Supplementary Online Content

Ossenkoppele R, Rabinovici GD, Smith R, et al. Discriminative Accuracy of [18F]flortaucipir Positron Emission Tomography for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA.* doi:10.1001/jama.2018.12917

eFigure 3. [18F]flortaucipir SUVR in Aβ-positive (A) and Aβ-negative (B) participants

eFigure 4. Differences in specificity for [18F]flortaucipir PET versus Aβ status

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Diagnostic criteria

Diagnosis	Criteria	Ref
Alzheimer disease dementia	NIA-AA	1
Mild cognitive impairment	Petersen	2
Prodromal AD	NIA-AA	3
Behavioral variant FTD	FTDC	4
Non-fluent variant PPA	Gorno-Tempini	5
Semantic variant PPA	Gorno-Tempini	5
Dementia with Lewy bodies	DLB consortium	6
Progressive supranuclear palsy	PSP study group	7
Corticobasal syndrome	Armstrong	8
Parkinson disease	New International PD and MD Society criteria	9
Vascular dementia	NINDS-AIREN	10

NIA-AA = National Institute on Aging and Alzheimer's Association workgroup; FTDC = International Behavioural Variant FTD Criteria Consortium; PD = Parkinson's disease; MD = Movement disorders; NINDS-AIREN = National Institute of Neurological Disorders (NINDS) and the Association Internationale our la Recherche er l'Enseignement en Neuroscience (AIREN).

References:

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eTable 2. Methods to determine Aβ-positivity across centers

Cohort	Modality	Methodology	Cut-off
Seoul[1]	[^{18}F]Florbetaben PET	Neocortical SUVR for the 90-110min interval p.i. with cerebellar reference region	>1.4 SUVR
BioFINDER[2,3]	[^{18}F]Flutemetamol PET	Global neocortical composite SUVR for the 90-110min interval p.i. with cerebellar cortex, pons and eroded white matter as reference region	>0.69 SUVR
	CSF Aβ42	ELISA (INNOTEST)	<650 ng/L
UCSF[4,5]	[^{11}C]PIB PET	Global neocortical composite SUVR for the 60-90min interval p.i. with cerebellar GM as reference tissue.	>1.21 SUVR
	CSF Aβ42	INNO-BIA AlzBio3	<250 ng/L

Note that several studies[6-10] have shown high (~90%) concordance between PET and CSF for determining Aβ-positivity.

References:

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4. Ossenkoppele R et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 2016;139(5):1551-1567.
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eTable 3. PET and MRI protocols

PET acquisition: A Biograph mCT PET/CT scanner (Siemens Medical Solutions) in Seoul, Discovery 690 PET scanner (GE medical systems) in BioFINDER, a Biograph 6 Truepoint PET/CT scanner (Siemens Medical Solutions) at Lawrence Berkeley National Laboratory for UCSF patients, and a Discovery VCT PET/CT scanner (GE medical systems) at UCSF China Bassin for UCSF controls, following a bolus injection of ~370 MBq (BioFINDER and UCSF) or ~280MBq (Seoul) of [^{18}F]flortaucipir.
MRI acquisition: Images were acquired on a 3.0T Discovery MR750 scanner (GE medical systems) in Seoul, 3.0T Tim Trio or Skyra scanner (Siemens Medical Solutions) in BioFINDER and a 3.0T Tim Trio or Prisma scanner (Siemens Medical Solutions) at UCSF.
Voxelwise analyses (Fig. 2+3): [^{18}F]flortaucipir images were warped into MNI standard space using the non-linear transformation calculated by normalizing the T1-weighted MR image to the MNI152 1x1x1 mm^3 template with Advanced Normalization ToolS (ANTS). Prior to voxelwise analyses, images were smoothed with an 8mm FWHM Gaussian kernel.
MRI processing (Fig. 3, eTable 15): Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analyses pipeline v6.0. T1-weighted images underwent correction for intensity homogeneity, removal of non-brain tissue and segmentation into gray matter and white matter. Reconstructed datasets were visually inspected for accuracy, and segmentation errors were corrected.

eTable 4. Youden index to derive [^{18}F]flortaucipir cut-offs

ROC analysis in BioFINDER data (52 AD patients vs 66 controls)				
	Cut-off	*Youden's J*	*Sensitivity*	*Specificity*
Entorhinal cortex	1.2572	0.76	92.3	83.3
Inferior temporal cortex	1.3512	0.90	96.2	93.9
Temporal Meta-ROI	1.2677	0.88	98.1	89.4
Temporoparietal cortex	1.2081	0.87	94.2	92.4
Braak V/VI	1.2685	0.89	98.1	90.9
ROC analysis in Seoul data (55 AD dementia patients vs 90 controls)				
	Cut-off	*Youden's J*	*Sensitivity*	*Specificity*
Entorhinal cortex	1.4125	0.85	90.0	94.4
Inferior temporal cortex	1.2936	0.82	85.5	96.7
Temporal Meta-ROI	1.2743	0.83	87.3	95.6
Temporoparietal cortex	1.2667	0.78	80.0	97.8
Braak V/VI	1.2052	0.68	78.2	90.0

eTable 5. Subject characteristics by diagnostic group

	MCI-due-to-AD *(n=83)*	**bvFTD** *(n=33)*	**nfvPPA** *(n=17)*	**svPPA** *(n=11)*	**DLB** *(n=24)*	**PSP** *(n=40)*	**CBS** *(n=23)*	**PD MCI/dementia** *(n=70)*	**PD Cog. Normal** *(n=23)*	**VaD** *(n=7)*
Age	70.1 (9.3)	64.8 (9.8)	66.8 (8.7)	66.9 (7.9)	72.7 (7.8)	69.9 (6.6)	69.1 (6.3)	69.4 (7.0)	67.3 (5.8)	78.6 (7.3)
Age, range	40-89	37-86	56-85	59-85	52-84	57-85	59-80	55-87	56-76	70-89
Sex, % male	51.8	63.6	29.4	63.6	58.3	67.5	52.0	52.9	65.2	42.9
Education	12.9 (4.6)	14.6 (4.9)	14.0 (4.5)	13.7 (5.2)	9.4 (4.0)	14.9 (5.0)	12.7 (4.8)	13.2 (5.3)	11.2 (3.5)	7.4 (8.3)
MMSE	25.7 (3.1)	22.8 (6.6)	26.5 (2.7)	23.2 (5.7)	20.2 (6.4)	24.7 (5.1)	26.1 (4.4)	21.7 (7.0)	27.6 (1.9)	18.9 (5.1)
CDR	0.5 (0.3)	1.1 (0.5)	0.5 (0.7)	0.8 (0.5)	1.1 (0.8)	0.7 (0.4)	0.4 (0.5)	0.6 (0.6)	0.1 (0.2)	1.0 (0.5)
Amyloid-β positivity, %	100 (83/83)	13.3 (4/30)	11.8 (2/17)	36.4 (4/11)	59.1 (13/22)	24.3 (9/37)	13.0 (3/23)	35.9 (14/39)	9.5 (2/21)	14.3 (1/7)
APOE ε4 positivity, %	56.9 (41/79)	8.3 (2/24)	33.3 (3/9)	20.0 (2/10)	47.6 (10/21)	24.0 (6/25)	46.2 (6/13)	45.0 (9/20)	16.7 (2/12)	42.9 (3/7)
Cohort (n, Seoul/ BioFINDER/ UCSF)	40/28/15	6/6/21	1/3/13	4/5/2	18/6/0	13/12/15	6/10/9	22/18/30	12/11/0	4/3/0
[^{18}F]flortaucipir SUVR										
Entorhinal cortex	1.58 (0.38)	1.20 (0.18)	1.16 (0.14)	1.33 (0.32)	1.37 (0.32)	1.12 (0.15)	1.09 (0.12)	1.18 (0.16)	1.09 (0.08)	1.28 (0.28)
Inferior temporal cortex	1.60 (0.46)	1.25 (0.14)	1.21 (0.10)	1.62 (0.52)	1.33 (0.28)	1.17(0.07)	1.18 (0.08)	1.21 (0.18)	1.14 (0.06)	1.29 (0.27)
Temporal meta-ROI	1.54 (0.37)	1.20 (0.10)	1.18 (0.09)	1.50 (0.45)	1.33 (0.27)	1.15(0.08)	1.14 (0.06)	1.20 (0.18)	1.13 (0.06)	1.26 (0.28)
Temporoparietal cortex	1.44 (0.38)	1.13 (0.08)	1.14 (0.07)	1.40 (0.48)	1.26 (0.26)	1.10 (0.07)	1.10 (0.06)	1.15 (0.15)	1.09 (0.07)	1.21 (0.29)
Braak stage V/VI	1.38 (0.36)	1.11 (0.11)	1.12 (0.10)	1.35 (0.39)	1.25 (0.26)	1.10 (0.06)	1.10 (0.06)	1.14 (0.12)	1.11 (0.06)	1.21 (0.22)

MCI, Mild cognitive impairment; AD, Alzheimer's Disease; bvFTD = Behavioral variant of frontotemporal dementia; nfvPPA = Non-fluent variant of primary progressive aphasia; svPPA = Semantic variant of primary progressive aphasia; DLB = Dementia with Lewy bodies; PSP = Progressive supranuclear palsy; CBS = Corticobasal syndrome; PD = Parkinson's disease; NC = Normal cognition; Dem = Dementia; VaD = Vascular dementia.

eTable 6. Subject characteristics for each center

	Cognitively normal			Mild cognitive impairment due to AD			AD dementia			Non-AD disorders		
	Seoul (n=90)	BioFINDER (n=66)	UCSF (n=4)	Seoul (n=64)	BioFINDER (n=29)	UCSF (n=33)	Seoul (n=55)	BioFINDER (n=52)	UCSF (n=72)	Seoul (n=89)	BioFINDER (n=73)	UCSF (n=92)
Age	65.9 (9.5)	74.0 (6.9)	57.8 (11.0)	70.5 (9.4)	71.5 (9.2)	62.7 (11.0)	73.2 (9.5)	70.9 (8.2)	64.0 (8.5)	70.9 (7.5)	70.6 (6.9)	65.2 (7.9)
Age, range	41-90	52-88	44-70	49-89	40-88	32-88	47-91	44-84	48-83	52-89	56-87	37-80
Sex (% male)	35.6	45.5	75.0	40.6	65.5	57.6	21.8	55.8	44.4	57.3	61.6	54.3
Education	12.1 (4.4)	12.2 (3.6)	19.0 (1.7)	11.6 (4.5)	12.5 (3.4)	17.5 (3.2)	10.1 (5.6)	12.4 (3.6)	16.8 (3.0)	9.8 (5.2)	12.3 (4.1)	17.1 (3.4)
MMSE	28.2 (1.8)	29.0 (1.1)	28.8 (1.5)	25.8 (2.9)	25.8 (2.9)	27.1 (2.6)	18.7 (5.3)	21.4 (5.2)	20.7 (5.7)	23.1 (5.9)	24.2 (5.7)	23.8 (6.6)
CDR	0 (0.0)	0.1 (0.2)	0.2 (0.3)	0.5 (0.0)	0.6 (0.5)	0.5 (0.2)	1.1 (0.6)	1.2 (0.7)	0.8 (0.3)	0.7 (0.6)	0.8 (0.6)	0.5 (0.5)
Amyloid-β+,%	11.1 (10/90)	47.0 (31/66)	25.0 (1/4)	62.5 (40/64)	96.6 (28/29)	45.5 (15/33)	100 (55/55)	100 (52/52)	100 72/72	22.5 (20/89)	35.0 (21/60)	14.8 (9/61)
APOE ε4+, %	18.9 (17/90)	48.4 30/62	50.0 (2/4)	35.9 (23/64)	75.0 (18/24)	25.0 (5/20)	50.0 (27/54)	63.6 (28/44)	56.9 (33/58)	30.8 (24/78)	38.5 (10/26)	23.1 (9/39)
[^{18}F]flortaucipir SUVR												
Entorhinal	1.19(0.13)	1.13(0.18)	1.13(0.06)	1.50(0.40)	1.44(0.29)	1.40(0.37)	1.86(0.33)	1.59(0.25)	1.74(0.30)	1.27(0.25)	1.09(0.17)	1.16(0.13)
Inf. temporal	1.15(0.08)	1.21(0.11)	1.14(0.06)	1.34(0.27)	1.72(0.57)	1.45(0.42)	1.90(0.58)	2.06(0.50)	2.25(0.55)	1.26(0.28)	1.23(0.20)	1.20(0.10)
Temporal meta-ROI	1.16(0.08)	1.18(0.10)	1.15(0.04)	1.34(0.27)	1.61(0.44)	1.40(0.36)	1.84(0.50)	1.90(0.42)	2.09(0.46)	1.25(0.26)	1.17(0.17)	1.17(0.08)
Temporoparietal cortex	1.11(0.08)	1.12(0.09)	1.10(0.03)	1.25(0.22)	1.50(0.45)	1.36(0.38)	1.67(0.48)	1.80(0.47)	2.12(0.52)	1.20(0.25)	1.13(0.16)	1.12(0.07)
Braak stage V/VI	1.12(0.08)	1.18(0.10)	1.08(0.05)	1.19(0.14)	1.62(0.46)	1.20(0.24)	1.46(0.33)	1.91(0.44)	1.75(0.37)	1.17(0.19)	1.18(0.17)	1.08(0.07)

eTable 7. Diagnostic performance of partial volume corrected [^{18}F]flortaucipir PET in distinguishing AD dementia from non-AD neurodegenerative disorders

Region-of-interest (threshold)		**Threshold approach: mean+2*SD in all controls**				
	AUC	Accuracy	Sensitivity	Specificity	+LR	−LR
Entorhinal cortex (SUVR: 1.82)	0.92	84.3	78.8	88.2	6.7	0.24
	[0.89-0.95]	[80.5-87.6]	[72.1-84.5]	[83.6-91.9]	[4.7-9.4]	[0.18-0.32]
Inferior temporal cortex (SUVR: 1.59)	0.94	88.2	89.9	87.0	6.9	0.12
	[0.92-0.97]	[84.8-91.1]	[84.6-93.9]	[82.2-90.9]	[5.0-9.6]	[0.07-0.18]
Temporal Meta-ROI (SUVR: 1.51)	0.95	89.6	91.1	88.6	8.0	0.10
	[0.93-0.97]	[86.3-92.3]	[85.9-94.8]	[84.0-92.2]	[5.7-11.3]	[0.06-0.16]
Temporoparietal cortex (SUVR: 1.49)	0.94	90.5	88.3	92.1	11.2	0.13
	[0.91-0.96]	[87.4-93.1]	[82.6-92.6]	[88.1-95.1]	[7.3-17.1]	[0.09-0.19]
Braak stage V/VI (SUVR: 1.52)	0.93	88.9	83.2	92.9	11.8	0.18
	[0.90-0.95]	[85.6-91.7]	[77.0-88.4]	[89.0-95.8]	[7.5-18.4]	[0.13-0.25]

eTable 8. Diagnostic performance of [^{18}F]flortaucipir using a cut-off derived in AD dementia vs non-AD neurodegenerative disorders

Region-of-interest (threshold, Youden's *J* in Seoul cohort)	**A. Threshold approach: Youden Index derived in Seoul cohort (55 AD dementia vs 89 non-AD diseases) applied to BioFINDER & UCSF cohorts**				
N=289	Accuracy	Sensitivity	Specificity	+LR	−LR
Entorhinal cortex (SUVR: 1.45, *J*: 0.68)	90.3 [86.3-93.5]	79.8 [71.7-86.5]	98.2 [94.8-99.6]	43.9 [14.3-135.2]	0.21 [0.14-0.29]
Inferior temporal cortex (SUVR: 1.36, *J*: 0.68)	93.1 [89.5-95.7]	95.2 [89.8-98.2]	91.5 [86.2-95.3]	11.2 [6.8-18.5]	0.05 [0.02-0.12]
Temporal Meta-ROI (SUVR: 1.36, *J*: 0.69)	93.9 [90.1-96.5]	92.7 [86.7-96.6]	95.0 [89.5-98.2]	18.7 [8.6-40.9]	0.08 [0.04-0.14]
Temporoparietal cortex (SUVR: 1.26, *J*: 0.68)	93.4 [89.9-96.0]	90.3 [83.7-94.9]	95.8 [91.5-98.3]	21.3 [10.3-44.1]	0.10 [0.06-0.17]
Braak stage V/VI (SUVR: 1.23, *J*: 0.59)	91.7 [87.9-94.6]	92.7 [86.7-96.6]	90.9 [85.5-94.8]	10.2 [6.3-16.6]	0.08 [0.04-0.15]
Region-of-interest (threshold, Youden's *J* in BioFINDER cohort)	**B. Threshold approach: Youden Index derived in BioFINDER cohort (52 AD dementia vs 73 non-AD diseases) applied to Seoul & UCSF cohorts**				
N=308	Accuracy	Sensitivity	Specificity	+LR	−LR
Entorhinal cortex (SUVR: 1.34, *J*: 0.72)	88.0 [83.8-91.4]	92.9 [87.0-96.7]	84.5 [78.4-89.5]	6.0 [4.3-8.5]	0.08 [0.04-0.16]
Inferior temporal cortex (SUVR: 1.38, *J*: 0.85)	89.6 [85.7-92.8]	88.2 [81.3-93.2]	90.6 [85.4-94.4]	9.4 [6.0-14.8]	0.13 [0.08-0.21]
Temporal Meta-ROI (SUVR: 1.35, *J*: 0.84)	89.6 [85.7-92.8]	89.0 [82.2-93.8]	90.1 [84.7-94.0]	9.0 [5.8-13.9]	0.12 [0.07-0.20]
Temporoparietal cortex (SUVR: 1.22, *J*: 0.83)	87.7 [83.5-91.1]	89.0 [82.2-93.8]	86.7 [80.9-91.3]	6.7 [4.6-9.8]	0.13 [0.08-0.21]
Braak stage V/VI (SUVR: 1.28, *J*: 0.83)	87.3 [83.1-90.8]	76.4 [68.0-83.5]	95.0 [90.8-97.7]	15.4 [8.1-29.3]	0.25 [0.18-0.34]

eTable 9. Diagnostic performance of [^{18}F]flortaucipir PET using the closest cut-off at 95% sensitivity in AD dementia vs controls

Region-of-interest (threshold, SENS/SPEC in Seoul cohort)	**A. Threshold approach: Closest cut-off to 95% sensitivity derived in Seoul cohort (55 AD dementia vs 90 controls) applied to BioFINDER & UCSF cohorts**				
N=289	Accuracy	Sensitivity	Specificity	+LR	−LR
Entorhinal cortex (SUVR: 1.36; 94.5%/90.0%)	89.6 [85.5-92.9]	85.5 [78.0-91.2]	92.7 [87.6-96.2]	11.8 [6.8-20.4]	0.16 [0.10-0.24]
Inferior temporal cortex (SUVR: 1.18; 94.5%/64.6%)	68.2 [62.5-73.5]	99.2 [95.6-100.0]	44.9 [37.1-52.8]	1.8 [1.6-2.1]	0.02 [0.00-0.13]
Temporal Meta-ROI (SUVR: 1.18; 94.5%/67.8%)	94.8 [91.6-97.1]	92.7 [86.7-96.6]	96.4 [92.3-98.7]	25.5 [11.6-56.0]	0.08 [0.04-0.14]
Temporoparietal cortex (SUVR: 1.10; 94.5%/52.2%)	65.4 [59.6-70.9]	98.4 [94.3-99.8]	40.6 [33.0-48.5]	1.7 [1.5-1.9]	0.04 [0.01-0.16]
Braak stage V/VI (SUVR: 1.06; 94.5%/20.0%)	55.4 [49.4-61.2]	98.4 [94.3-99.8]	23.0 [16.8-30.2]	1.3 [1.2-1.4]	0.07 [0.02-0.28]
Region-of-interest (threshold, SENS/SPEC in BioFINDER cohort)	**B. Threshold approach: Closest cut-off to 95% sensitivity derived in BioFINDER cohort (52 AD dementia vs 66 controls) applied to Seoul & UCSF cohorts**				
N=308	Accuracy	Sensitivity	Specificity	+LR	−LR
Entorhinal cortex (SUVR: 1.16; 96.2%/69.7%)	67.5 [62.0-72.7]	98.4 [94.4-99.8]	45.9 [38.4-53.4]	1.8 [1.6-2.1]	0.03 [0.01-0.14]
Inferior temporal cortex (SUVR: 1.35; 96.2%/93.9%)	89.6 [85.7-92.8]	88.2 [81.3-93.2]	90.6 [85.4-94.4]	9.4 [6.0-14.8]	0.13 [0.08-0.21]
Temporal Meta-ROI (SUVR: 1.28; 96.2%/89.4%)	89.6 [85.7-92.8]	89.0 [82.2-93.8]	90.1 [84.7-94.0]	9.0 [5.8-13.9]	0.12 [0.07-0.20]
Temporoparietal cortex (SUVR: 1.17; 96.2%/80.3%)	77.6 [72.5-82.1]	92.1 [86.0-96.2]	67.4 [60.1-74.2]	2.8 [2.3-3.5]	0.12 [0.06-0.21]
Braak stage V/VI (SUVR: 1.28; 96.2%/90.9%)	87.7 [83.5-91.1]	77.2 [68.9-84.1]	95.0 [90.8-97.7]	15.5 [8.2-29.6]	0.24 [0.17-0.33]

eTable 10. Diagnostic performance of [^{18}F]flortaucipir PET using the closest cut-off at 95% specificity in AD dementia vs controls

Region-of-interest (threshold, SENS/SPEC in Seoul cohort)	**A. Threshold approach: Closest cut-off to 95% specificity derived in Seoul cohort (55 AD dementia vs 90 controls) applied to BioFINDER & UCSF cohorts**				
N=289	Accuracy	Sensitivity	Specificity	+LR	−LR
Entorhinal cortex (SUVR: 1.46; 85.5%/95.6%)	90.3 [86.3-93.5]	79.8 [71.7-86.5]	98.2 [94.8-99.6]	43.9 [14.3-135.2]	0.21 [0.14-0.29]
Inferior temporal cortex (SUVR: 1.28; 85.5%/95.6%)	88.6 [84.3-92.0]	97.6 [93.1-99.5]	81.8 [75.1-87.4]	5.4 [3.9-7.4]	0.03 [0.01-0.09]
Temporal Meta-ROI (SUVR: 1.27; 87.3%/95.6%)	91.7 [87.9-94.6]	96.8 [92.0-99.1]	87.9 [81.9-92.4]	8.0 [5.3-12.1]	0.04 [0.01-0.10]
Temporoparietal cortex (SUVR: 1.25; 80.0%/95.6%)	93.4 [89.9-96.0]	91.9 [85.7-96.1]	94.6 [89.9-97.5]	16.9 [8.9-31.9]	0.09 [0.05-0.15]
Braak stage V/VI (SUVR: 1.26; 70.9%/95.6%)	92.7 [89.1-95.5]	91.9 [85.7-96.1]	93.3 [88.4-96.6]	13.8 [7.8-24.5]	0.09 [0.05-0.16]
Region-of-interest (threshold, SENS/SPEC in BioFINDER cohort)	**B. Threshold approach: Closest cut-off to 95% specificity derived in BioFINDER cohort (52 AD dementia vs 66 controls) applied to Seoul & UCSF cohorts**				
N=308	Accuracy	Sensitivity	Specificity	+LR	−LR
Entorhinal cortex (SUVR: 1.53; 57.7%/95.5%)	86.4 [82.0-90.0]	78.0 [69.7-84.8]	92.3 [87.4-95.7]	10.1 [6.0-16.8]	0.24 [0.17-0.33]
Inferior temporal cortex (SUVR: 1.40; 90.4%/95.5%)	89.6 [85.7-92.8]	85.8 [78.5-91.4]	92.3 [87.4-95.7]	11.1 [6.7-18.4]	0.15 [0.10-0.24]

Temporal Meta-ROI (SUVR: 1.37; 90.4%/95.5%)	90.6 [86.8-93.6]	87.4 [80.4-92.6]	92.9 [88.0-96.1]	12.2 [7.2-20.6]	0.14 [0.09-0.21]
Temporoparietal cortex (SUVR: 1.32; 82.7%/95.5%)	89.9 [86.0-93.1]	82.7 [75.0-88.8]	95.0 [90.8-97.7]	16.6 [8.8-31.6]	0.18 [0.12-0.27]
Braak stage V/VI (SUVR: 1.36; 90.4%/95.5%)	85.7 [81.3-89.4]	70.9 [62.2-78.6]	96.1 [92.2-98.4]	18.3 [8.8-38.2]	0.30 [0.23-0.40]

eTable 11. Diagnostic accuracy in AD dementia (n=179) vs non-AD neurodegenerative disorders (n=254) and in combined Aβ+ and Aβ- (n=17) AD dementia vs non-AD neurodegenerative disorders

Region-of-interest	AUC Aβ+ AD dementia (95% CI)	AUC Aβ+ and Aβ- AD dementia (95% CI)	P for difference
Entorhinal cortex	0.94 (0.91-0.96)	0.92 (0.89-0.94)	0.24
Inferior temporal cortex	0.94 (0.92-0.97)	0.91 (0.88-0.94)	0.08
Temporal Meta-ROI	0.95 (0.93-0.97)	0.92 (0.90-0.95)	0.11
Temporoparietal cortex	0.93 (0.91-0.96)	0.91 (0.88-0.94)	0.21
Braak stage V/VI	0.92 (0.89-0.95)	0.89 (0.86-0.93)	0.28

eTable 12. Tau-positivity in the temporal Meta-ROI by amyloid status

Diagnosis	Aβ status	N total	N tau-positive (%)
Cognitively normal control	+	42	5 (11.9%)
	−	118	2 (1.7%)
Mild cognitive impairment	+	83	51 (61.4%)
	−	43	2 (4.7%)
Alzheimer dementia	+	179	161 (89.9%)
Behavioral variant frontotemporal dementia	+	4	0 (0%)
	−	26	1 (3.8%)
	?	3	3 (100%)
Non-fluent variant primary progressive aphasia	+	2	1 (50%)
	−	15	0 (0%)
Semantic variant primary progressive aphasia	+	4	4 (100%)
	−	7	0 (0%)
Dementia with Lewy bodies	+	13	7 (53.8%)
	-	9	1 (11.1%)
	?	2	0 (0%)
Progressive supranuclear palsy	+	9	0 (0%)
	−	28	0 (0%)
	?	3	0 (0%)
Corticobasal syndrome	+	1	0 (0%)
	−	19	0 (0%)
	?	3	0 (0%)
Parkinson disease with Cognitive impairment	+	14	3 (21.4%)
	−	25	1 (4.0%)
	?	31	1 (3.2%)
Parkinson disease with normal cognition	+	2	0 (0%)
	−	19	0 (0%)
	?	2	0 (0%)
Vascular dementia	+	1	1 (100%)
	-	6	1 (16.7%)

eTable 13. Factors contributing to tau-negativity in AD dementia and tau-positivity in non-AD diseases in the temporal meta-ROI.

			AD dementia			
	Tau-negative (n=18)	**Tau-positive (n=161)**	**OR (95% CI)**	**P**		
A. Bivariate model						
Age (n=179)	76.3 (8.1)	68.0 (9.4)	0.90 (0.84-0.96)	**0.001**		
Sex, %male (n=179)	44.4	40.4	0.85 (0.32-2.26)	0.739		
APOE ε4, % positive (n=156)	38.5	58.0	2.21 (0.69-7.10)	0.182		
MMSE (n=169)	24.1 (4.2)	19.8 (5.4)	0.81 (0.71-0.93)	**0.002**		
	Tau-negative (n=13)	**Tau-positive (n=138)**	**OR (95% CI)**	**P**	**Imputed OR (95%CI)**	**Imputed P**
B. Multivariable model* (n=151)						
Age	76.8 (9.0)	68.6 (5.3)	0.89 (0.82-0.97)	**0.006**	0.88 (0.81-0.95)	**0.001**
Sex, %male	38.5	38.4	0.96 (0.27-3.42)	0.946	0.84 (0.27-2.60)	0.759
APOE ε4, % positive	38.5	59.4	2.31 (0.65-8.15)	0.194	2.14 (0.63-7.24)	0.221
MMSE	22.9 (3.9)	19.9 (5.3)	0.82 (0.69-0.97)	**0.022**	0.77 (0.65-0.90)	**0.001**
			Non-AD neurodegenerative conditions			
	Tau-negative (n=230)	**Tau-positive (n=24)**	**OR (95% CI)**	**P**		
A. Bivariate model						
Age (n=254)	68.1 (7.7)	75.1 (7.2)	1.14 (1.07-1.21)	**<0.001**		
Sex, %male (n=254)	57.8	54.2	0.86 (0.37-2.01)	0.730		
APOE ε4 status, % positive (n=143)	28.2	42.1	1.85 (0.69-4.98)	0.220		
Aβ status, % positive (n=210)	17.9	80.0	2.08 (1.27-3.41)	**0.004**		
MMSE (n=212)	24.3 (5.7)	17.7 (5.9)	0.87 (0.82-0.93)	**<0.001**		
	Tau-negative (n=118)	**Tau-positive (n=15)**	**OR (95% CI)**	**P**	**Imputed OR (95%CI)**	**Imputed P**
B. Multivariable model* (n=133)						
Age	68.1 (7.8)	76.3 (7.6)	1.16 (1.03-1.31)	**0.016**	1.09 (1.01-1.18)	**0.020**
Sex, %male	60.2	46.7	1.04 (0.22-4.88)	0.959	1.04 (0.37-2.94)	0.949
APOE ε4 status, % positive	27.1	46.7	1.10 (0.22-5.55)	0.909	0.99 (0.21-4.75)	0.990
Aβ status, % positive	16.1	86.7	34.58 (4.92-243.19)	**<0.001**	8.90 (2.21-35.87)	**0.002**
MMSE	24.1 (5.0)	17.1 (6.3)	0.85 (0.75-0.96)	**0.009**	0.90 (0.84-0.98)	**0.009**

Reported odds ratios, 95% confidence intervals and p-values were derived from bivariate (A) and multivariable (B) binary logistic regression models. * The multivariable model only included participants with all four variables available. The multivariable analyses

were also done on imputed data sets, with results shown in the two right-most columns (with N=179 for AD dementia, upper part; and N=254 for non-AD neurodegenerative conditions, lower part).

eTable 14. Tau-negativity in the temporal Meta-ROI in AD dementia by age

	Total N	**N Tau PET negative**	**% Tau PET negative**
Early-onset AD (<65 yr)	65	1	1.5
Late-onset AD (≥65 yr)	114	17	14.9
Age range (years):			
44-54	13	0	0
55-64	52	1	1.9
65-74	55	4	7.3
75-84	53	11	20.8
85+	6	2	33.3

eTable 15. Combined assessment of temporal Meta-ROI [^{18}F]flortaucipir and MRI measures

AD DEMENTIA vs NON-AD NEURODEGENERATIVE DISORDERS		
Measure	**AUC [95%CI]**	**P vs FTP-PET**
FTP-PET: temporal Meta-ROI	**0.95 [0.93 -0.97]**	**NA**
MRI: AD-signature cortical thickness	0.75 [0.71-0.80]	<0.001
MRI: Whole brain cortical thickness	0.71 [0.66-0.76]	<0.001
MRI: Hippocampal volumes	0.63 [0.57-0.68]	<0.001
FTP-PET: temporal Meta-ROI + MRI: AD-signature cortical thickness	0.95 [0.93 -0.97]	0.97
FTP-PET: temporal Meta-ROI + MRI: Whole brain cortical thickness	0.95 [0.93 -0.97]	0.94
FTP-PET: temporal Meta-ROI + MRI: Hippocampal volumes	0.95 [0.93 -0.97]	0.97
MCI-DUE-TO-AD vs NON-AD NEURODEGENERATIVE DISORDERS		
FTP-PET: temporal Meta-ROI	**0.82 [0.76-0.88]**	**NA**
MRI: AD-signature cortical thickness	0.56 [0.49-0.64]	<0.001
MRI: Whole brain cortical thickness	0.49 [0.41-0.64]	<0.001
MRI: Hippocampal volumes	0.59 [0.52-0.66]	<0.001
FTP-PET: temporal Meta-ROI + MRI: AD-signature cortical thickness	0.81 [0.75-0.87]	0.73
FTP-PET: temporal Meta-ROI + MRI: Whole brain cortical thickness	0.81 [0.76-0.87]	0.83
FTP-PET: temporal Meta-ROI + MRI: Hippocampal volumes	0.82 [0.76-0.88]	0.99

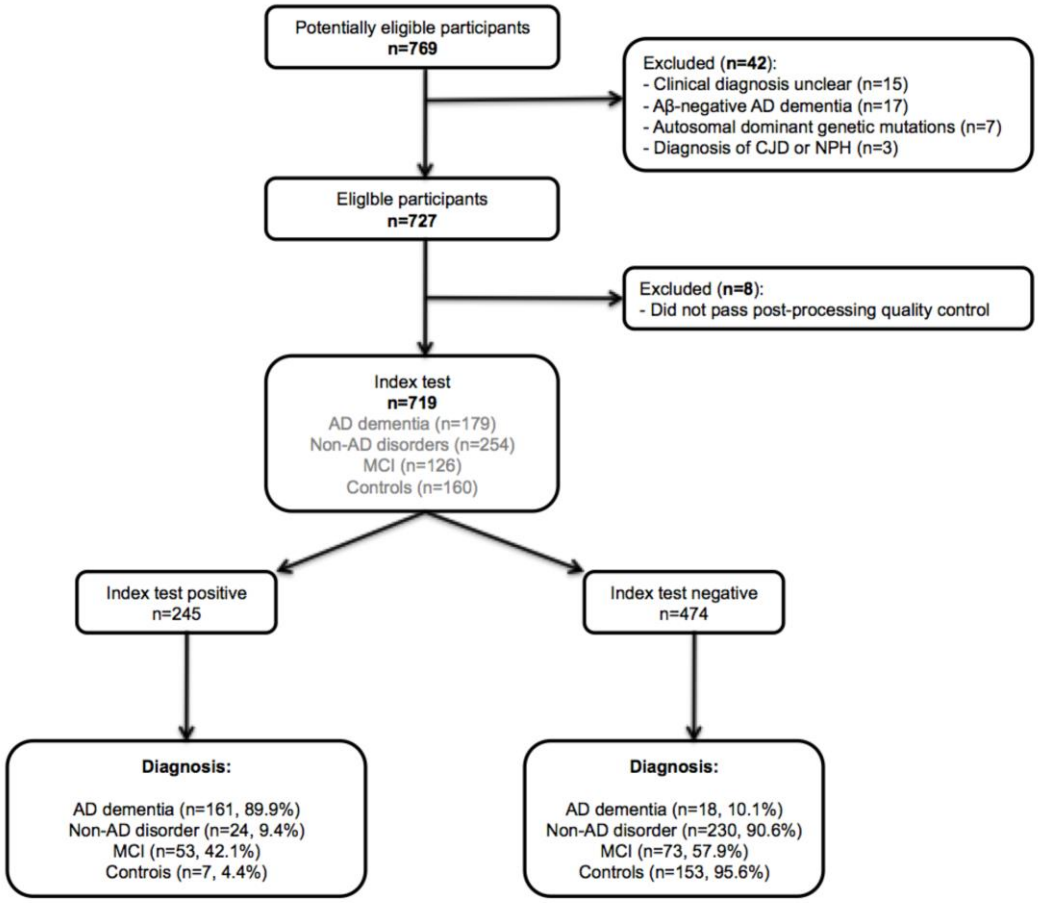
eTable 16. Specificity for [^{18}F]flortaucipir in AD dementia versus non-AD disorders and controls

	AD dementia vs non-AD neurodegenerative disorders		
Region-of-interest	**Specificity % (95%CI)**	**Difference vs Aβ status % (95%CI)**	**P for difference**
Temporal Meta-ROI	90.4 (86.2-94.3)	14.3 (9.0-19.5)	<0.001
Entorhinal cortex	91.5 (87.6-95.2)	15.3 (10.0-21.0)	<0.001
Inferior temporal cortex	90.0 (86.2-93.8)	13.8 (8.6-19.0)	<0.001
Temporoparietal cortex	92.8 (89.4-96.2)	16.7 (11.4-21.9)	<0.001
Braak V-VI	93.8 (90.5-97.1)	17.7 (12.4-22.9)	<0.001
	AD dementia vs controls		
Region-of-interest	**Specificity % (95%CI)**	**Difference vs Aβ status % (95%CI)**	**P for difference**
Temporal Meta-ROI	95.6 (91.9-98.8)	21.8 (15.0-28.1)	<0.001
Entorhinal cortex	95.0 (90.6-98.1)	21.1 (14.4-27.5)	<0.001
Inferior temporal cortex	96.9 (93.8-99.4)	23.0 (16.2-30.0)	<0.001
Temporoparietal cortex	96.2 (93.1-98.8)	22.4 (15.6-29.4)	<0.001
Braak V-VI	95.6 (91.9-98.8)	21.8 (15.0-28.1)	<0.001

eTable 17. Specificity for [^{18}F]flortaucipir in AD dementia versus non-AD disorders and controls in younger and older patient groups

	AD dementia vs non-AD neurodegenerative disorders		
Region-of-interest	**Specificity % (95%CI)**	**Difference vs Aβ status % (95% CI)**	**P for difference vs Aβ status**
Younger patients (<69 years):			
Temporal Meta-ROI	96.3 (92.2-99.0)	10.8 (4.9-17.5)	<0.001
Entorhinal cortex	97.2 (93.2-100.0)	11.8 (4.9-19.4)	<0.001
Inferior temporal cortex	94.1 (89.3-98.1)	8.7 (1.9-16.5)	<0.001
Temporoparietal cortex	97.1 (93.2-100.0)	11.7 (5.8-18.4)	<0.001
Braak V-VI	97.1 (93.2-100.0)	11.7 (5.8-18.4)	<0.001
Older patients (≥69 years):			
Temporal Meta-ROI	85.1 (77.6-91.6)	17.8 (9.3-27.1)	<0.001
Entorhinal cortex	86.1 (78.5-92.5)	18.8 (10.3-28.0)	<0.001
Inferior temporal cortex	85.9 (79.4-92.5)	18.6 (11.2-27.1)	<0.001
Temporoparietal cortex	88.8 (82.2-94.4)	21.5 (14.0-29.9)	<0.001
Braak V-VI	90.6 (84.1-96.3)	23.3 (15.0-32.7)	<0.001
	AD dementia vs controls		
Younger patients (<69 years):			
Temporal Meta-ROI	95.5 (89.7-100.0)	8.8 (1.5-17,6)	<0.001
Entorhinal cortex	97.0 (92.6-100.0)	10.2 (2.9-17.6)	<0.001
Inferior temporal cortex	98.6 (95.6-100.0)	11.8 (4.4-19.2)	<0.001
Temporoparietal cortex	97.0 (92.6-100.0)	10.2 (1.5-19.1)	<0.001
Braak V-VI	95.5 (89.7-100.0)	21.8 (15.0-28.1)	<0.001
Older patients (≥69 years):			
Temporal Meta-ROI	95.6 (90.2-98.9)	31.6 (21.7-41.3)	<0.001
Entorhinal cortex	93.6 (88.0-97.8)	29.5 (19.6-40.2)	<0.001
Inferior temporal cortex	95.6 (90.2-98.9)	31.6 (21.7-41.3)	<0.001
Temporoparietal cortex	95.6 (90.2-98.9)	31.6 (21.7-41.3)	<0.001
Braak V-VI	95.6 (90.2-98.9)	31.6 (21.7-41.3)	<0.001

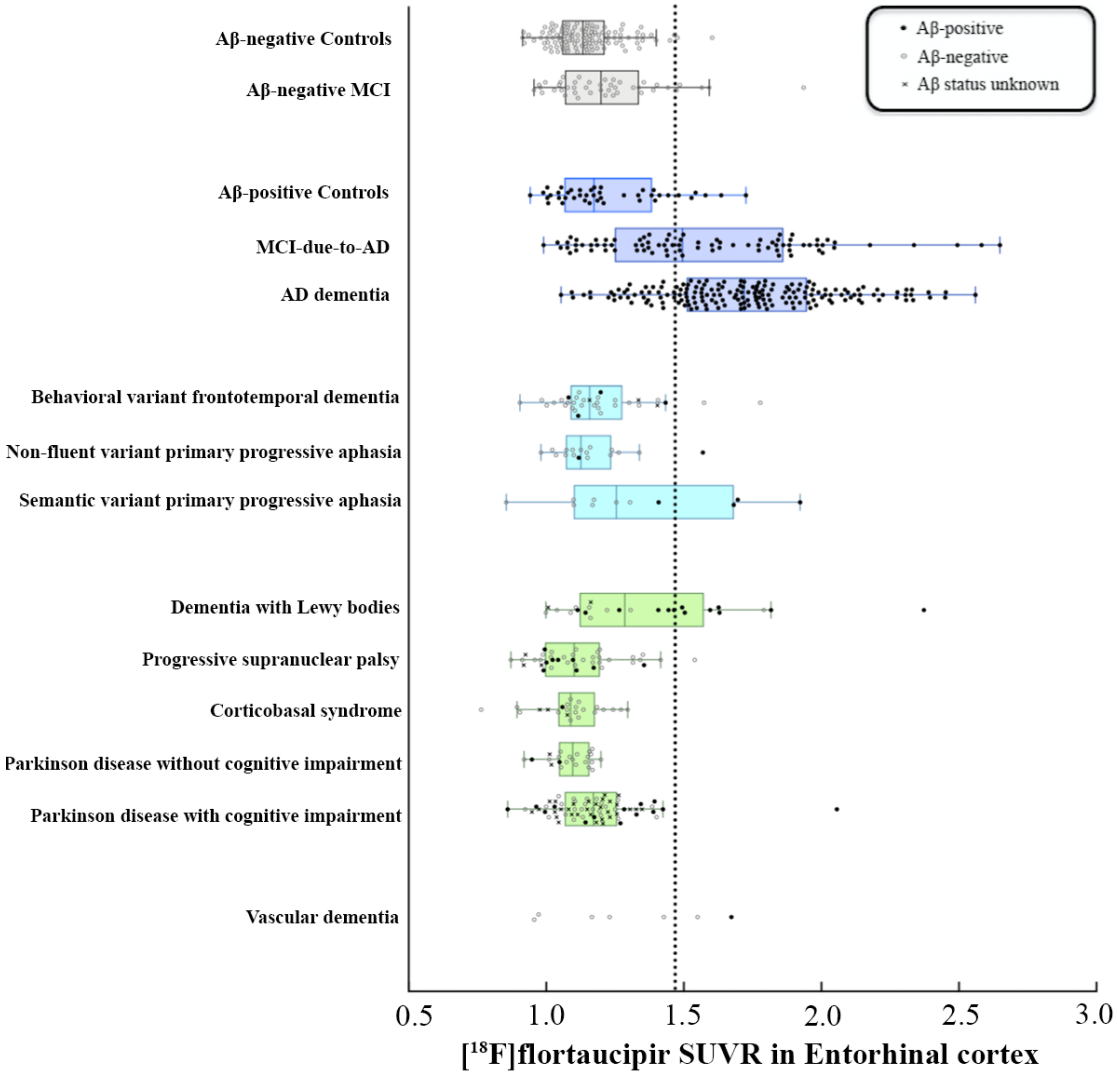
eFigure 1. Flow diagram of participant inclusion



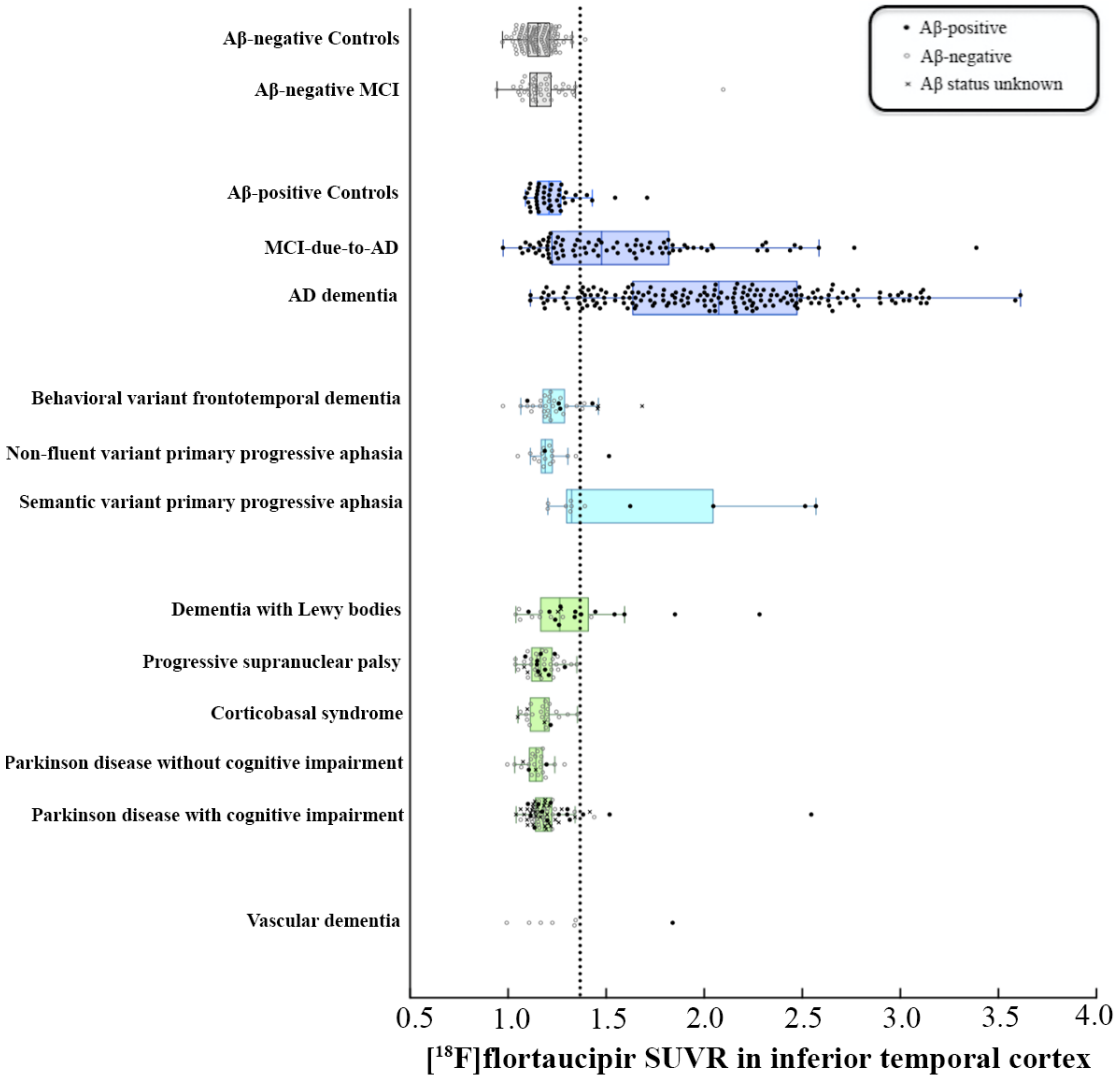
eFigure 1 Legend:
The majority of patients visiting the memory clinics of the three sites were invited to participate in this study, and controls were recruited through advertisements or had subjective cognitive decline (i.e. cognitive complaints but normal neuropsychological performance). 796 persons underwent [^{18}F]flortaucipir PET and 42 were excluded due to various reasons. Of 727 eligible participants, 8 did not pass quality control and were excluded, resulting in a total of 719 participants that were included in the current study.

eFigure 2. [^{18}F]flortaucipir uptake in predefined ROIs per group

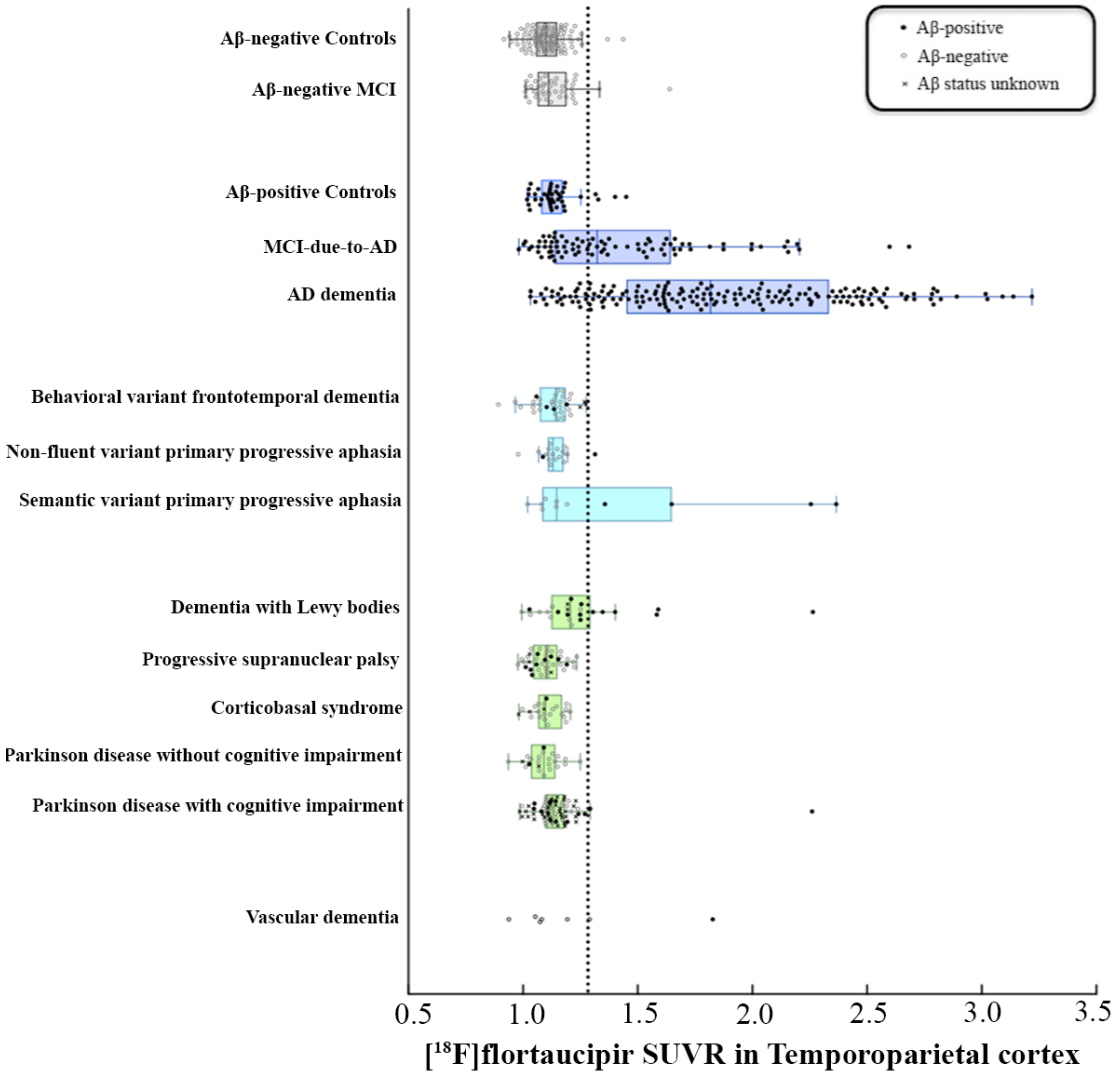
eFigure_2A: Entorhinal cortex



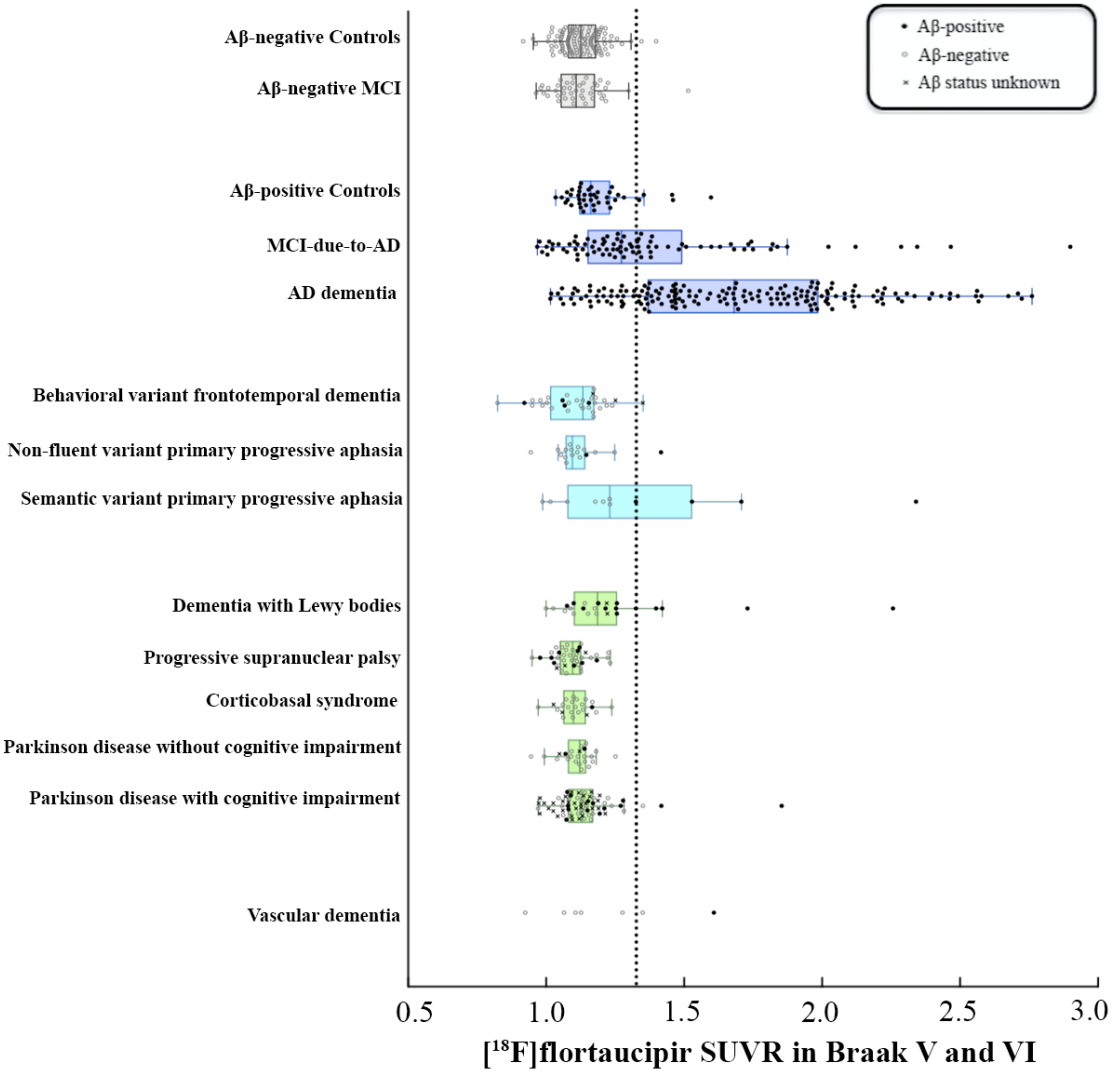
eFigure_2B: Inferior temporal cortex



eFigure_2C: Temporoparietal cortex



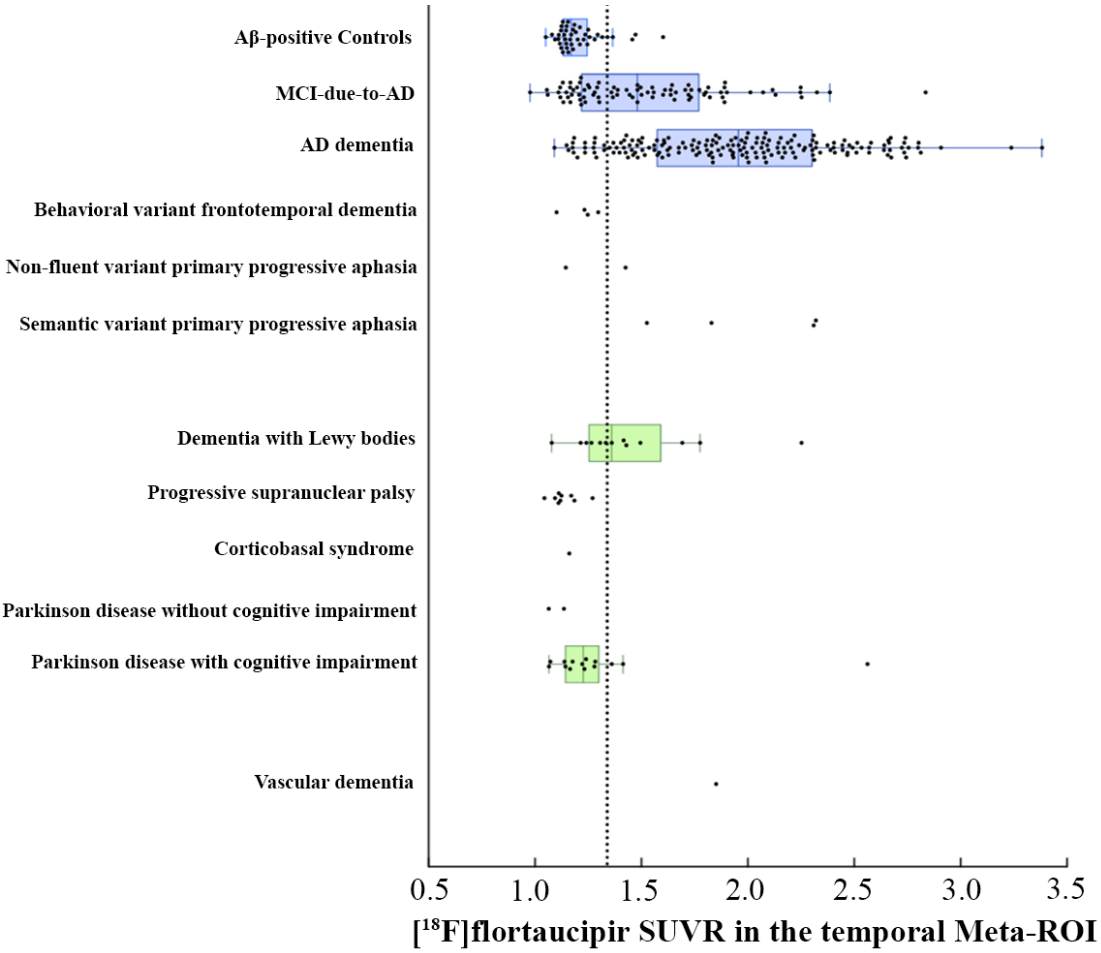
eFigure_2D: Braak stage V/VI



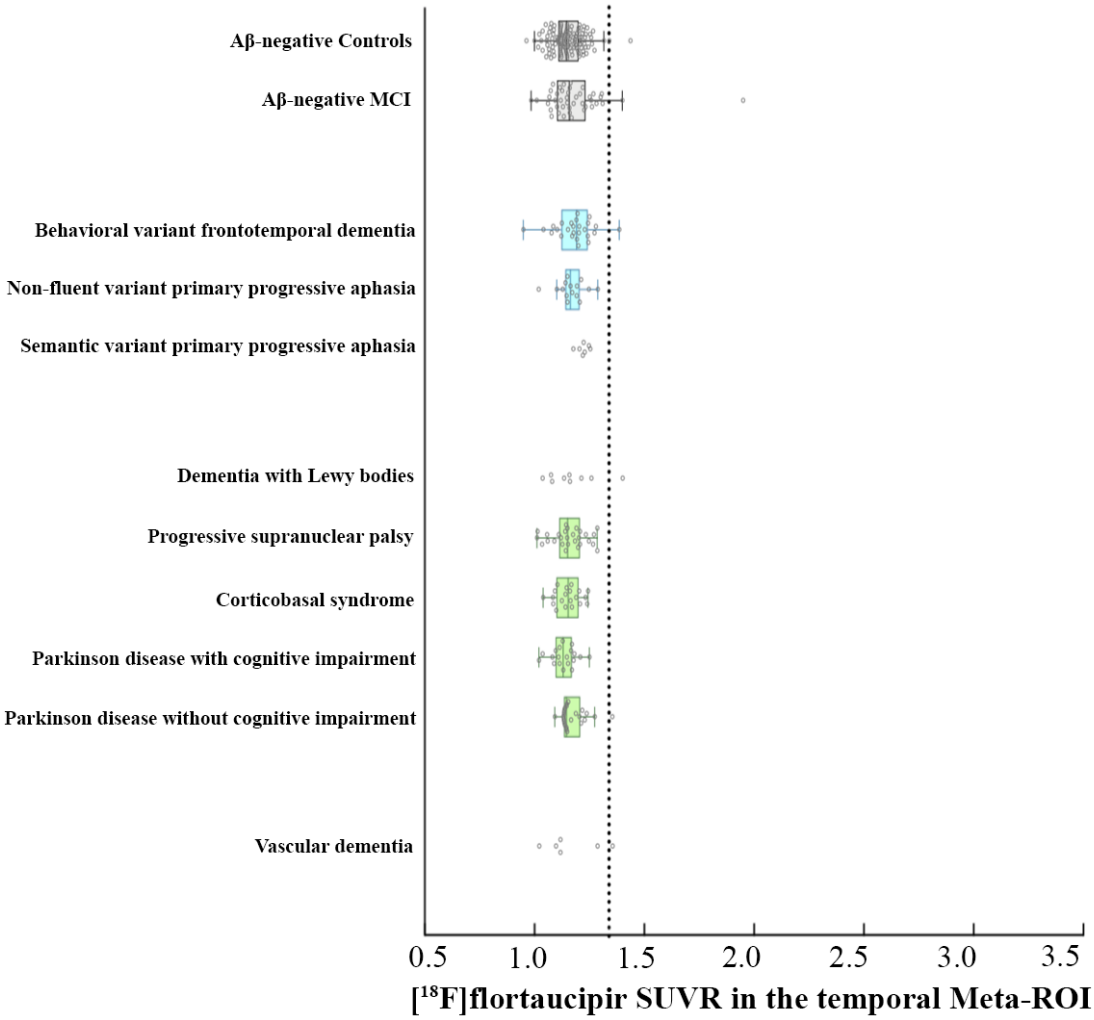
eFigure 2 Legend:
Mean [^{18}F]flortaucipir uptake across diagnostic groups in the enthorinal cortex (2A), ínferior temporal cortex (2B), temporoparietal cortex (2C) and Braak stage V/VI (2D). The dots indicate individuals within the diagnostic groups (filled dots are amyloid-β positive, open dots are amyloid-β positive, a cross indicates that amyloid-β status is unknown). Box-and-Whisker plots are only shown for groups with at least 10 participants. The box ranges from the first to the third quartile, the vertical line represents the median of the diagnostic group and the whiskers indicate the range from the minimum to quartile 1 and from quartile 3 to the maximum excluding outliers. Outliers were defined as SUVR's less than quartile 1 or greater than quartile 3 by more than 1.5 times the interquartile range, and were shown as separate plotted points. The dotted line represents the cut-off, defined using the mean + 2*SD in all controls for each specific region-of-interest.

SUVR = Standardized uptake value ratio; MCI = Mild cognitive impairment; AD = Alzheimer disease.

eFigure 3A. [^{18}F]flortaucipir SUVR in Aβ-positive participants only



eFigure 3B. [^{18}F]flortaucipir SUVR in Aβ-negative participants only

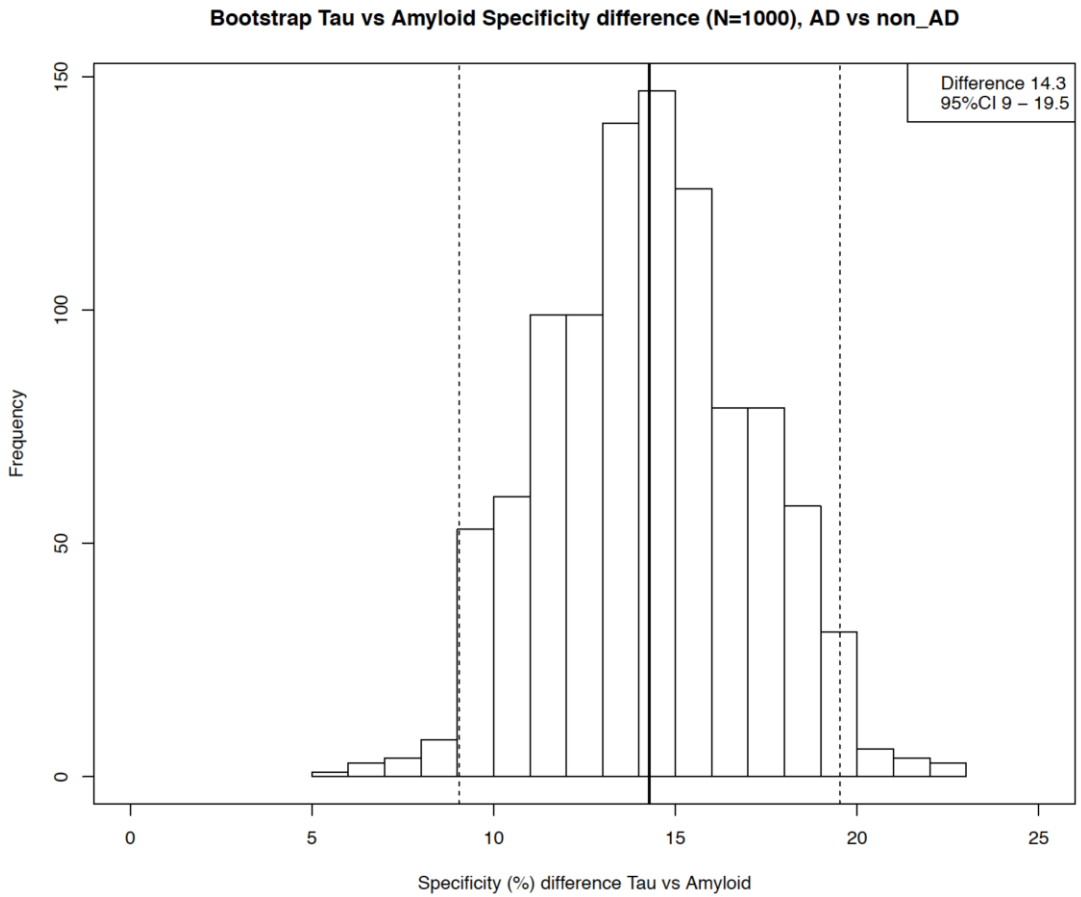


eFigure 3 Legend:
Mean [^{18}F]flortaucipir uptake across diagnostic groups in the temporal Meta-ROI. The dots indicate individuals within the diagnostic groups. The amyloid-β positive cases are presented in Figure 3A and amyloid-β negative cases in Figure 3B (filled dots are amyloid-β positive, open dots are amyloid-β positive). Box-and-Whisker plots are only shown for groups with at least 10 participants. The box ranges from the first to the third quartile, the vertical line represents the median of the diagnostic group and the whiskers indicate the range from the minimum to quartile 1 and from quartile 3 to the maximum excluding outliers. Outliers were defined as SUVR's less than quartile 1 or greater than quartile 3 by more than 1.5 times the interquartile range, and were shown as separate plotted points. The dotted line represents the cut-off (SUVR: 1.34, defined using the mean + 2*SD in all controls).

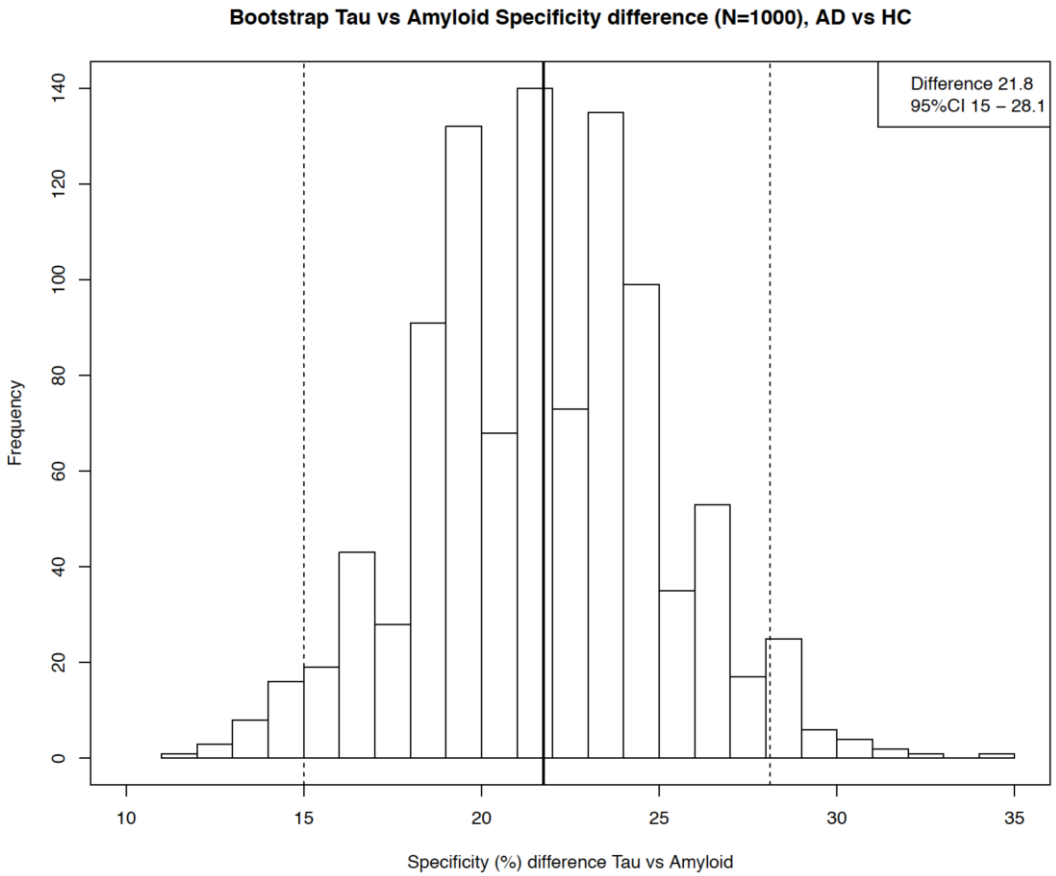
Amyloid-β negative; SUVR = Standardized uptake value ratio; ROI = Region-of-interest; MCI = Mild cognitive impairment; AD = Alzheimer disease.

eFigure 4. Differences in specificity between [^{18}F]flortaucipir SUVR in the temporal Meta-ROI vs Aβ status

eFigure 4A. AD dementia vs non-AD neurodegenerative disorders:



eFigure 4B. AD dementia vs controls:



eFigure 4 Legend:
Histograms of bootstrapped specificities for the difference between [^{18}F] flortaucipir SUVR in the temporal Meta-ROI vs Aβ status, for AD dementia vs non-AD neurodegenerative disorders (Figure 4A) and AD dementia vs controls (Figure 4B).