SUPPLEMENT

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SUPPLEMENTARY METHODS

Generation of an off-target ROI

The mask for extracting off-target binding outside the FreeSurfer segmented gray matter was constructed via a series of morphological filters. First, the FreeSurfer Grey Matter, White Matter and Cerebrospinal Fluid ROIs were merged and dilated 5 mm (to approximate PET resolution), followed by a fill-hole operation. Eroding 5 mm again and removing the resulting mask voxels from the dilated mask yielded the exterior region used to probe the off-target signal. To compensate for true cortical signal in the off-target ROI dividing the off-target ROI mean SUVR by that of the interior mask yielded a more accurate measure in identifying subjects with primarily artefactual uptake. Dilating and then eroding causes the deep sulci to be excluded from the exterior region.

SUPPLEMENTARY TABLES

Supplementary Table 1. Clinical characteristics of participants in the four subcohorts

ADNI	**Aβ- CU**	**Aβ- MCI**	**Aβ+ CU**	**Aβ+ MCI**	**AD**	**p-value**
Number (n=123)	21	23	46	32	1	
Age ± SD	76.0 ± 6.5	74.2 ± 7.0	78.8 ± 6.8	75.4 ± 7.0	56.2	d*, i*, j*
Sex (F/M)	12/9	9/14	25/21	14/18	0/1	n.s.
Education ± SD	16.6 ± 2.1	16.4 ± 2.9	16.8 ± 2.3	16.3 ± 2.7	13	n.s.
MMSE ± SD	29.3 ± 1.1	28.0 ± 3.1	28.0 ± 2.4	26.9 ± 3.2	21	c*, d*
APOE ε4-alleles (0/1/2)	16/5/0	20/3/0	25/18/3	11/15/6	1/0/0	c**, e**, f***, h*
AVID	**Aβ- CU**	**Aβ- MCI**	**Aβ+ CU**	**Aβ+ MCI**	**AD**	**p-value**
Number (n=157)	51	35	3	42	26	
Age ± SD	68.0 ± 10.4	69.6 ± 10.0	79.7 ± 2.1	72.1 ± 8.3	74.8 ± 10.2	d*
Sex (F/M)	23/28	17/18	1/2	19/23	15/11	n.s.
Education ± SD	15.7 ± 2.0	15.1 ± 3.1	14.7 ± 2.3	16.3 ± 2.8	15.2 ± 2.9	n.s.
MMSE ± SD	29.5 ± 0.5	28.4 ± 1.7	29.3 ± 0.6	27.5 ± 1.9	21.6 ± 3.9	c***, d***, g***, i***, j***
APOE ε4-alleles (0/1/2)	38/9/1	22/10/1	2/1/0	18/15/7	7/13/6	c***, d***, f*, g**
Expedition 3	**Aβ- CU**	**Aβ- MCI**	**Aβ+ CU**	**Aβ+ MCI**	**AD**	**p-value**
Number (n=82)	0	0	0	0	82	N/A
Age ± SD	-	-	-	-	73.3 ± 8.4	N/A
Sex (F/M)	-	-	-	-	45/37	N/A
Education ± SD	-	-	-	-	14.2 ± 3.2	N/A
MMSE ± SD	-	-	-	-	23.1 ± 1.7	N/A
APOE ε4-alleles (0/1/2)	-	-	-	-	23/42/15	N/A
BioFINDER (n=57)	**Aβ- CU**	**Aβ- MCI**	**Aβ+ CU**	**Aβ+ MCI**	**AD**	**p-value**
Number	16	0	16	7	18	
Age ± SD	74.6 ± 4.3	-	74.8 ± 6.9	72.7 ± 6.6	69.8 ± 10.5	n.s.
Sex (F/M)	5/11	-	11/5	5/2	7/11	n.s.
Education ± SD	12.5 ± 4.1	-	10.6 ± 3.2	11.1 ± 2.7	13.5 ± 3.3	n.s.
MMSE ± SD	29.2 ± 0.9	-	29.1 ± 1.2	25.6 ± 2.9	22.1 ± 5.2	d***, i ***
APOE ε4-alleles (0/1/2)	16/0/0	-	6/9/1	3/3/1	7/7/4	b***, c**, d***

Table legend. Statistical comparisons between [a] Aβ- CU and Aβ- MCI; [b] Aβ- CU and Aβ+ CU; [c] Aβ- CU and Aβ+ MCI; [d] Aβ- CU and AD; [e] Aβ- MCI and Aβ+ CU; [f] Aβ- MCI and Aβ+ MCI; [g] Aβ- MCI and AD; [h] Aβ+ CU and Aβ+ MCI; [i] Aβ+ CU and AD; [j] Aβ+ MCI and AD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Aβ- -β amyloid negative; Aβ+ -β amyloid positive; AD – Alzheimer's Disease dementia; CU – cognitively unimpaired; F – female; M – male; MCI – mild cognitive impairment; SD – standard deviation.

Supplementary Table 2. Between cohort comparisons

	ADNI	AVID	Expedition 3	BioFINDER	p-value
Number	123	157	82	57	
Age ± SD	76.4 ± 7.2	70.7 ± 9.9	73.3 ± 8.4	72.9 ± 7.8	a***
Sex (F/M)	60/63	76/81	45/37	28/29	n.s.
Education ± SD	16.5 ± 2.5	15.6 ± 2.6	14.2 ± 3.2	12.1 ± 3.6	a*, b***, c***, d**, e***, f***
MMSE ± SD	27.9 ± 2.8	27.4 ± 3.4	23.1 ± 1.7	26.5 ± 4.5	a*, b***, c***, d**, e***, f***
APOE ε4-alleles (0/1/2)	73/41/9	87/48/15	23/42/15	32/19/6	b***, d***, f**

Table legend. Statistical comparisons between [a] ADNI and AVID; [b] ADNI and Expedition 3; [c] ADNI and BioFINDER; [d] AVID and Expedition 3; [e] AVID and BioFINDER; [f] Expedition 3 and BioFINDER. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. F – female; M – male; SD – standard deviation.

Supplementary Table 3. Distribution of *APOE* ε4-genotype in males and females

	Number with available data	No *APOE* ε4 allele	One *APOE* ε4 allele	Two *APOE* ε4 allele
Males	210	118	69	20
Females	207	97	81	25

Kruskal-Wallis test p = 0.09

Supplementary Table 4. Demographics for young participants (< 65 years)

	Aβ- CU	**Aβ- MCI**	**Aβ+ CU**	**Aβ+ MCI**	**AD**
Number (n=69)	20	13	3	11	22
Age ± SD [median (IQR)]	57.2 ± 4.3 [57.5 (7.25)]	58.7 ± 3.9 [59 (5)]	62.2 ± 1.3 [62 (1.25)]	60.2 ± 4.3 [62 (3.5)]	58.3 ± 5.7 [59.1 (6.3)]
Sex (F/M)	7/13	10/3	3/0	9/2	14/8
Education ± SD [median (IQR)]	14.8 ± 1.8 [16 (3.25)]	14.5 ± 3.1 [14 (6)]	12.3 ± 3.5 [12 (3.5)]	15.8 ± 1.9 [16 (0.5)]	14.8 ± 3.5 [15 (4)]
MMSE ± SD [median (IQR)]	29.5 ± 0.5 [29.5 (1)]	28.1 ± 1.8 [29 (2)]	29.0 ± 1.7 [30 (1.5)]	27.2 ± 2.5 [28 (2)]	22.2 ± 3.7 [23 (2.5)]
APOE ε4-alleles (0/1/2)	14/4/1	5/7/0	1/2/0	4/4/3	8/8/5°
Baseline tau					
Temporal meta-ROI SUVR (mean ± SD) [median (IQR)]	1.12 ± 0.08 [1.11 (0.08)]	1.09 ± 0.07 [1.07 (0.04)]	1.17 ± 0.09 [1.16 (0.09)]	1.66 ± 0.48 [1.39 (0.91)]	1.93 ± 0.36 [2.0 (0.48)]
Neocortical ROI SUVR (mean ± SD) [median (IQR)]	1.06 ± 0.09 [1.06 (0.12)]	1.0 ± 0.05 [1.0 (0.06)]	1.10 ± 0.09 [1.06 (0.08)]	1.44 ± 0.37 [1.31 (0.68)]	1.67 ± 0.36 [1.77 (0.44)]
Tau slopes					
Temporal meta-ROI (SUVR/year) mean ± SD [median (IQR)]	-0.002 ± 0.023 [-0.002 (0.027)]	0.001 ± 0.022 [0.006 (0.034)]	0.021 ± 0.012 [0.017 (0.012)]	0.136 ± 0.169 [0.133 (0.153)]	0.085 ± 0.204 [0.059 (0.134)]
Neocortical ROI (SUVR/year) mean ± SD [median (IQR)]	0.001 ± 0.022 [0.001 (0.019)]	0.004 ± 0.037 [0.013 (0.035)]	0.040 ± 0.054 [0.017 (0.050)]	0.098 ± 0.146 [0.076 (0.160)]	0.062 ± 0.158 [0.031 (0.126)]

Table legend. Aβ- -β amyloid negative; Aβ+ -β amyloid positive; AD – Alzheimer's Disease dementia; CU – cognitively unimpaired; F – female; M – male; MCI – mild cognitive impairment; SD – standard deviation. ° One individual with missing data.

Supplementary Table 5. Cohort characteristics and the rate of Aβ accumulation in ADNI.

ADNI	**Aβ- CU**	**Aβ- MCI**	**Aβ+ CU**	**Aβ+ MCI**	**AD**	**p-value**
Number	155	145	101	204	34	
Age	73.5 ± 6.5	70.6 ± 8.0	74.8 ± 6.5	72.3 ± 7.0	75.4 ±7.1	a**, e***, g**, h*
Sex (F/M)	67/88	66/79	35/66	89/115	20/14	b***, e**, h***
APOE ε4-status (neg/pos)	127/28	113/32	56/45	74/130	4/30	b***, c***, d***, e***, f***, g***, h**, i***, j**
Aβ Slopes ± SD	0.0032 ± 0.0094	0.0019 ± 0.0088	0.0112 ± 0.0162	0.0089 ± 0.0164	0.0095 ± 0.0183	b***, c***, e***, f***, g*

Table legend. Statistical comparisons between [a] Aβ- CU and Aβ- MCI; [b] Aβ- CU and Aβ+ CU; [c] Aβ- CU and Aβ+ MCI; [d] Aβ- CU and AD; [e] Aβ- MCI and Aβ+ CU; [f] Aβ- MCI and Aβ+ MCI; [g] Aβ- MCI and AD; [h] Aβ+ CU and Aβ+ MCI; [i] Aβ+ CU and AD; [j] Aβ+ MCI and AD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Aβ- -β amyloid negative; Aβ+ -β amyloid positive; AD – Alzheimer's Disease dementia; CU – cognitively unimpaired; F – female; M – male; MCI – mild cognitive impairment; SD – standard deviation.

Additional statistics:

Comparison to ^{18}F-Flortaucipir demographics (Main manuscript Table 1).

Comparisons were performed within diagnostic groups (i.e. Aβ- CU in the tau cohort versus Aβ- CU in the Aβ cohort etc.). Age: Aβ- CU $p<0.05$; Aβ+ CU $p<0.01$. Sex: no significant differences. *APOE* ε4-status: AD $p<0.05$.

Supplementary Table 6. Results of linear models for Tau-accumulation, PVE-corrected

Coefficient	Estimate ± SE	T value	P value
Temporal meta-ROI			
APOE ε4 status	-0.0041 ± 0.011	-0.374	0.708
Aβ Status	0.0430 ± 0.0138	**3.100**	**0.002 ****
Age	-0.0015 ± 0.0006	**-2.504**	**0.013 ***
Sex	0.0255 ± 0.0100	**2.540**	**0.011 ***
Baseline tau	0.0571 ± 0.0144	**3.952**	**<0.001 *****
Study Avid 05	0.021 ± 0.013	1.597	0.111
Study Exp 3	-0.008 ± 0.022	-0.355	0.723
Study BF1	0.028 ± 0.017	1.659	0.098
CU	0.002 ± 0.022	0.088	0.930
MCI	0.012 ± 0.020	0.608	0.543
Neocortical ROI			
APOE ε4 status	-0.0017 ± 0.0080	-0.216	0.829
Aβ Status	0.0199 ± 0.0101	**1.968**	**0.049 ***
Age	-0.0005 ± 0.0005	-1.202	0.230
Sex	0.0192 ± 0.0073	**2.626**	**0.009 ****
Baseline tau	0.0835 ± 0.0153	**5.470**	**<0.001 *****
Study Avid 05	0.019 ± 0.010	**1.977**	**0.049 ***
Study Exp 3	0.008 ± 0.017	0.480	0.631
Study BF1	0.021 ± 0.012	1.722	0.086
CU	-0.002 ± 0.015	-0.136	0.891
MCI	0.004 ± 0.015	0.242	0.809

Table legend. Linear models were analyzed for each region using the slopes of tau accumulation. Statistical model: Tau slopes ~ *APOE* ε4 status + Aβ status + Age + Sex + Study + Diagnosis + Baseline tau SUVR. CU – cognitively unimpaired; MCI – mild cognitive impairment; SE – standard error. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Supplementary Table 7. Results of linear model for Tau-accumulation in skull/meningeal "off-target ROI"

Coefficient	Estimate ± SE	T value	P value
Off-target ROI			
APOE ε4 status	0.0105 ± 0.0060	1.740	0.083
Aβ status	-0.0077 ± 0.0062	-1.253	0.211
Age	0.0002 ± 0.0004	0.492	0.623
Sex	0.0087 ± 0.0057	1.511	0.132
Baseline retention	-0.0912 ± 0.0214	**-4.245**	**<0.001** ***

Table legend. Linear models were analyzed for each region using the slopes of tau accumulation. Statistical model: Slope off-target ROI ~ *APOE* ε4 status + Aβ status + Age + Sex + Study + Baseline retention.
SE – standard error. * $p < 0.05$.

Supplementary Table 8. Results of linear model for Tau-accumulation in basal ganglia, putamen and globus palidus

Coefficient	Estimate ± SE	T value	P value
Putamen			
APOE ε4 status	-0.0093 ± 0.0078	-1.192	0.233
Aβ status	0.0185 ± 0.0088	**2.113**	**0.035** *
Age	0.0001 ± 0.0004	0.291	0.772
Sex	0.0032 ± 0.0071	0.455	0.650
Baseline tau	-0.0525 ± 0.0205	**-2.555**	**0.011** *
Globus pallidus			
APOE ε4 status	-0.0138 ± 0.0087	-1.595	0.111
Aβ status	0.0092 ± 0.0096	0.950	0.343
Age	0.0005 ± 0.0005	1.095	0.274
Sex	0.0065 ± 0.0079	0.815	0.416
Baseline tau	-0.0743 ± 0.0205	**-3.623**	**<0.001** ***
Choroid plexus			
APOE ε4 status	-0.0060 ± 0.0079	-0.764	0.445
Aβ status	-0.0165 ± 0.0089	-1.862	0.063
Age	-0.00005 ± 0.0004	-0.107	0.915
Sex	0.0012 ± 0.0072	0.170	0.865
Baseline tau	-0.0441 ± 0.0151	**-2.915**	**0.004** **

Table legend. Linear models were analyzed for each region using the slopes of tau accumulation. Statistical model: Tau slopes ~ *APOE* ε4 status + Aβ status + Age + Sex + Study + Diagnosis + Baseline tau SUVR. Aβ - β amyloid; SE – standard error. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Supplementary Table 9. Results of linear model for Tau-accumulation in amygdala and precuneus/posterior cingulate ROIs

Coefficient	Estimate ± SE	T value	P value
Amygdala			
APOE ε4 status	-0.0052 ± 0.0094	-0.551	0.582
Aβ status	0.0254 ± 0.0114	**2.227**	**0.027** *
Age	-0.0010 ± 0.0005	**-2.054**	**0.041** *
Sex	0.0276 ± 0.0083	**3.313**	**0.001** **
Baseline tau	-0.0350 ± 0.0178	-1.966	0.050
Precuneus/ Posterior cingulate cortex			
APOE ε4 status	-0.0085 ± 0.0084	-1.011	0.312
Aβ status	0.0270 ± 0.0105	**2.581**	**0.010** *
Age	-0.0007 ± 0.0005	-1.404	0.161
Sex	0.0261 ± 0.0076	**3.411**	**<0.001** ***
Baseline tau	0.0701 ± 0.0137	**5.129**	**<0.001** ***

Table legend. Linear models were analyzed for each region using the slopes of tau accumulation. Statistical model: Tau slopes ~ *APOE* ε4 status + Aβ status + Age + Sex + Study + Diagnosis + Baseline tau SUVR. Aβ - β amyloid; SE – standard error. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

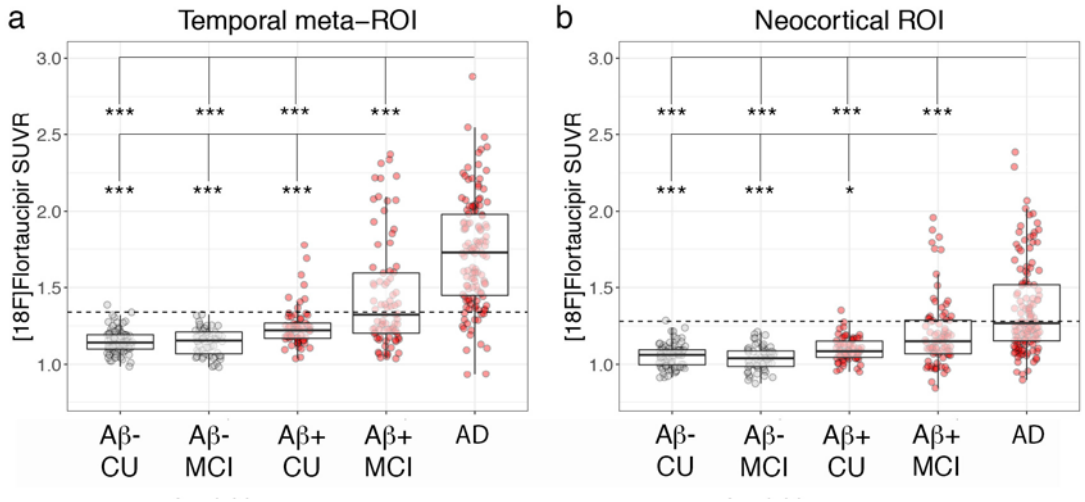
Supplementary Table 10. Results of linear model for Aβ accumulation in ADNI

Coefficient	Estimate ± SE	T value	P value
Neocortical composite			
APOE ε4 status	0.0024 ± 0.0012	**1.980**	**0.0482 ***
Aβ status	0.0057 ± 0.0012	**4.818**	**<0.001 *****
Age	0.00019 ± 0.00008	**2.445**	**0.0148 ***
Sex	0.00075 ± 0.0011	0.692	0.4894

Statistical model: Aβ Slope ~ *APOE* ε4 status + Aβ status + Age + Sex. SE – standard error. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

SUPPLEMENTARY FIGURES

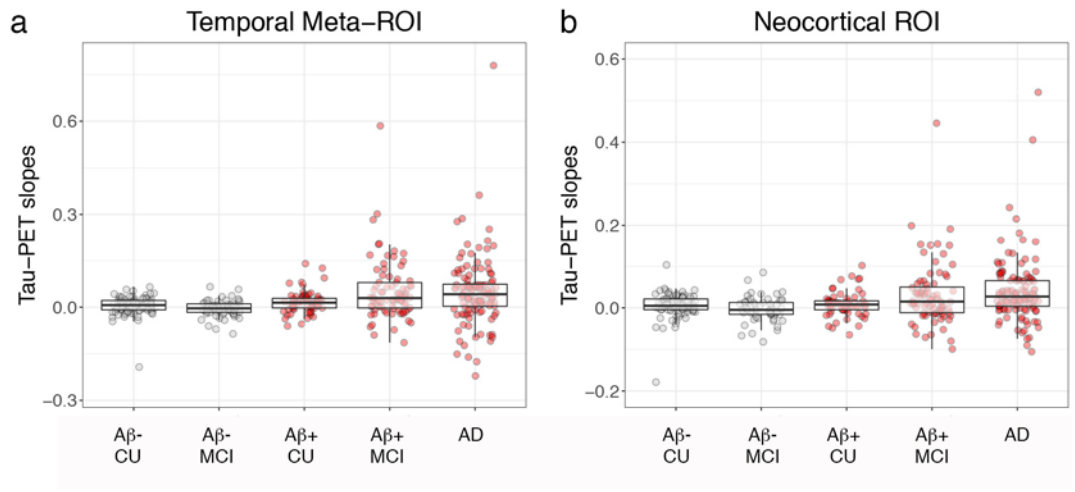
Supplementary Figure 1



Baseline ^{18}F-Flortaucipir SUVRs.

Baseline ^{18}F-Flortaucipir SUVRs in a) the temporal meta-region SUVRs, b) the neocortex meta-ROI. Red dots indicate Aβ+ participants; grey dots indicate Aβ- participants. AD – Alzheimer's Disease Dementia; CU – cognitively unimpaired; MCI – mild cognitive impairment; SUVR – standardized uptake value ratio. Boxplots depict median value and the interquartile range.

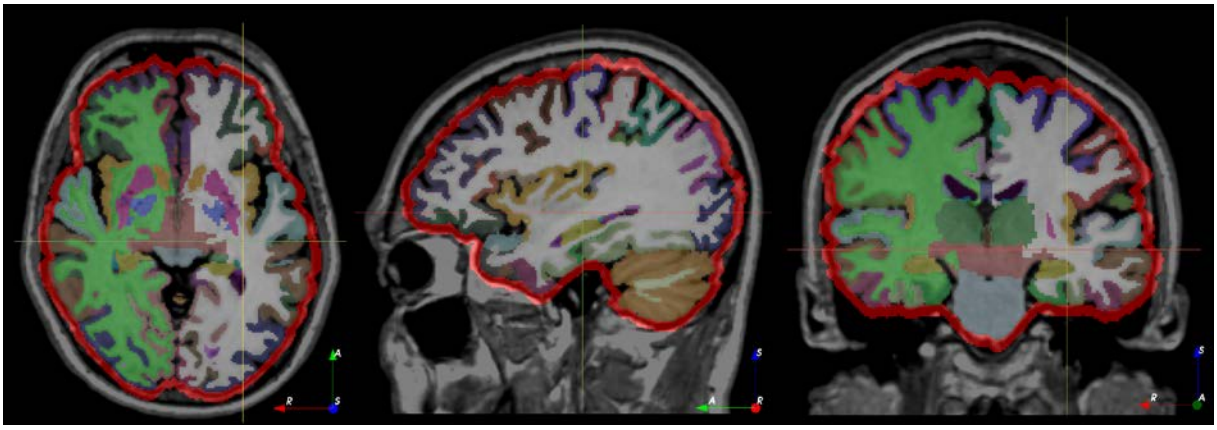
Supplementary Figure 2



^{18}F-Flortaucipir slopes, full range y-axes.

^{18}F-Flortaucipir SUVR/year slopes in a) the temporal meta-ROI, b) the neocortical ROI. Boxplots depict median value and the interquartile ranges. Red dots indicate Aβ+; grey dots indicate Aβ-. AD – Alzheimer's Disease Dementia; CU – cognitively unimpaired; MCI – mild cognitive impairment; SUVR – standardized uptake value ratio.

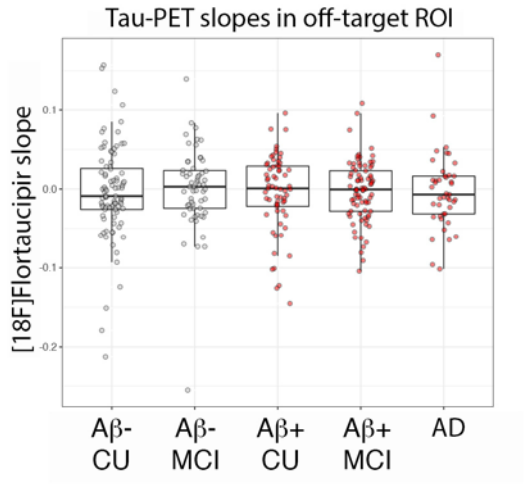
Supplementary Figure 3



Creating an off-target ROI for skull/meninges.

Supplementary Figure 3 shows an example of the off-target ROI used to control for binding in meninges and skull. The ROI was created as detailed in the eMethods section. The aim was to capture possible off-target binding in structures overlying the cortex and possibly influencing the cortical signal.

Supplementary Figure 4



^{18}F-Flortaucipir slopes in off-target ROI.

Tau PET slopes in off-target (skull/meningeal) ROI adjusted for within brain signal across diagnostic groups. Red dots indicate Aβ+; grey dots indicate Aβ-. AD – Alzheimer's Disease Dementia; CU – cognitively unimpaired; MCI – mild cognitive impairment.