Within the AD continuum, CSF Aβ42, **unlike pTau**, is associated with **reduced hippocampal subfields** in cognitively normal individuals.

This effect is found in **A+T-** against A-T- , but **not against A+T+**.

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Interactive effect of CSF Abeta42 and p-Tau on hippocampal subfield volumetry in cognitively unimpaired subjects

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INTRODUCTION

- Cerebrospinal fluid (CSF) biomarkers are used extensively in Alzheimer's Disease (AD) to monitor disease progression [1].
- Hippocampus is a crucial target in the AD neurodegenerative process [2]. However, previous reports of the relation between **biomarkers** and the **hippocampus** in **cognitively normal individuals** led to **inconsistent results**.
- Aim: we study here the association between **hippocampal subfield volumes** and **CSF levels** of **Aβ42** and **pTau** in a **cognitively unimpaired** population.

METHODS

- **N=334 cognitively unimpaired participants** aged between 49 and 77 from the **ALFA study** [3]. Thresholds of <1100 pg/mL for Aβ42 and >19.2 pg/mL for pTau were used to define **amyloid** (A) and **tau** (T) positive status (**Table 1**) in the AT(N) framework. Determinations of tTau were highly correlated with those of pTau and hence the "N" category was **not included** in this analysis.

	A+		A-		Total	
	N	mean age (SD)	N	mean age (SD)	N	mean age (SD)
T+	29	66.33 (4.05)	65	63.21 (5.29)	94	64.17 (5.13)
T-	79	60.89 (5.98)	161	61.64 (5.25)	240	61.39 (5.50)
Total	108	62.35 (6.02)	226	62.09 (5.29)	334	62.17 (5.53)

Table 1. Sample distribution based on CSF amyloid and tau statuses. Amyloid-positive (A+) subjects (negative (A-), respectively) have levels of Aβ42 lower (higher) than 1100 pg/mL. Tau-positive (T+) subjects (negative (T-), respectively) have levels of p-Tau higher (lower) than 19.2 pg/mL

- T1 MR images were acquired at 3T with 0.75mm-isotropic voxels and hippocampal subfields were segmented using FreeSurfer 6.0 [4].
- Two separate analyses were considered. First, subjects **within the AD continuum** (**A+T-**, **A+T+**) were compared to A-T- controls.
Second, **A-T+ subjects** were compared to controls.
- Finally, we looked for associations between subfields and **continuous measurements of Aβ42 and pTau**, after covarying for age, sex, education, and total intracranial volume. Aβ42 and pTau were log-transformed to correct for distribution skewness. Results are presented at p<0.005 uncorrected. .

RESULTS

- In the "AD continuum", subfield volumes showed **significant association with Aβ42** (the lower the CSF amyloid, the lower the volume) in the right hemisphere (**Figure 1**) but not with p-Tau.
- Group comparisons revealed **significantly lower volumes in A+T-** against **A-T-** in the same subfields, but **not against A+T+** (**Figure 2**).
- In the "non-amyloid group", **A-T+ subjects showed larger right hippocampal tail volumes** than A-T- (**Figure 3**).

CONCLUSIONS

- Within the AD continuum, CSF Abeta42, **unlike pTau**, is associated with **lower hippocampal subfield volumes**.
- Interestingly, this pattern seemed to revert in A+T+ subjects, possibly related to an **inflammatory peak** linked to **early tau pathology**.
- Tau-positive amyloid-negative subjects showed larger subfieds
- This might reflect the expression of **distinct neurobiological**, potentially pathological, **pathways**, in different populations.

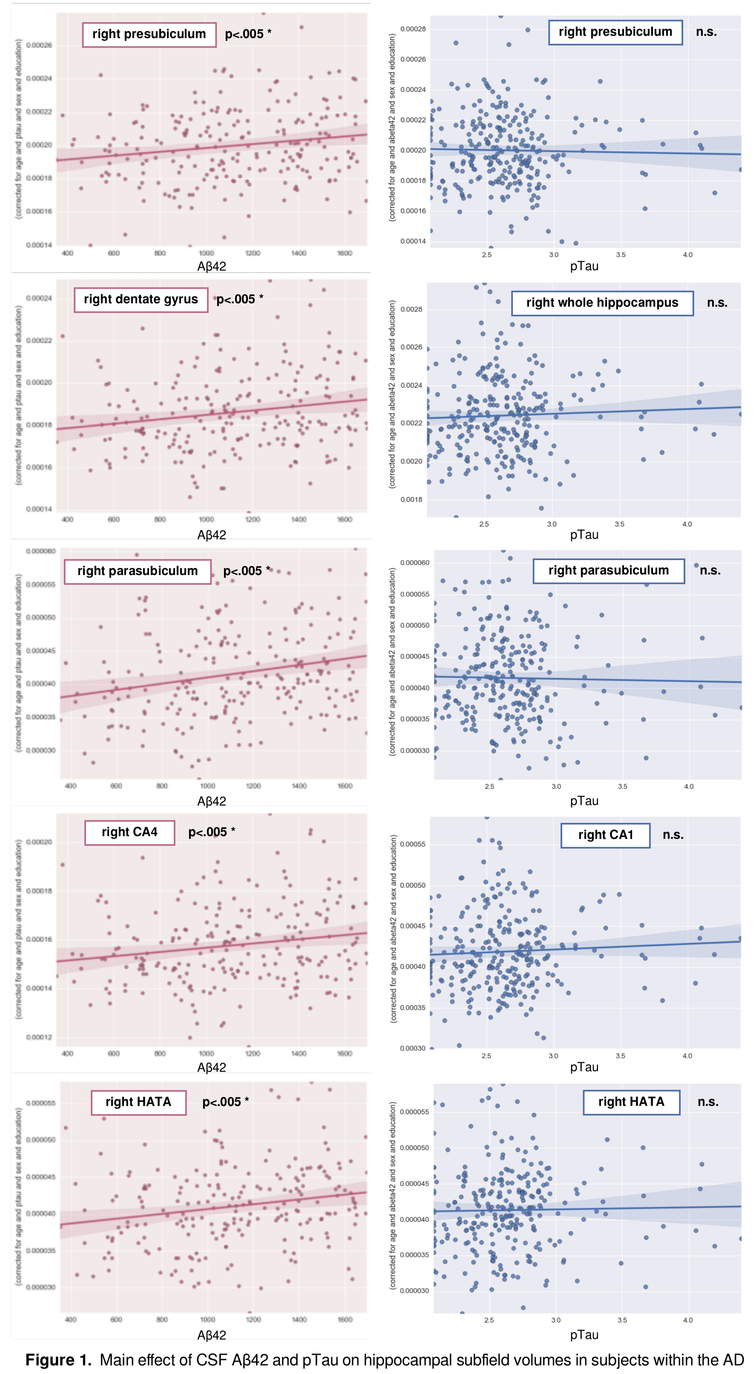

Figure 1. Main effect of CSF Aβ42 and pTau on hippocampal subfield volumes in subjects within the AD continuum (A-T-, A+T-, A+T+) (corrected for total intracranial volume, age, sex, education).
All subfields show significant associations with Aβ42 but none with p-Tau (p<.005 uncorr.)

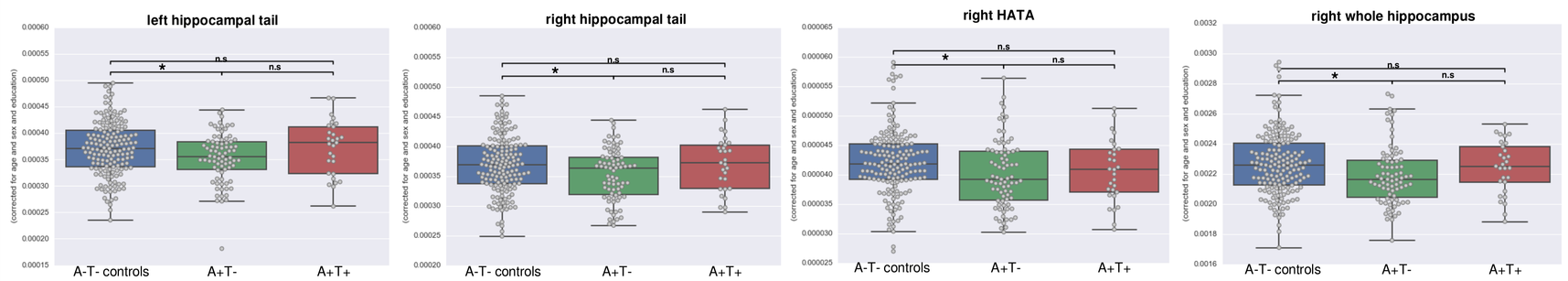

Figure 2. Main effect of CSF Aβ42/pTau status on hippocampal subfield volumes in subjects within the AD continuum (A-T-, A+T-, A+T+) (corrected for total intracranial volume, age, sex, education)

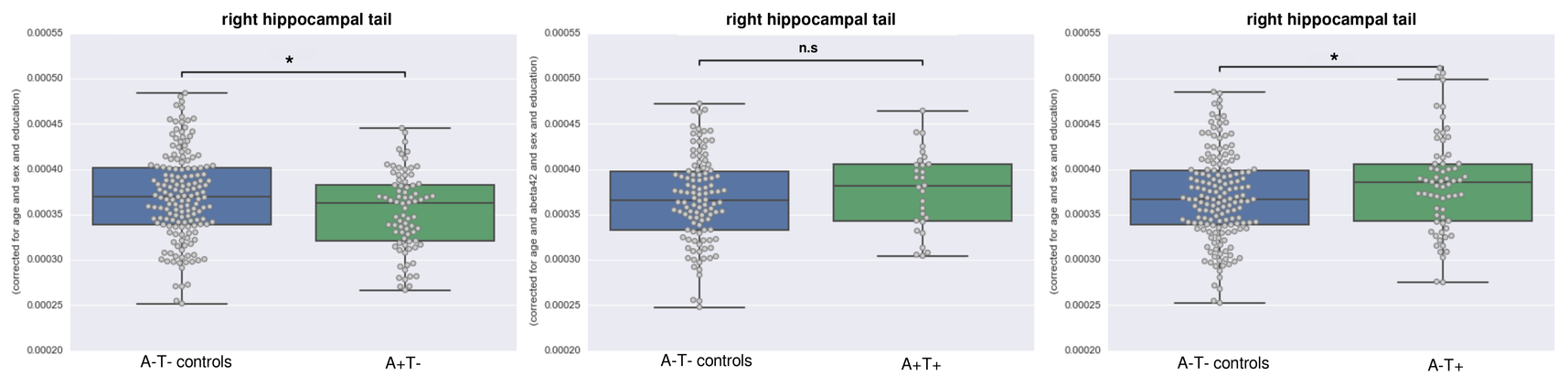

Figure 3. Main effect of CSF status on right hippocampal tail volumes (corrected for total intracranial volume, age, sex, education)
The two plots on the left show subjects within the AD continuum whereas the one on the right involves amyloid-negative subjects only.

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