Supplementary material

Longitudinal [^{18}F]MK-6240 tau tangles accumulation follows Braak stages

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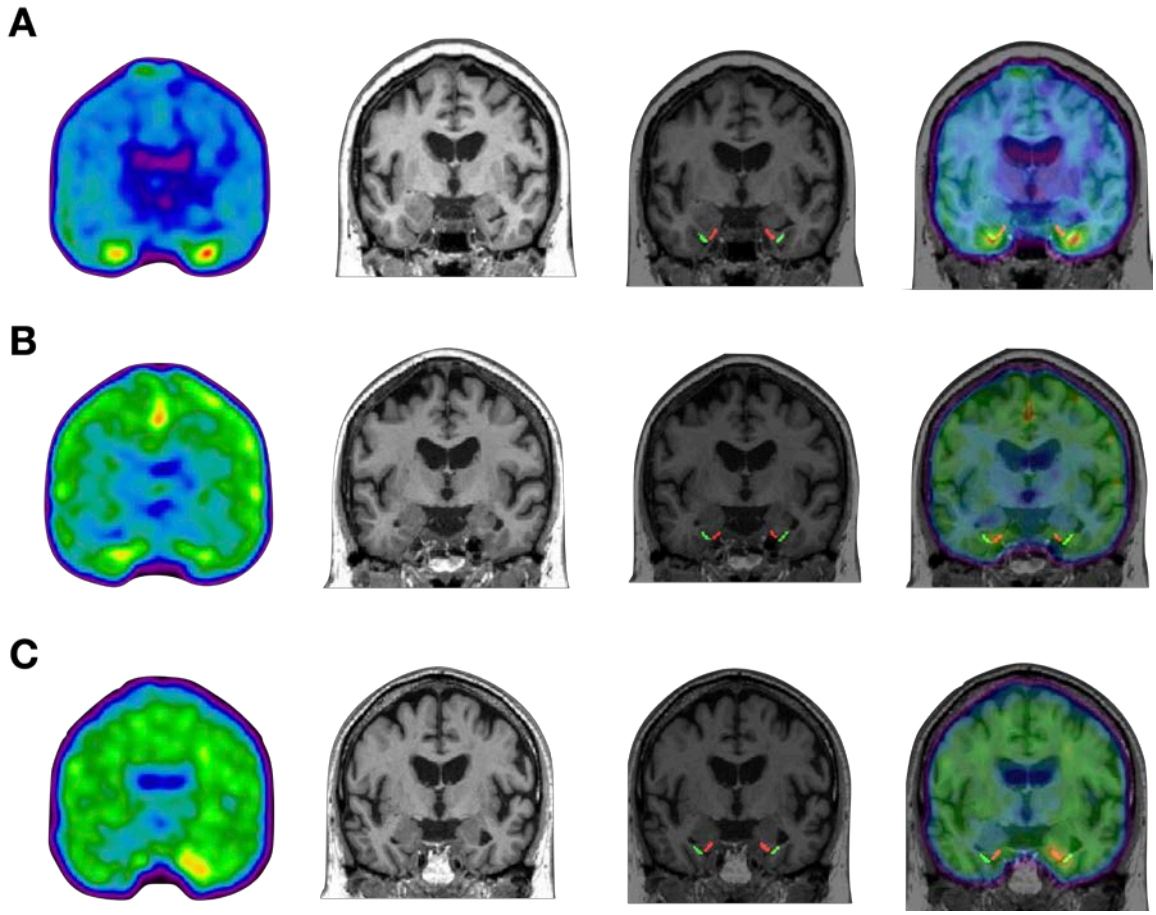
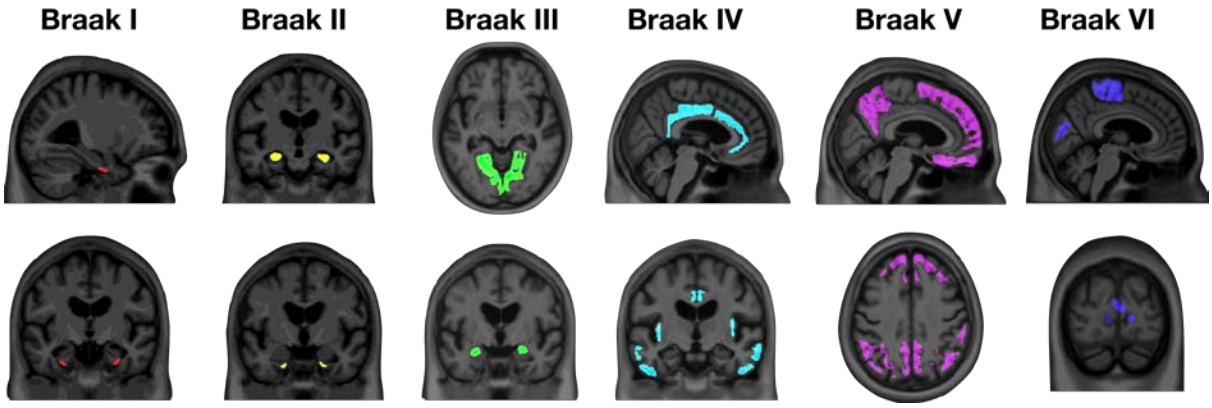
Supplementary Fig. 1. Representative segmentation of transentorhinal and entorhinal cortices.



Each row show images obtained from a different study participant. (A) CU individuals, 74 years old, female, MMSE=28, CDR = 0, and Aβ PET positive. (B) CU individuals, 73 years old, female, MMSE = 30, CDR = 0, and Aβ PET negative. (C) MCI, 73 years old, male, MMSE = 27, CDR=0.5, and Aβ PET positive. The column on the left side represents [^{18}F]MK-6240 PET scans, the second column from left to right shows nonlinearly transformed MRI to the reference MNI space, the third column from left to right shows MRI with transentorhinal (green) and entorhinal (red) ROI overlaid, and the column in the left side shows all three aforementioned images overlaid. In these three individuals, [^{18}F]MK-6240 SUVR was above threshold for tau abnormality in the transentorhinal but not in the entorhinal cortex. The 2 mm Jacobian (deformation) field used in our image transformations mitigated the well known rhinal sulcus anatomical variability. In our final image, our algorithms (followed by visual QC) assured that all individuals present a

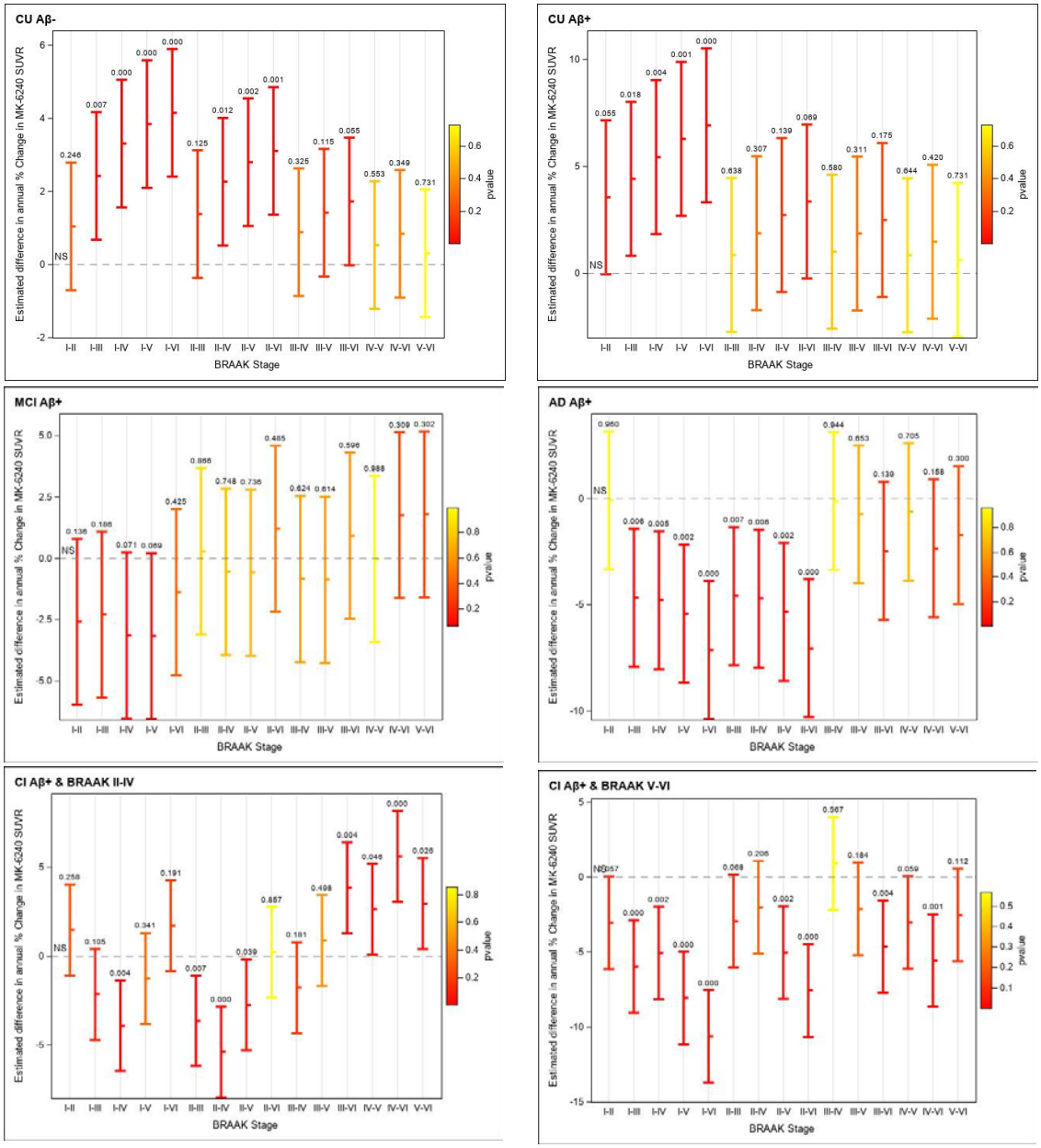
transentorhinal cortex with a similar shape and size, conforming to the reference MNI space template.

Supplementary Fig. 2. PET Braak-like regions used in the analysis.



The figure shows Braak-like stages ROIs overlaid on a structural MRI template. PET Braak-like regions segmentation was previously described elsewhere (Pascoal *et al.*, 2020) and were based on postmortem observations (Braak and Braak, 1991, 1997), as follows: Braak I (transentorhinal), Braak II (entorhinal and hippocampus), Braak III (amygdala, parahippocampal gyrus, fusiform gyrus, lingual gyrus), Braak IV (insula, inferior temporal, lateral temporal, posterior cingulate, and inferior parietal), Braak V (orbitofrontal, superior temporal, inferior frontal, cuneus, anterior cingulate, supramarginal gyrus, lateral occipital, precuneus, superior parietal, superior frontal, rostro medial frontal), and Braak VI (paracentral, postcentral, precentral, and pericalcarine). The brain regions were based on the Desikan-Killiany-Tourville atlas (Klein and Tourville, 2012), only voxels with a probability higher than 90% to be located in the cerebral cortex were included in our ROI. We also removed from these Braak masks, using probabilistic uptake maps across the cognitively unimpaired population, edge voxels with a high probability (90%) of suffering spillover from meningeal off-target bindings.

Supplementary Fig. 3. Estimates from the repeated measures analysis.



The figure shows in the y-axes the estimated differences in the annual percentage of change in [^{18}F]MK-6240 SUVR, and each bar represents the 95% CI for that specific difference. At the top of each bar line, we show the p value obtained by testing whether the difference between Braak regions differs significantly from 0. Also, the bars are colored such that darker shades show lower p values, and shades towards orange and yellow represent higher p values. A horizontal line (y = 0) is presented as a dotted line and shows which 95% CI includes (or cross) the 0 value; thus, those differences are not statistically

significant. The x-axes show the differences between which Braak regions are being presented in the bars, starting with Braak stage I versus Braak stage II and so on.

Supplementary Table 1. Longitudinal progression in the transentorinal cortex after correction for partial volume effects

CU Aβ-			CU Aβ+			MCI Aβ+			AD dementia Aβ+		
ΔSUVR mean (SD)	**95% CI**	**CV**	**ΔSUVR mean (SD)**	**95% CI**	**CV**	**ΔSUVR mean (SD)**	**95% CI**	**CV**	**ΔSUVR mean (SD)**	**95% CI**	**CV**
Braak I (Transentorhinal cortex)											
0.0296 (0.106)	0.003, 0.056	3.5	0.078 (0.111)	0.028, 0.128	1.4	0.015 (0.206)	-0.081, 0.111	13.7	0.076 (0.255)	-0.060, 0.211	3.3

Partial volume correction of [^{18}F]MK-6240 SUVR values in the newly segmented transentorhinal cortex (Braak I) using region-based voxel-wise method [41]. Subsequent studies are underway to address the effects of partial volume correction in other Braak regions most affected by meningeal spillover.

Supplementary Table 2. CU Aβ negative (df = 382)

Comparison	Estimate	*P* value	95% CI		99% CI	
I - II	1.044	0.504	-2.022	4.109	-2.993	5.080
I - III	2.425	0.121	-0.641	5.491	-1.612	6.461
I - IV	3.310	0.034	0.244	6.376	-0.726	7.347
I - V	3.843	0.014	0.778	6.909	-0.193	7.880
I - VI	4.152	0.008	1.086	7.218	0.116	8.188
II - III	1.381	0.376	-1.684	4.447	-2.655	5.418
II - IV	2.266	0.147	-0.799	5.332	-1.770	6.303
II - V	2.800	0.073	-0.266	5.865	-1.237	6.836
II - VI	3.108	0.047	0.043	6.174	-0.928	7.145
III - IV	0.885	0.571	-2.181	3.951	-3.151	4.922
III - V	1.418	0.364	-1.647	4.484	-2.618	5.455
III - VI	1.727	0.269	-1.339	4.793	-2.309	5.764
IV - V	0.533	0.733	-2.533	3.599	-3.503	4.570
IV - VI	0.842	0.590	-2.224	3.908	-3.195	4.878
V - VI	0.309	0.843	-2.757	3.374	-3.728	4.345

The table shows estimates from the repeated measure analysis corrected for sex and age.

Supplementary Table 3. CU Aβ positive (df = 124).

Comparison	Estimate	p-value	95% CI		99% CI	
I - II	3.557	0.128	-1.036	8.151	-2.514	9.628
I - III	4.421	0.059	-0.172	9.014	-1.650	10.492
I - IV	5.437	0.021	0.844	10.030	-0.634	11.508
I - V	6.287	0.008	1.694	10.880	0.216	12.358
I - VI	6.919	0.003	2.326	11.513	0.848	12.990
II - III	0.864	0.710	-3.730	5.457	-5.207	6.934
II - IV	1.880	0.419	-2.713	6.473	-4.191	7.951
II - V	2.730	0.242	-1.864	7.323	-3.341	8.801
II - VI	3.362	0.150	-1.231	7.955	-2.709	9.433
III - IV	1.016	0.662	-3.577	5.609	-5.055	7.087
III - V	1.866	0.423	-2.727	6.459	-4.205	7.937
III - VI	2.498	0.284	-2.095	7.092	-3.573	8.569
IV - V	0.850	0.715	-3.743	5.443	-5.221	6.921
IV - VI	1.482	0.524	-3.111	6.075	-4.589	7.553
V - VI	0.632	0.786	-3.961	5.225	-5.439	6.703

The table shows estimates from the repeated measure analysis corrected for sex and age.

Supplementary Table 4. MCI Aβ positive (df = 118)

Comparison	Estimate	p-value	95% CI		99% CI	
I - II	-2.586	0.342	-7.955	2.783	-9.685	4.512
I - III	-2.296	0.399	-7.665	3.073	-9.394	4.803
I - IV	-3.142	0.249	-8.511	2.227	-10.240	3.956
I - V	-3.168	0.245	-8.537	2.201	-10.267	3.930
I - VI	-1.380	0.612	-6.749	3.990	-8.478	5.719
II - III	0.290	0.915	-5.079	5.659	-6.808	7.389
II - IV	-0.556	0.838	-5.925	4.813	-7.654	6.542
II - V	-0.582	0.830	-5.951	4.787	-7.681	6.516
II - VI	1.207	0.657	-4.162	6.576	-5.892	8.305
III - IV	-0.846	0.755	-6.215	4.523	-7.945	6.252
III - V	-0.873	0.748	-6.242	4.496	-7.971	6.226
III - VI	0.916	0.736	-4.453	6.285	-6.182	8.015
IV - V	-0.026	0.992	-5.395	5.343	-7.125	7.072
IV - VI	1.763	0.517	-3.606	7.132	-5.336	8.861
V - VI	1.789	0.511	-3.580	7.158	-5.310	8.887

The table shows estimates from the repeated measure analysis corrected for sex and age.

Supplementary Table 5. AD Aβ positive (df = 94)

Comparison	Estimate	p-value	95% CI		99% CI	
I - II	-0.084	0.984	-8.344	8.177	-11.021	10.854
I - III	-4.669	0.265	-12.929	3.591	-15.606	6.269
I - IV	-4.786	0.253	-13.046	3.474	-15.724	6.152
I - V	-5.413	0.196	-13.673	2.847	-16.351	5.524
I - VI	-7.133	0.090	-15.393	1.127	-18.070	3.805
II - III	-4.585	0.273	-12.845	3.675	-15.523	6.353
II - IV	-4.702	0.261	-12.962	3.558	-15.640	6.235
II - V	-5.330	0.203	-13.590	2.930	-16.267	5.608
II - VI	-7.049	0.093	-15.309	1.211	-17.987	3.889
III - IV	-0.117	0.978	-8.377	8.143	-11.055	10.821
III - V	-0.745	0.858	-9.005	7.516	-11.682	10.193
III - VI	-2.464	0.555	-10.724	5.796	-13.402	8.474
IV - V	-0.627	0.880	-8.887	7.633	-11.565	10.310
IV - VI	-2.347	0.574	-10.607	5.913	-13.285	8.591
V - VI	-1.720	0.680	-9.980	6.541	-12.657	9.218

The table shows estimates from the repeated measure analysis corrected for sex and age.

Supplementary Table 6. CI Aβ positive Braak II-IV (df = 88)

Comparison	Estimate	p-value	95% CI		99% CI	
I - II	1.486	0.538	-3.290	6.263	-4.841	7.814
I - III	-2.139	0.376	-6.915	2.637	-8.467	4.189
I - IV	-3.903	0.108	-8.679	0.873	-10.230	2.425
I - V	-1.250	0.604	-6.026	3.526	-7.577	5.078
I - VI	1.722	0.476	-3.055	6.498	-4.606	8.049
II - III	-3.625	0.135	-8.402	1.151	-9.953	2.702
II - IV	-5.389	0.027	-10.165	-0.613	-11.717	0.939
II - V	-2.736	0.258	-7.512	2.040	-9.064	3.592
II - VI	0.235	0.922	-4.541	5.011	-6.092	6.563
III - IV	-1.764	0.465	-6.540	3.012	-8.091	4.564
III - V	0.889	0.712	-3.887	5.665	-5.438	7.217
III - VI	3.861	0.112	-0.915	8.637	-2.467	10.188
IV - V	2.653	0.273	-2.123	7.429	-3.675	8.981

IV - VI	5.624	0.022	0.848	10.400	-0.703	11.952
V - VI	2.971	0.220	-1.805	7.748	-3.356	9.299

The table shows estimates from the repeated measure analysis corrected for sex and age.

Supplementary Table 7. CI Aβ positive Braak V-VI (df = 100).

Comparison	Estimate	p-value	95% CI		99% CI	
I - II	-3.043	0.494	-11.835	5.750	-14.680	8.594
I - III	-5.962	0.182	-14.755	2.830	-17.599	5.675
I - IV	-5.054	0.257	-13.846	3.738	-16.691	6.583
I - V	-8.078	0.071	-16.870	0.715	-19.715	3.559
I - VI	-10.613	0.018	-19.405	-1.820	-22.250	1.024
II - III	-2.920	0.512	-11.712	5.872	-14.557	8.717
II - IV	-2.011	0.651	-10.803	6.781	-13.648	9.626
II - V	-5.035	0.259	-13.827	3.757	-16.672	6.602
II - VI	-7.570	0.091	-16.362	1.222	-19.207	4.067
III - IV	0.909	0.838	-7.884	9.701	-10.728	12.546
III - V	-2.115	0.634	-10.907	6.677	-13.752	9.522
III - VI	-4.650	0.297	-13.442	4.142	-16.287	6.987
IV - V	-3.024	0.497	-11.816	5.769	-14.661	8.613
IV - VI	-5.559	0.213	-14.351	3.234	-17.196	6.078
V - VI	-2.535	0.569	-11.327	6.257	-14.172	9.102

The table shows estimates from the repeated measure analysis corrected for sex and age.