# Supplementary S3 – Sensitivity analyses

## External cohorts

Three external cohorts (see Table S3.1 for demographics) were used to validate the findings between the asymmetries of Aβ and tau – Open Access Series of Imaging Studies (OASIS-3; <https://sites.wustl.edu/oasisbrains/>), Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4; <https://www.a4studydata.org/>), and Alzheimer’s Disease Neuroimaging Initiative (ADNI; <https://adni.loni.usc.edu/>). For each cohort, only subjects with evidence of both Aβ and tau (A+T+) were selected. All these cohorts used [18F] florbetapir PET for Aβ imaging and [18F] flortaucipir PET for tau imaging. Aβ positivity was pre-defined by the cohort creators for OASIS-3 and ADNI datasets, but a cut-off of Global Aβ-PET SUVR > 1.11 was used for A4. Tau positivity was defined based on a Temporal meta-ROI SUVR > 1.34 cut-off for each external cohort.

**Table S3.1**. Demographics of the external cohorts.   
Categorical variables have been presented as 'count (%)', normally distributed continuous variables as 'mean (SD)' and non-normally distributed variables as ‘median [IQR]’. OASIS-3 – Open Access Series of Imaging Studies; A4 – Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease; ADNI – Alzheimer’s Disease Neuroimaging Initiative; M – male; F – female; CU – cognitively unimpaired; CI – cognitively impaired; SUVR – standardised uptake value ratio; Aβ – amyloid-beta.

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| --- | --- | --- | --- | --- |
|  |  | **OASIS-3  (A+T+; n=46)** | **A4  (A+T+; n=55)** | **ADNI  (A+T+; n=133)** |
| **Age, years** | | 74.61 (6.77) | 72.65 (5.06) | 72.39 (6.72) |
| **Sex** | **M** | 21 (46%) | 21 (38%) | 56 (42%) |
| **F** | 25 (54%) | 34 (62%) | 77 (58%) |
| **Education, years** | | 15.78 (2.60) | 16.60 (2.66) | 15.69 (2.40) |
| **Diagnosis** | **CU** | 15 (33%) | 55 (100%) | 23 (17%) |
| **CI** | 31 (67%) | 0 (0%) | 110 (83%) |
| **Temporal tau, SUVR** | | 1.57 [1.45,1.85] | 1.38 [1.34,1.46] | 1.57 [1.39,1.82] |
| **Global Aβ, SUVR** | | 1.40 [1.27,1.59] | 1.37 [1.27,1.46] | 1.42 [1.32,1.53] |

## Partial volume corrected PET

In the main analysis, we decided to use non-partial volume corrected PET SUVR values for Aβ and tau uptake, but to further check that our main analysis findings did not arise from this methodological choice, we decided to perform a sensitivity analysis using partial volume corrected PET SUVR values. This replication displayed similarly strong effect between Aβ laterality and tau laterality in all main ROIs after removing one outlier (Fig. S3.1; Global: β=0.648, p<0.001; Braak I-II: β=0.178, p=0.005; Braak III-IV: β=0.705, p<0.001; Braak V-VI: β=0.590, p<0.001).



**Figure S3.1**. Association between Aβ and tau laterality with using partial volume corrected SUVR values for calculating laterality.

## Association of the laterality of Aβ and tau with cerebral blood flow and cortical thickness

To test whether our main finding of strong associative effect between Aβ and tau asymmetries was not due to other biological confounders, we tested how Aβ laterality and tau laterality are associated to cerebral blood flow and cortical thickness. Only tau laterality was negatively related to laterality in cerebral blood flow (β=-0.527, p<0.001), but not Aβ (β=-0.241, p=0.085) (Fig. S3.2a). Furthermore, asymmetries of both pathologies were negatively associated with laterality in cortical thickness, but with greatly stronger effect with tau (β=-0.629, p<0.001) than Aβ (β=-0.185, p=0.005) (Fig. S3.2c). However, the association between the asymmetries of Aβ and tau was still present after adjusting for the laterality of either cerebral blood flow (Fig. S3.2b; β=0.498, p<0.001) or cortical thickness (Fig. S3.2d; β=0.560, p<0.001).



**Figure S3.2**. Associations between the laterality of both Aβ and tau to the laterality of CBF and CT: (a) between the laterality of Aβ/tau and CBF; (b) between the laterality of Aβ and tau after adjusting for CBF; (c) between the laterality of Aβ/tau and CT; (d) between the laterality of Aβ and tau after adjusting for CT.  
Aβ – amyloid-beta; CBF – cerebral blood flow; CT – cortical thickness

## Alternative brain parcellation

The main analysis of this study used Desikan-Killiany atlas for brain parcellation and segmentation. To make sure that our findings were not biased from this methodological choice, we replicated the main analysis using instead the Schaefer-400 atlas, which confirmed the association between Aβ laterality and tau laterality (Fig. S3.3; Global: β=0.640, p<0.001; Temporal: β=0.646, p<0.001).



**Figure S3.3**. Association between Aβ and tau laterality with using Schaefer-400 atlas for brain parcellation.