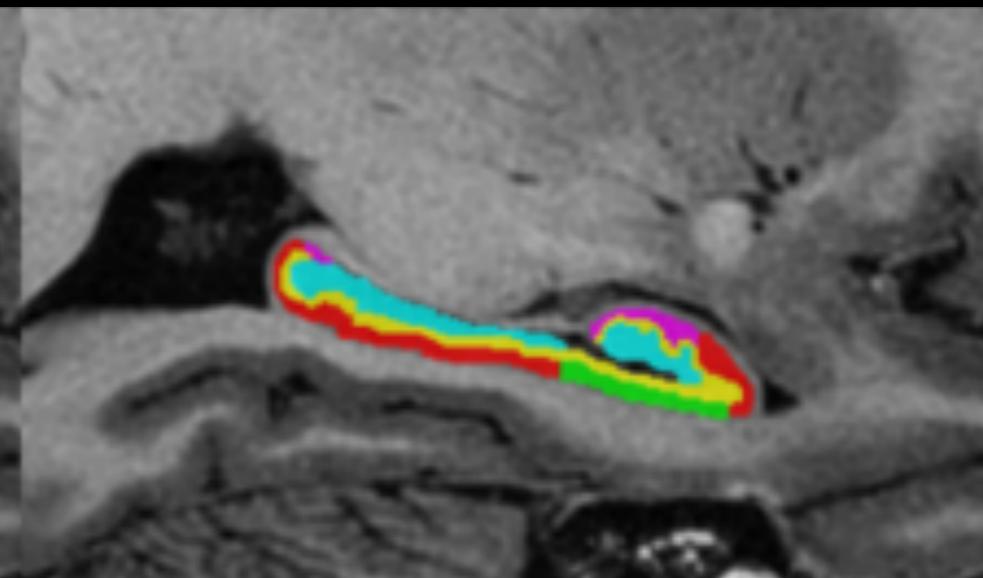
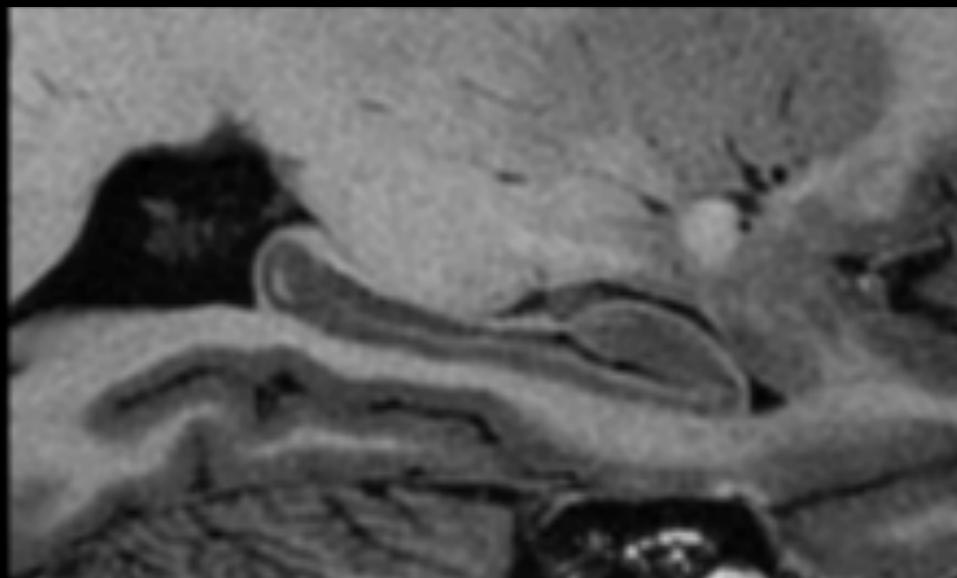
(Winterburn et al., NeuroImage 2013)



Sagittal view T1-weighted MRI

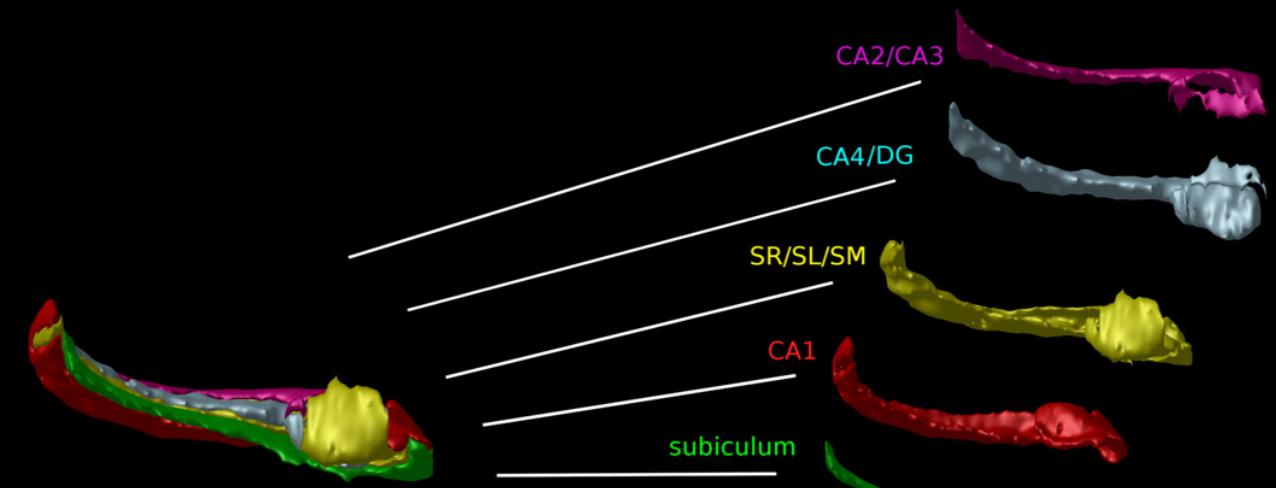
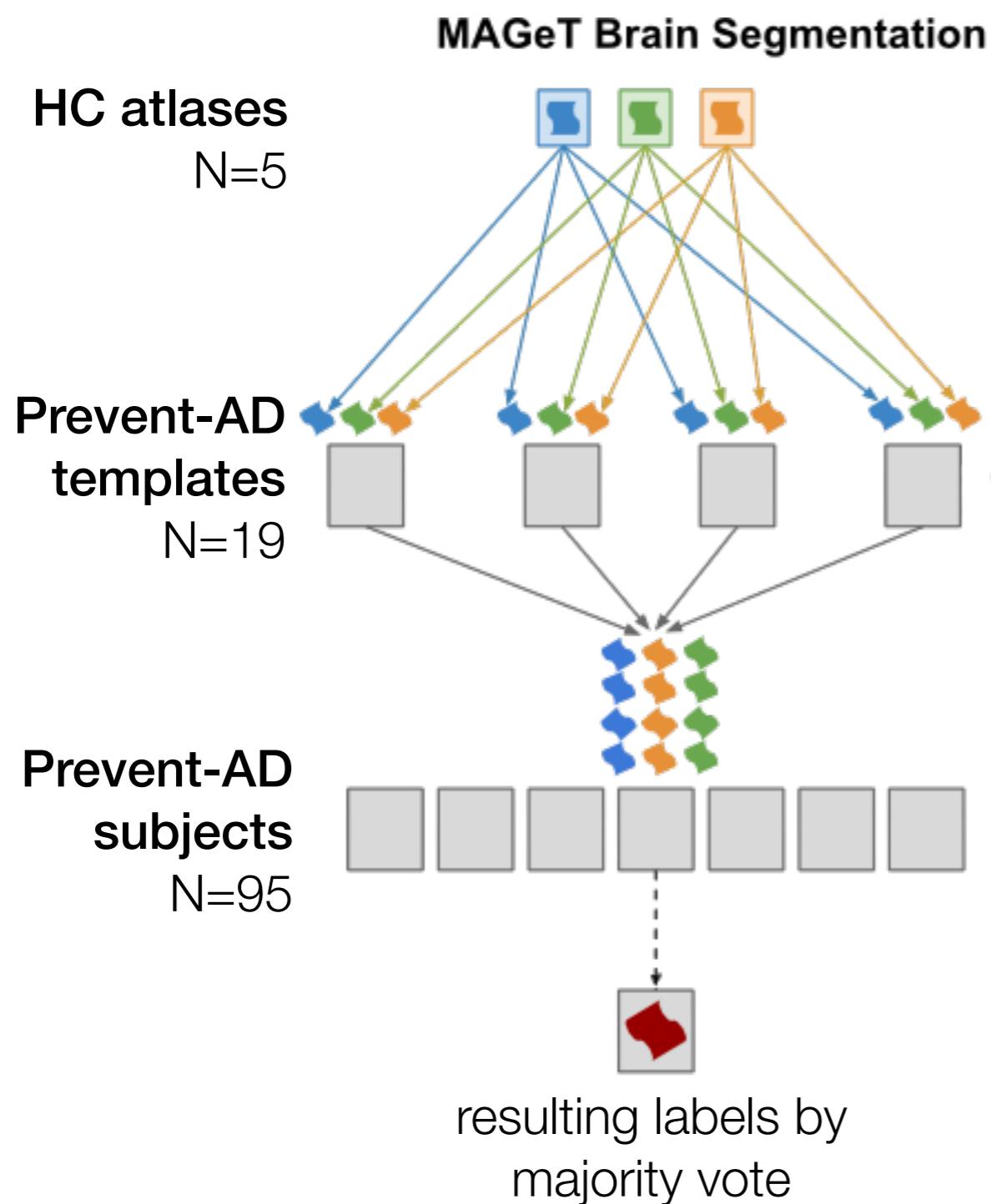


Hippocampal subfield labels

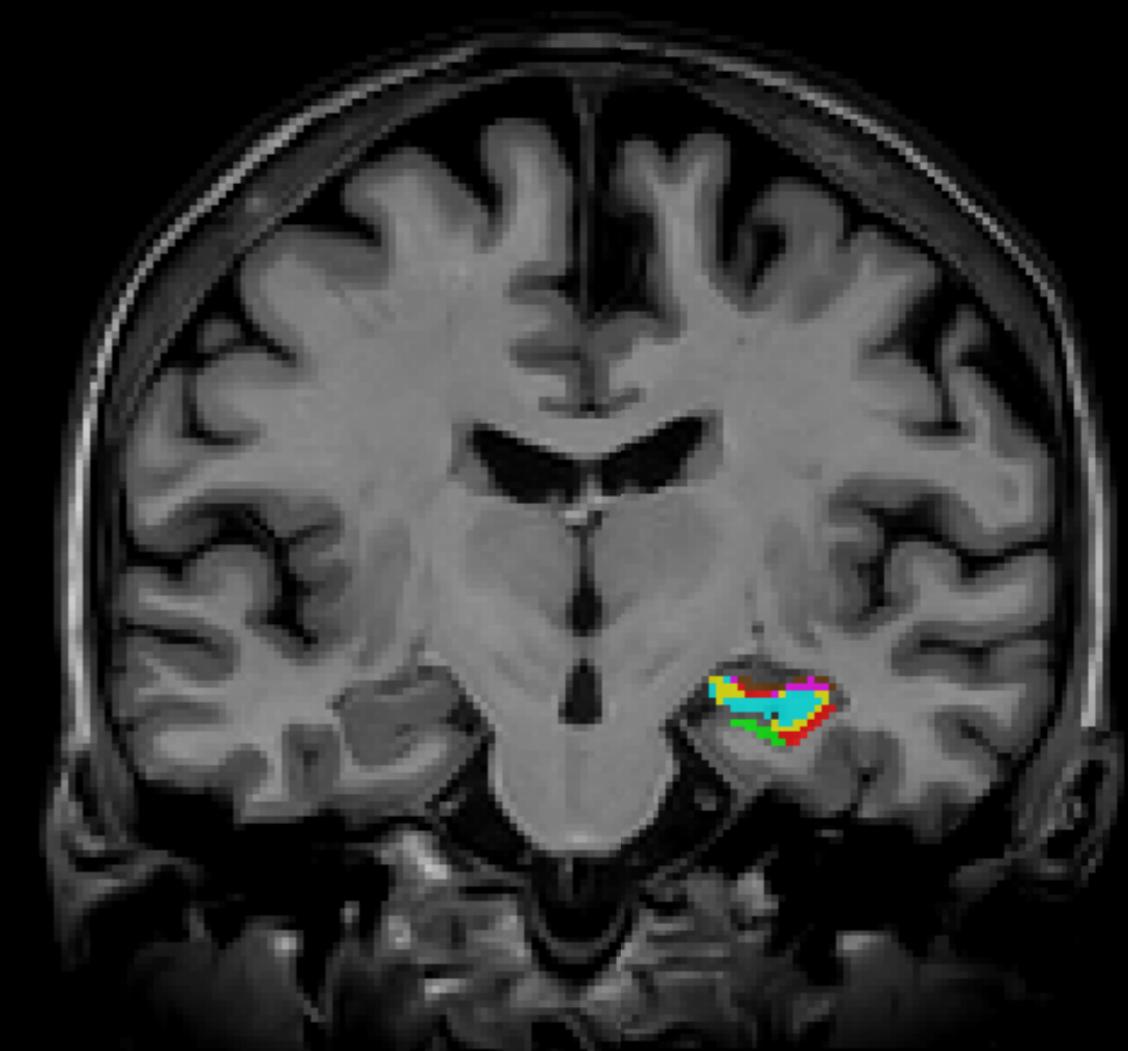


# HC subfield Atlas

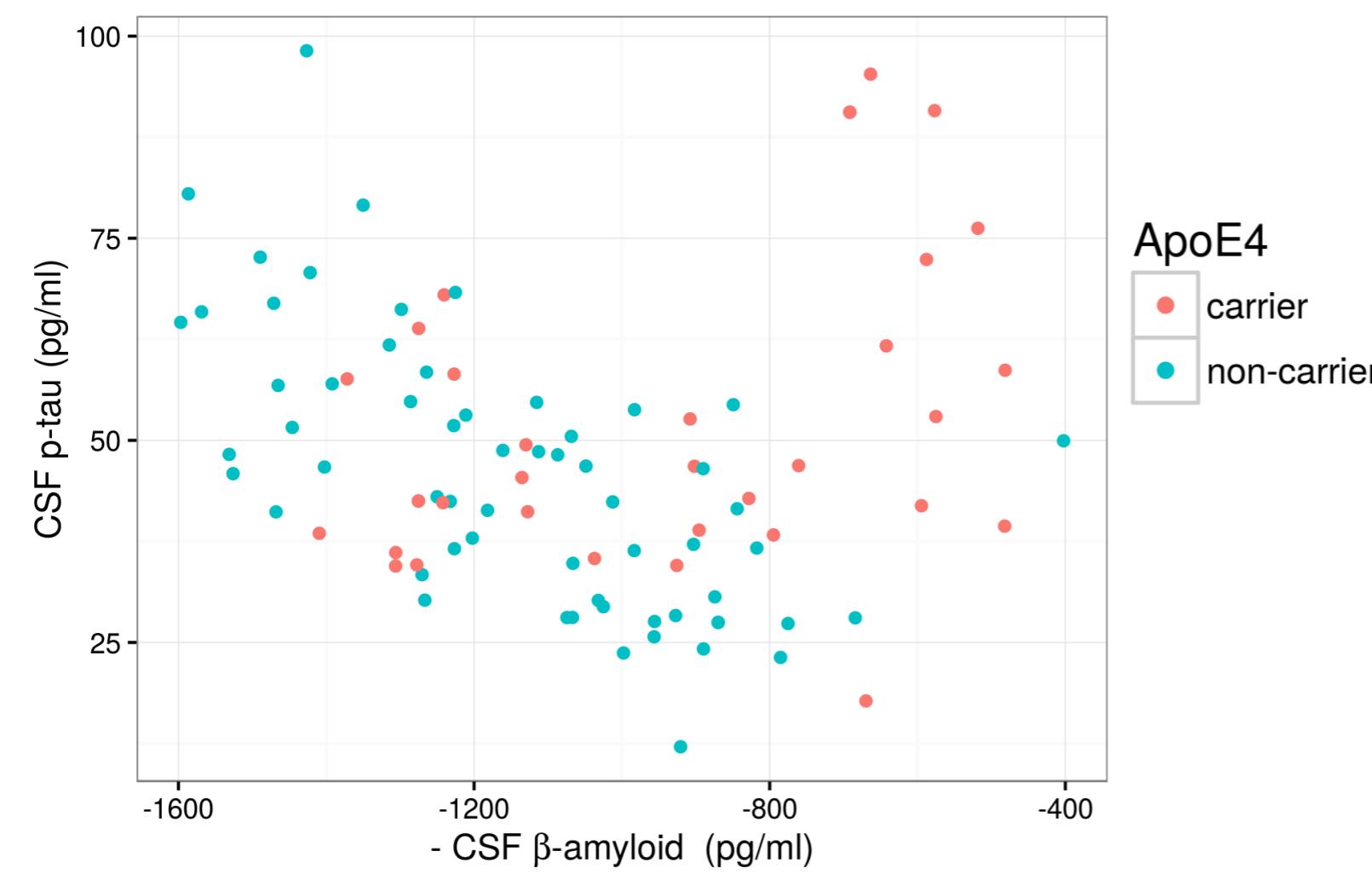
(Winterburn et al, 2013)



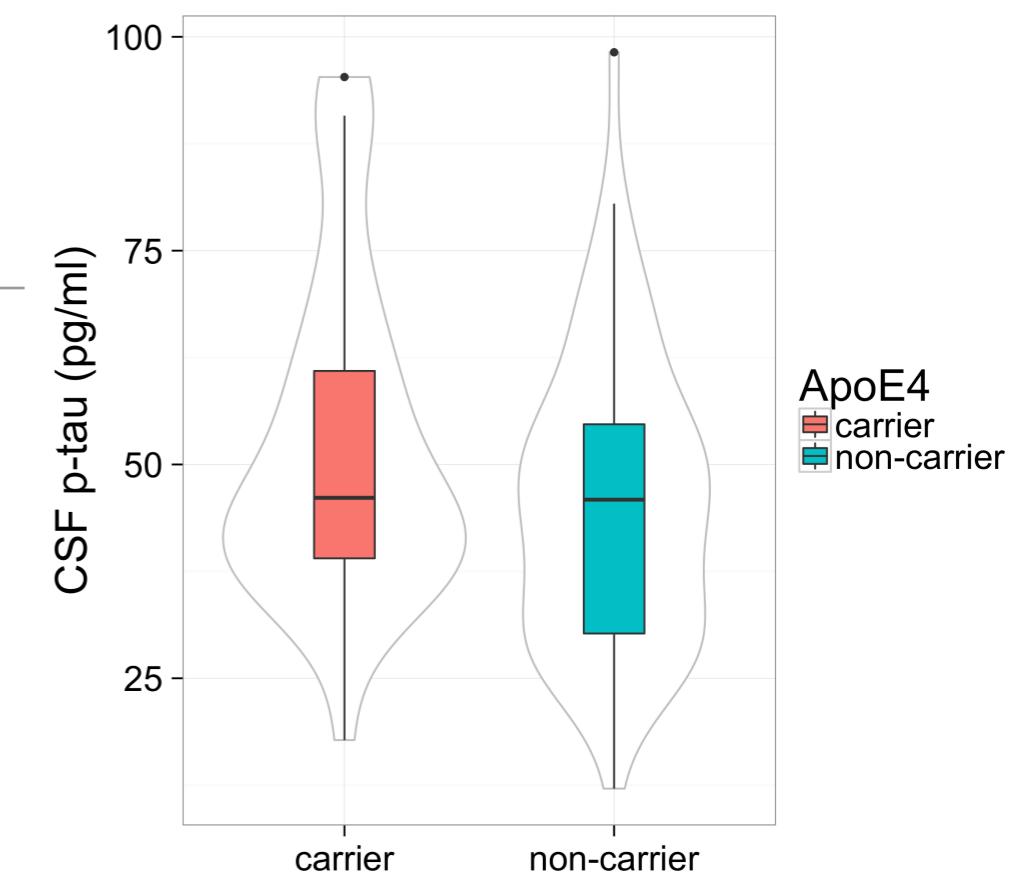
**Example subject segmentation**



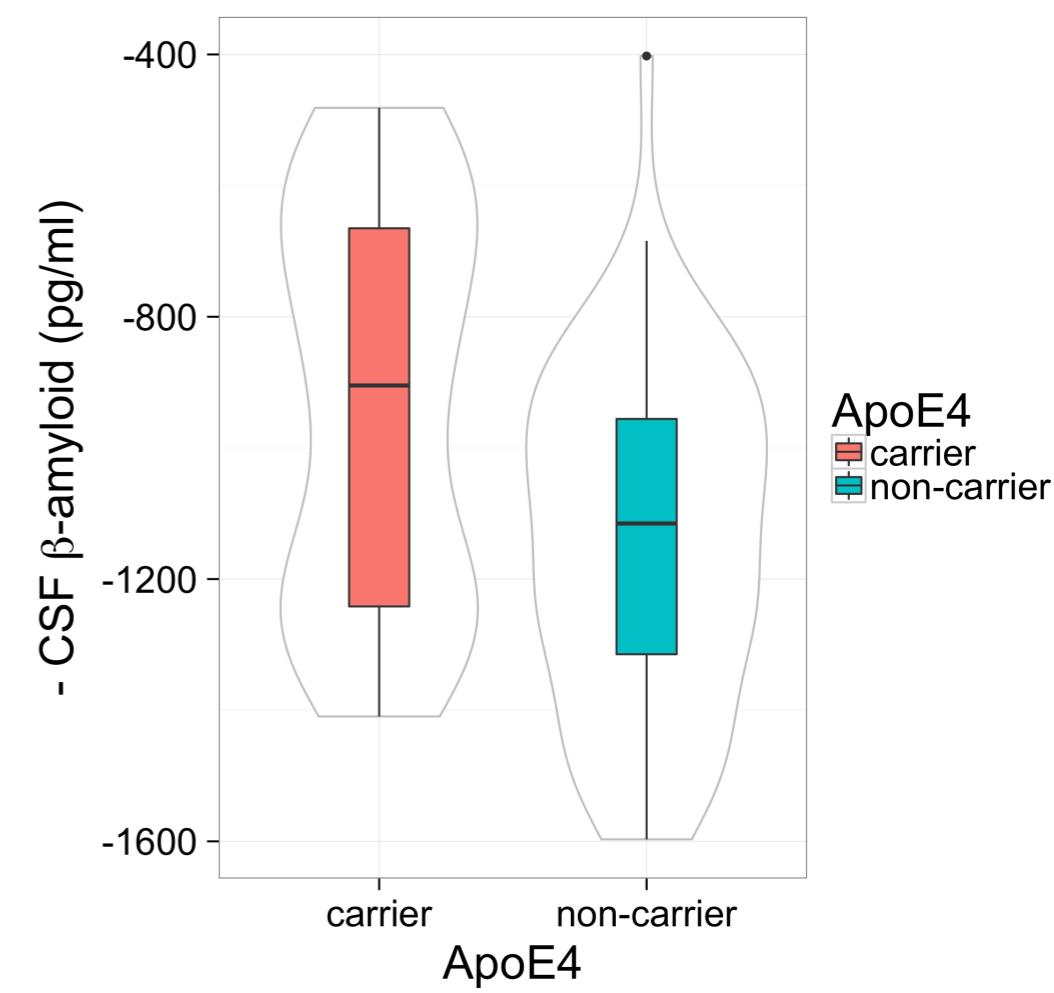
# CSF biomarker distribution



ApoE4  
carrier  
non-carrier



ApoE4  
carrier non-carrier



ApoE4  
carrier non-carrier

ApoE4  
carrier  
non-carrier

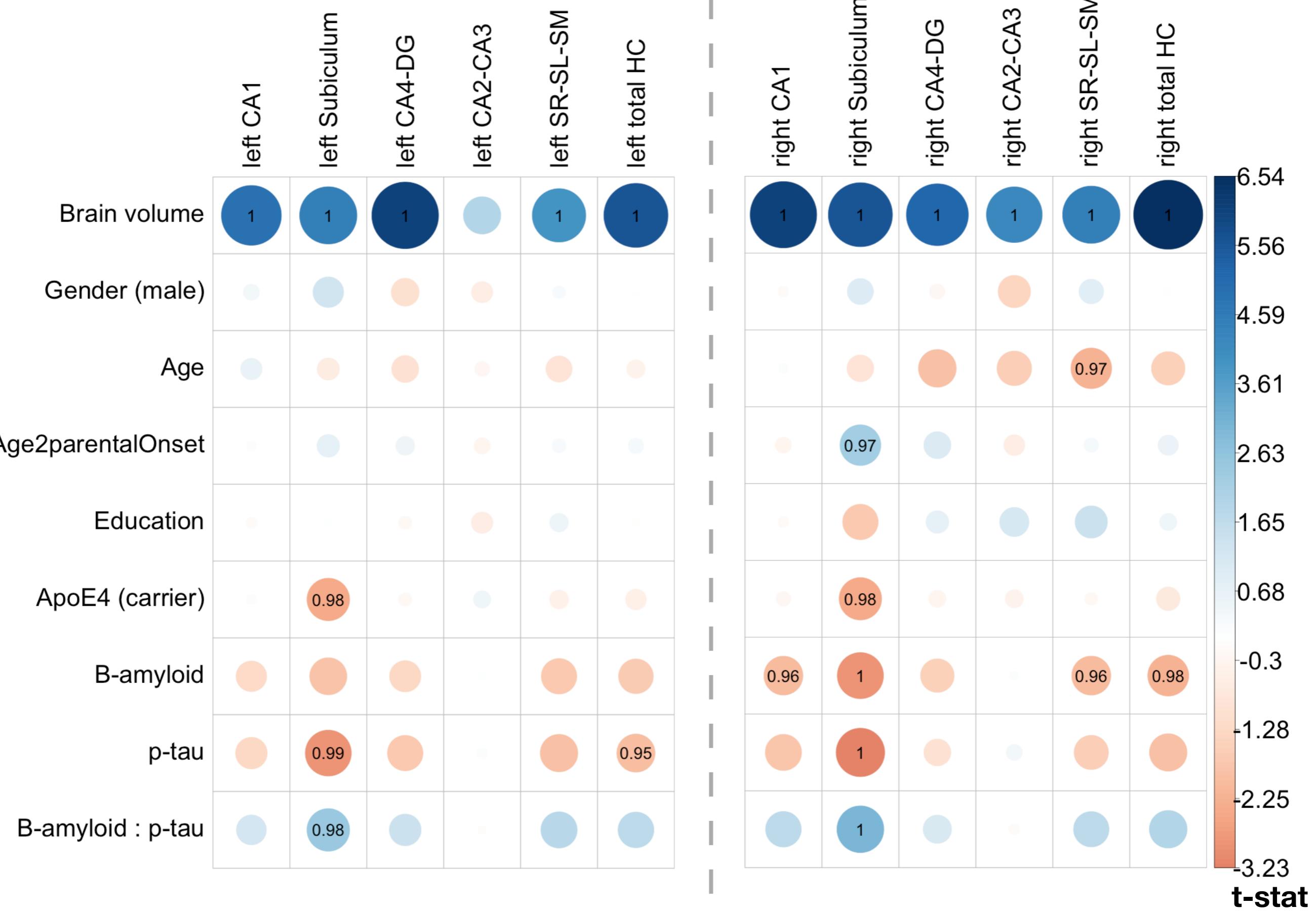
ApoE4  
carrier  
non-carrier

# Linear model

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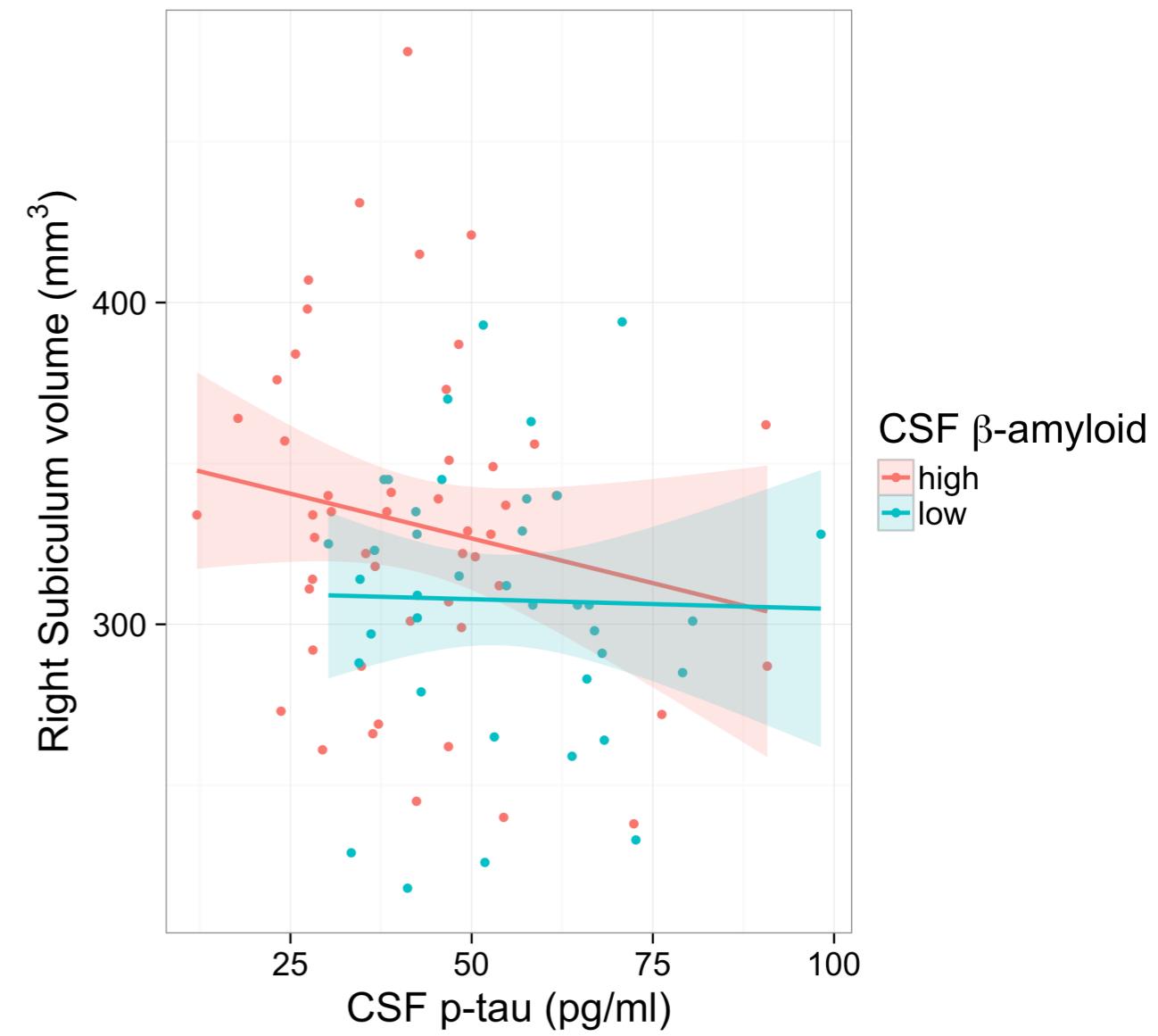
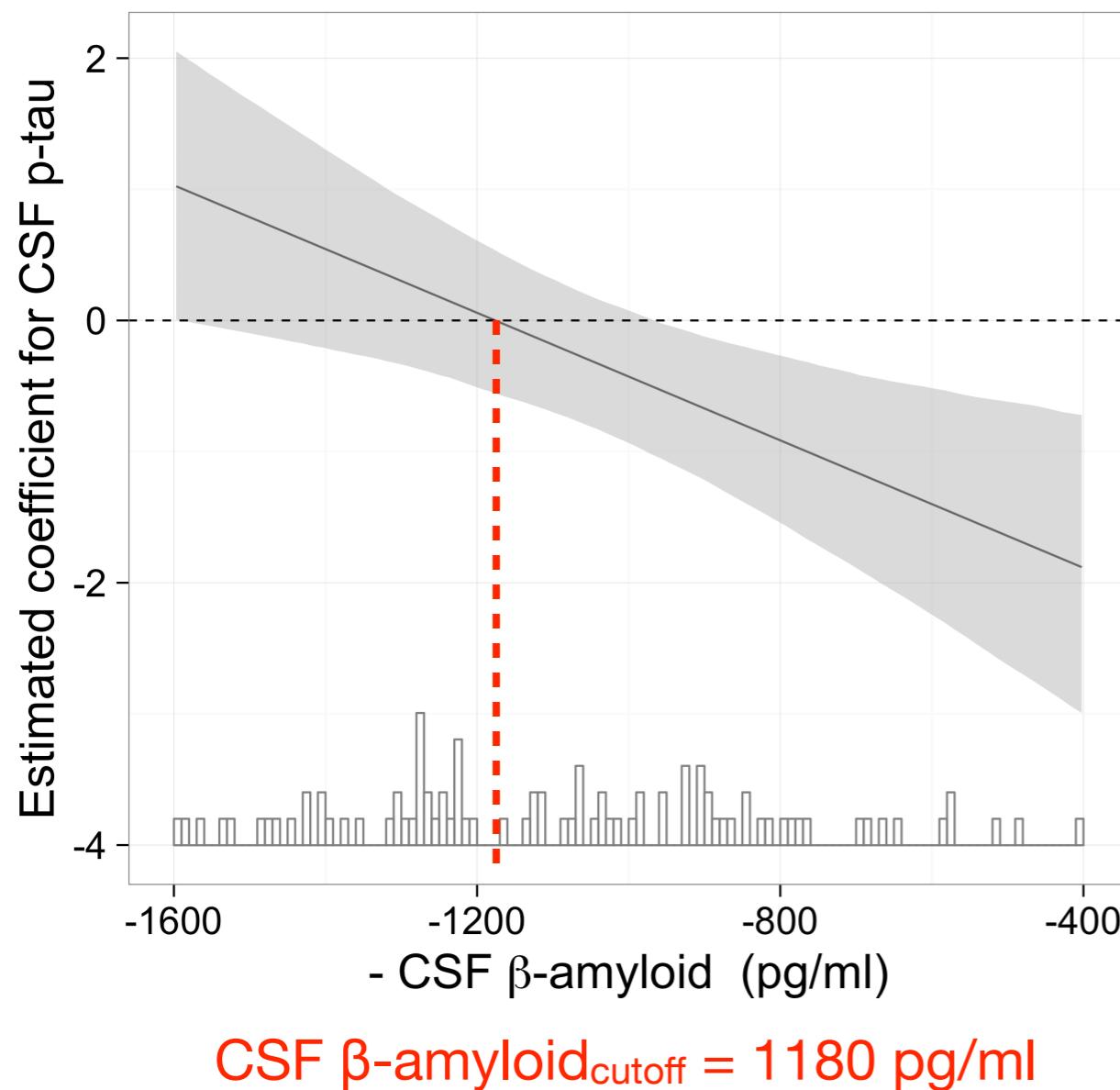
$$\begin{aligned} \text{HC volume} = & \beta_0 + \beta_1 (\text{Brain volume}) + \beta_2 (\text{Gender}) + \beta_3 (\text{Age}) \\ & + \beta_4 (\text{Age2ParentalOnset}) + \beta_5 (\text{Education}) \\ & + \beta_6 (\text{ApoE4 status}) + \beta_7 (\text{CSF p-tau}) + \beta_8 (\text{CSF } \beta\text{-amyloid}) \\ & + \beta_9 (\mathbf{p-tau} \times \mathbf{\beta-amyloid}) + \varepsilon \end{aligned}$$

# Left HC | Right HC



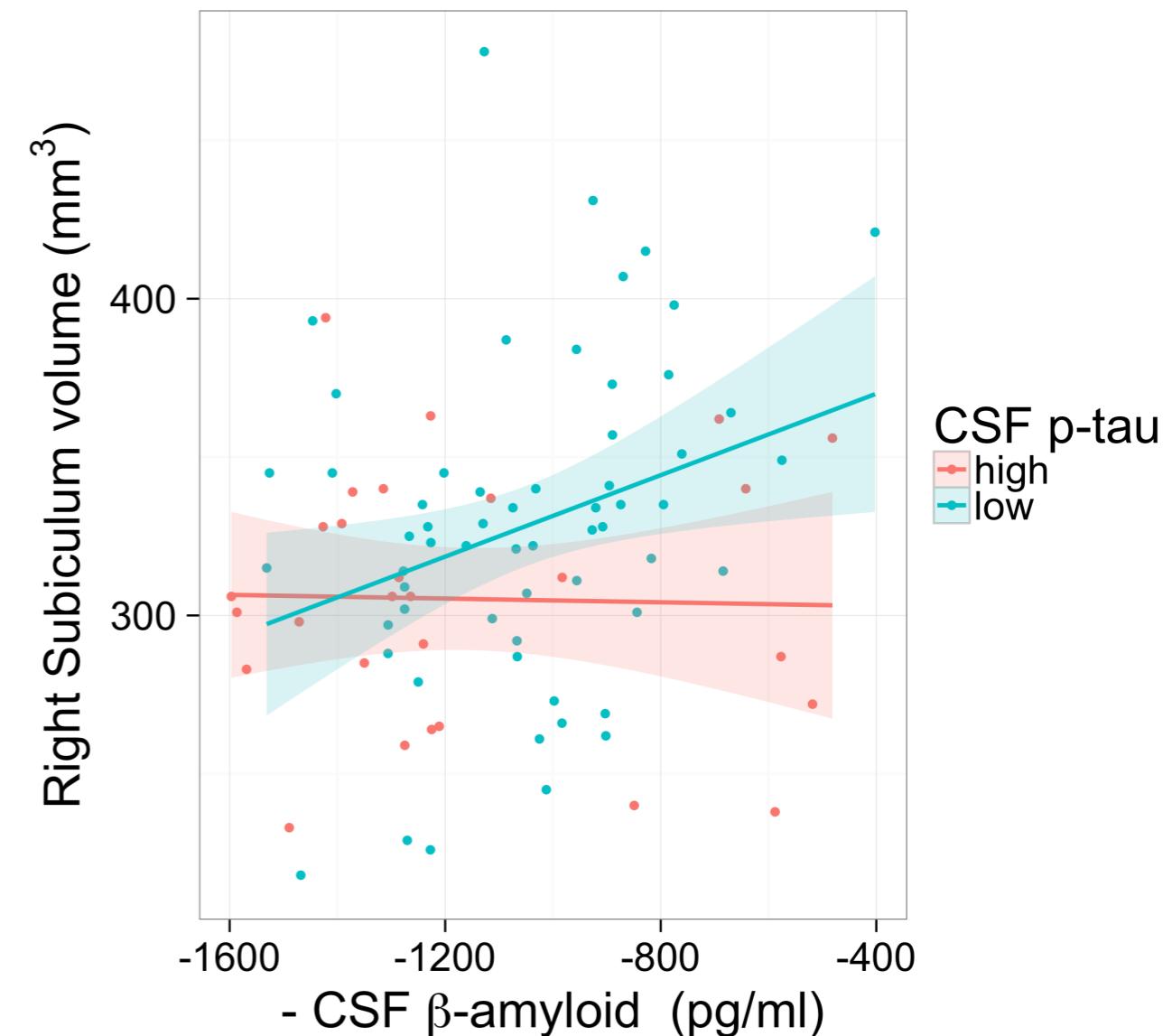
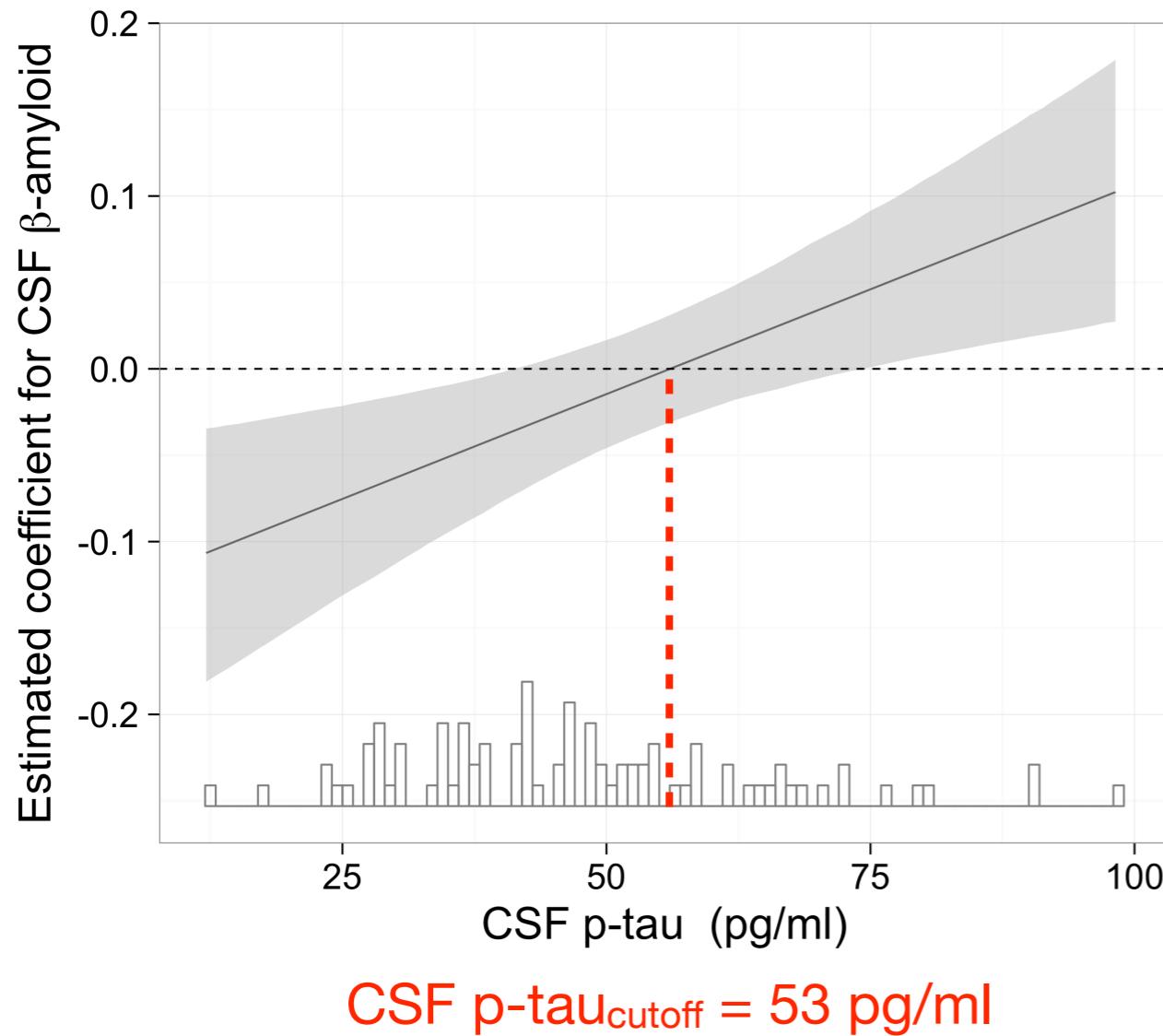
# p-tau : $\beta$ -amyloid interaction in the right subiculum

Subiculum volume **decreases** with  
increasing CSF p-tau for  
**high CSF  $\beta$ -amyloid group**



# p-tau : $\beta$ -amyloid interaction in the right subiculum

Subiculum volume ***increases*** with  
increasing -CSF  $\beta$ -amyloid for  
***low CSF p-tau group***

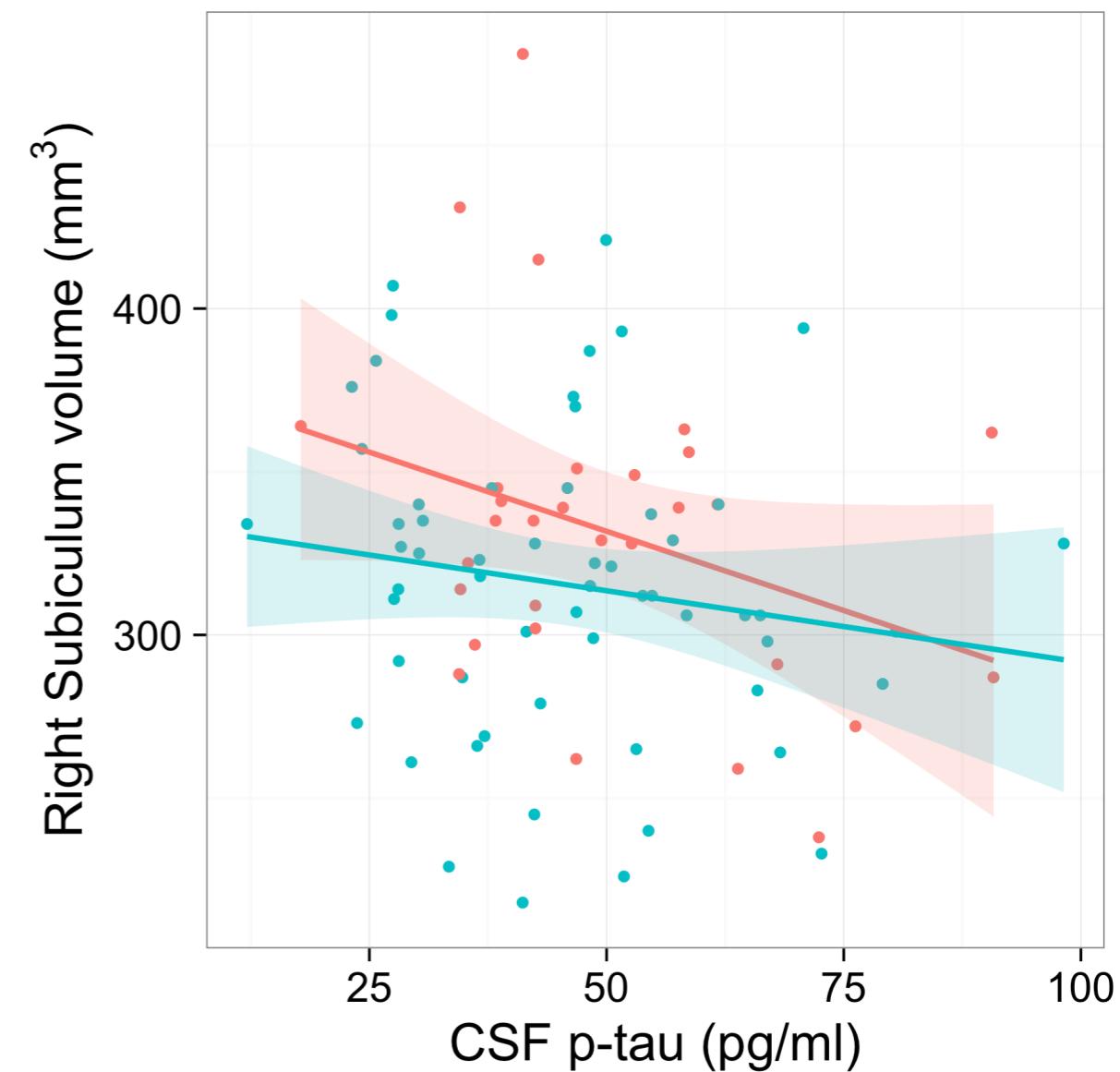
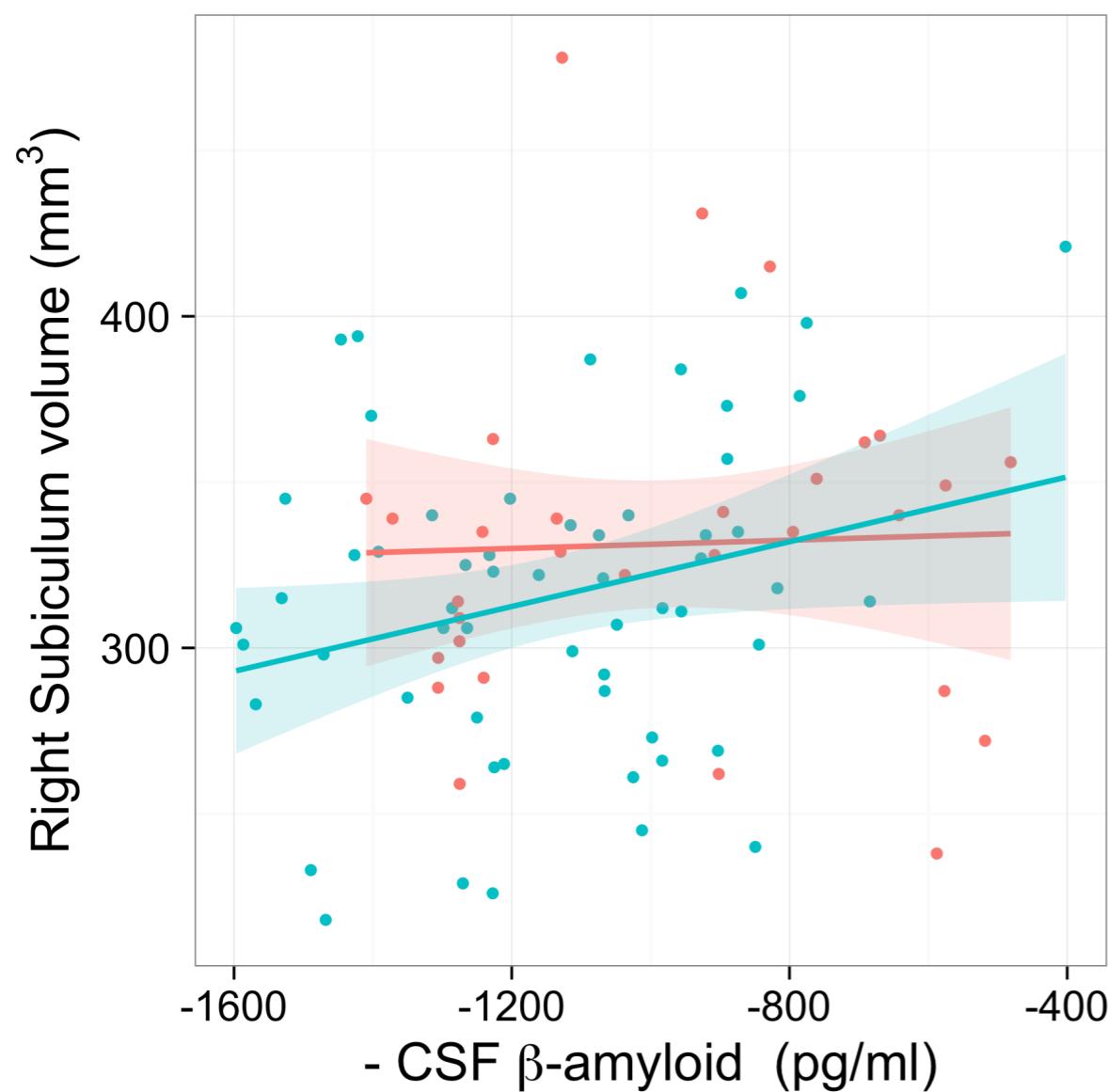


# Impact of ApoE4

Subiculum volume **increases** with decreasing CSF  $\beta$ -amyloid

carrier  
non-carrier

Subiculum volume **decreases** with increasing CSF p-tau



# Discussion

- 1 In subjects with high CSF  $\beta$ -amyloid:  
total hippocampal, CA1 and subiculum volumes decrease  
with increasing CSF p-tau
- 2 In subjects with high CSF p-tau:  
total hippocampal, CA1 and subiculum volumes increase  
with decreasing CSF  $\beta$ -amyloid
- 3 ApoE4 carriers have lower CSF  $\beta$ -amyloid

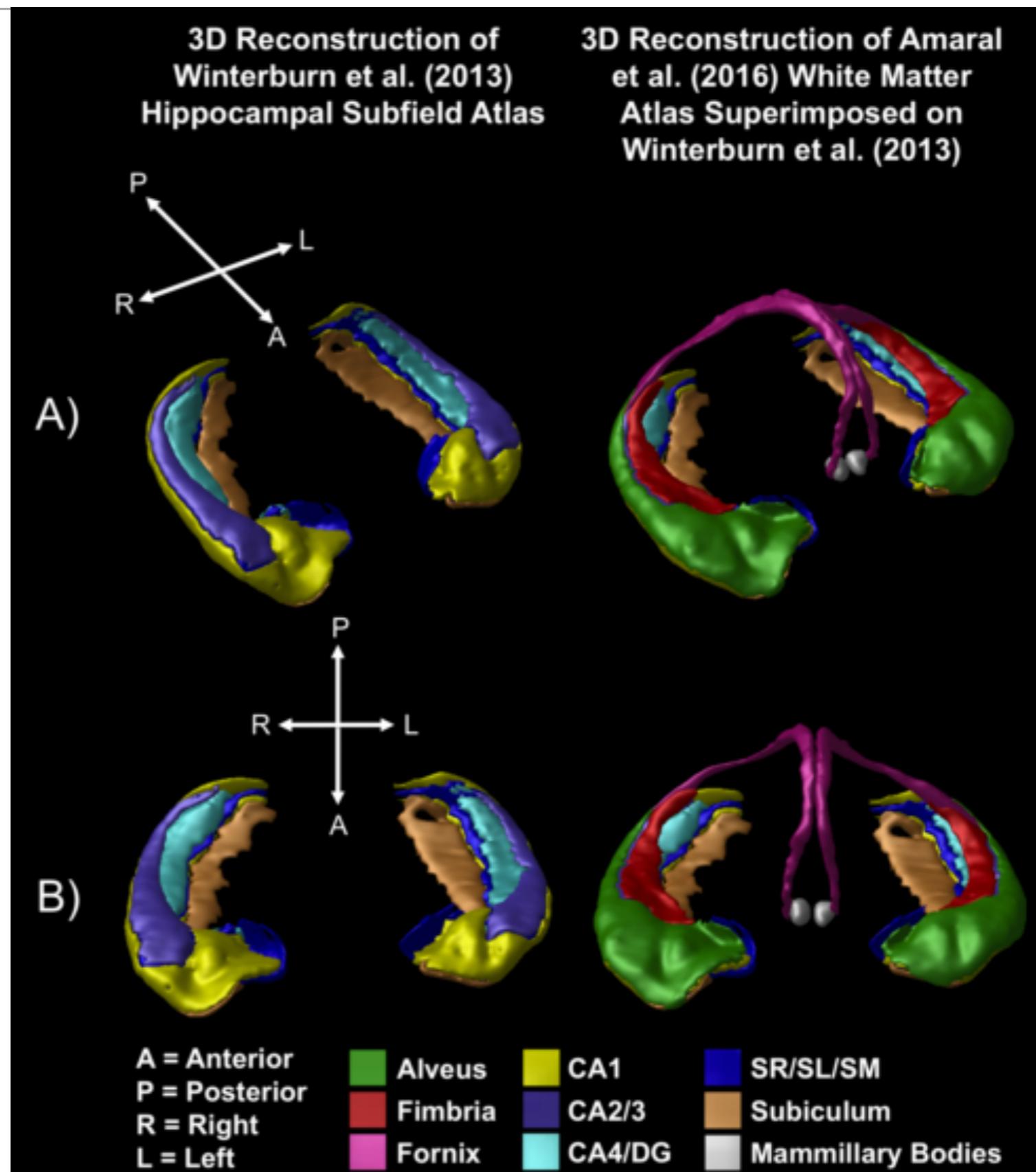


HC subfield volumes appear to be sensitive biomarkers of pathology in cognitively healthy individuals at familial risk for AD.

Combination of HC morphometry and CSF biomarkers gives a more complete characterization.

# Future work

- Investigate the relationship between hippocampal white matter and CSF biomarkers in this cohort
- Investigate whether baseline MR and CSF biomarkers predict subsequent decline



# Thank you!

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