Supplemental Materials

Supplementary Table 1 Associations between amyloid-β, tau, neurodegeneration and memory at the individual-level additionally corrected for *APOE* ε4 status

	Early-AD ROI	**AD signature ROI**
	GEE	GEE
Aβ-PET BP_{ND} vs. tau-PET BP_{ND}	**β=0.63, *p*<0.001 N=78**	**β=0.61, *p*<0.001 N=78**
Aβ-PET BP_{ND}/y vs. tau-PET BP_{ND}	**β=0.36, *p*<0.001 N=74**	**β=0.29, *p*=0.01 N=74**
Aβ-PET BP_{ND} vs. neurodegeneration	**β=-0.16, *p*=0.04 N=78**	β=-0.20, *p*=0.06 N=78
Aβ-PET BP_{ND}/y vs. neurodegeneration	β=-0.02, *p*=0.83 N=74	β=-0.01, *p*=0.99 N=74
Tau-PET BP_{ND} vs. neurodegeneration	**β=-0.18, *p*=0.04 N=78**	**β=-0.22, *p*=0.01 N=78**
Aβ-PET BP_{ND} vs. composite memory	**β=-0.45, *p*<0.001 N=78**	**β=-0.41, *p*<0.001 N=78**
Aβ-PET BP_{ND}/y vs. composite memory	**β=-0.24, *p*=0.01 N=74**	**β=-0.22, *p*=0.02 N=74**
Tau-PET BP_{ND} vs. composite memory	**β=-0.61, *p*<0.001 N=78**	**β=-0.53, *p*<0.001 N=78**
Neurodegeneration vs. composite memory	**β=0.41, *p*=0.01 N=78**	β=0.17, *p*=0.11 N=78

All GEE models are corrected for age, sex and *APOE* ε4 status. GEE models with Aβ-PET BPND/y as predictor are additionally corrected for initial Aβ-PET BPND. Aβ-PET BPND/y was missing for n=4 twins due to missing initial Aβ-PET. GEE models with memory functioning as outcome are additionally corrected for education. We scaled predictor and outcome variables within each GEE to enable comparison of effect sizes (except for hippocampal volume, which was a standardized residual corrected for intracranial volume).

Supplementary Table 2 Results for associations with retrospective annual change in Aβ-PET BP_{ND} without correcting for Aβ-PET at T=-4.

	Early-AD ROIs		**AD-signature ROIs**	
	GEE	**Twin-difference**	**GEE**	**Twin-difference**
Aβ-PET BP_{ND}/y vs. tau-PET BP_{ND}	**β=0.34, *p*=0.003 N=74**	**β=0.44, *p*=0.01 N=33**	**β=0.28, *p*=0.02 N=74**	β=0.31, *p*=0.08 N=33
Aβ-PET BP_{ND}/y vs. neurodegeneration	β=-0.02, *p*=0.83 N=74	β=-0.06, *p*=0.73 N=33	β=-0.01, *p*=0.95 N=74	β=0.15, *p*=0.42 N=33
Aβ-PET BP_{ND}/y vs. composite memory	**β=-0.24, *p*=0.04 N=74**	β=-0.25, *p*=0.17 N=33	**β=-0.26, *p*=0.02 N=74**	β=-0.29, *p*=0.11 N=33

This table represents similar results as reported in **Table 2**, but without correcting for Aβ-PET BP_{ND} at T=-4. GEE models are corrected for age and sex. GEE and twin-difference models with memory functioning as outcome are additionally corrected for (within-pair difference in) education. We scaled predictor and outcome variables within each GEE to enable comparison of effect sizes (except for hippocampal volume, which already was a standardized residual corrected for intracranial volume).

Supplementary Table 3 Associations between amyloid-β, tau, neurodegeneration and PACC

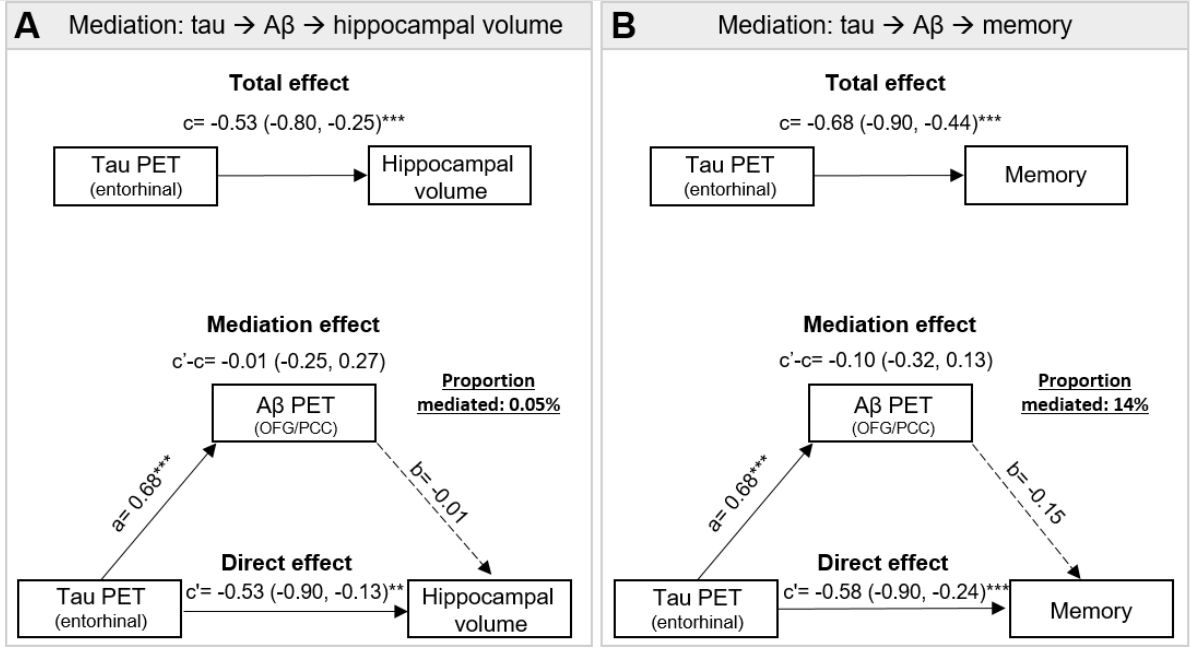
	Early-AD ROIs		**AD-signature ROIs**	
	GEE	Twin-difference	GEE	Twin-difference
Aβ-PET BP_{ND} vs. PACC-5	**β=-0.45, *p*<0.001 N=78**	**β=-0.54, *p*=0.001 N=37**	**β=-0.46, *p*<0.001 N=78**	**β=-0.55, *p*<0.001 N=37**
Aβ-PET BP_{ND}/y vs. PACC-5[a]	**β=-0.26, *p*<0.001 N=74**	β=-0.35, *p*=0.05 N=33	**β=-0.29, *p*<0.001 N=74**	**β=-0.36, *p*=0.04 N=33**
Aβ-PET BP_{ND}/y vs. PACC-5[b]	**β=-0.24, *p*=0.01 N=74**	**β=-0.36, *p*=0.04 N=33**	**β=-0.29, *p*<0.001 N=74**	**β=-0.42, *p*=0.02 N=33**
Tau-PET BP_{ND} vs. PACC-5	**β=-0.56, *p*<0.001 N=78**	**β=-0.67, *p*<0.001 N=37**	**β=-0.42 *p*<0.001 N=78**	**β=-0.65, *p*<0.001 N=37**
Neurodegeneration vs. PACC-5	**β=0.37, *p*=0.005 N=78**	**β=0.46, *p*=0.005 N=37**	β=0.19, *p*=0.05 N=78	**β=0.39, *p*=0.02 N=37**

All GEE models are corrected for age and sex. GEE models and twin-difference models with Aβ-PET BP_{ND}/y as predictor variable are additionally corrected for (within-pair difference in) baseline Aβ-PET BP_{ND}. GEE models and twin-difference models with memory functioning as outcome variable are additionally corrected for (within-pair difference in) education. We scaled predictor and outcome variables within each GEE to enable comparison of effect sizes (except for hippocampal volume, which was a standardized residual corrected for intracranial volume).

[a] With correction for Aβ-PET BP_{ND} at T=-4

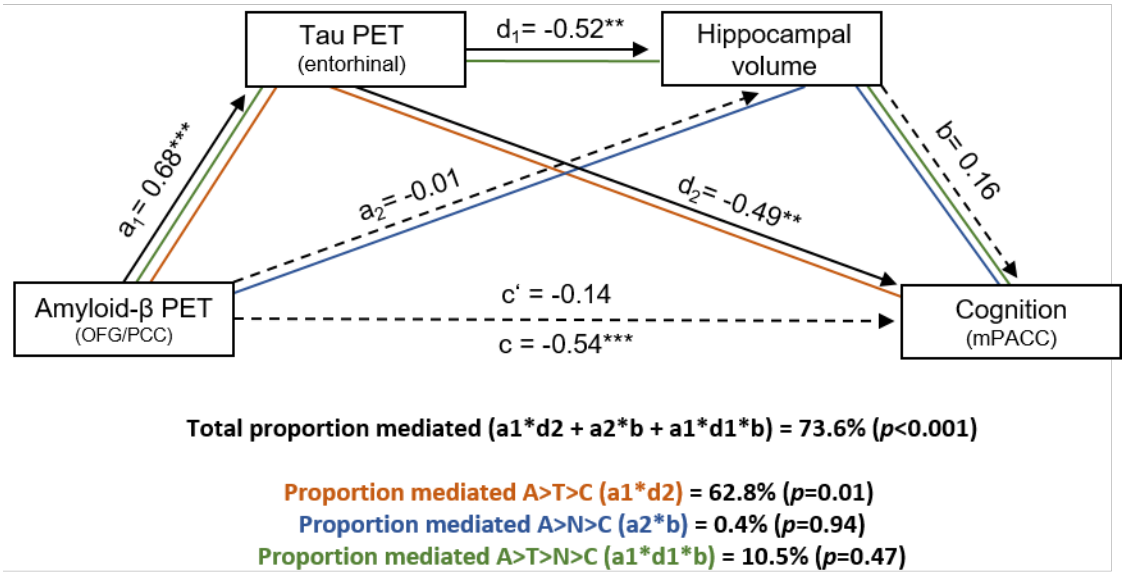
[b] Without correction for Aβ-PET BP_{ND} at T=-4

Supplementary Figure 1 Mediation analyses testing the mediating effect of Aβ in the associations between 1) tau and hippocampal volume, and 2) tau and memory



In **(A)** the direct effect of within-pair differences in tau PET on within-pair differences in hippocampal volume is shown, as well as the mediating effect of within-pair differences in amyloid-β PET in this association. In **(B)** the direct effect of within-pair differences in tau PET on within-pair differences in composite memory is shown, as well as the mediating effect of within-pair differences in amyloid-β PET in this association.

Supplementary Figure 2 Serial mediation model with mPACC as measure for cognition functioning



Serial mediation model including pathways between within-pair differences in amyloid-β, tau, hippocampal volume and mPACC-5. For the direct effect of amyloid-β on mPACC-5 functioning, the total proportion that was mediated via pathways including tau and neurodegeneration was 73.6%. The pathway leading from amyloid-β to tau to memory functioning (highlighted in orange) revealed the largest proportion mediated (62.8%). Dashed lines indicate pathways that were not significant. *p<0.05; **p<0.01; ***p<0.001