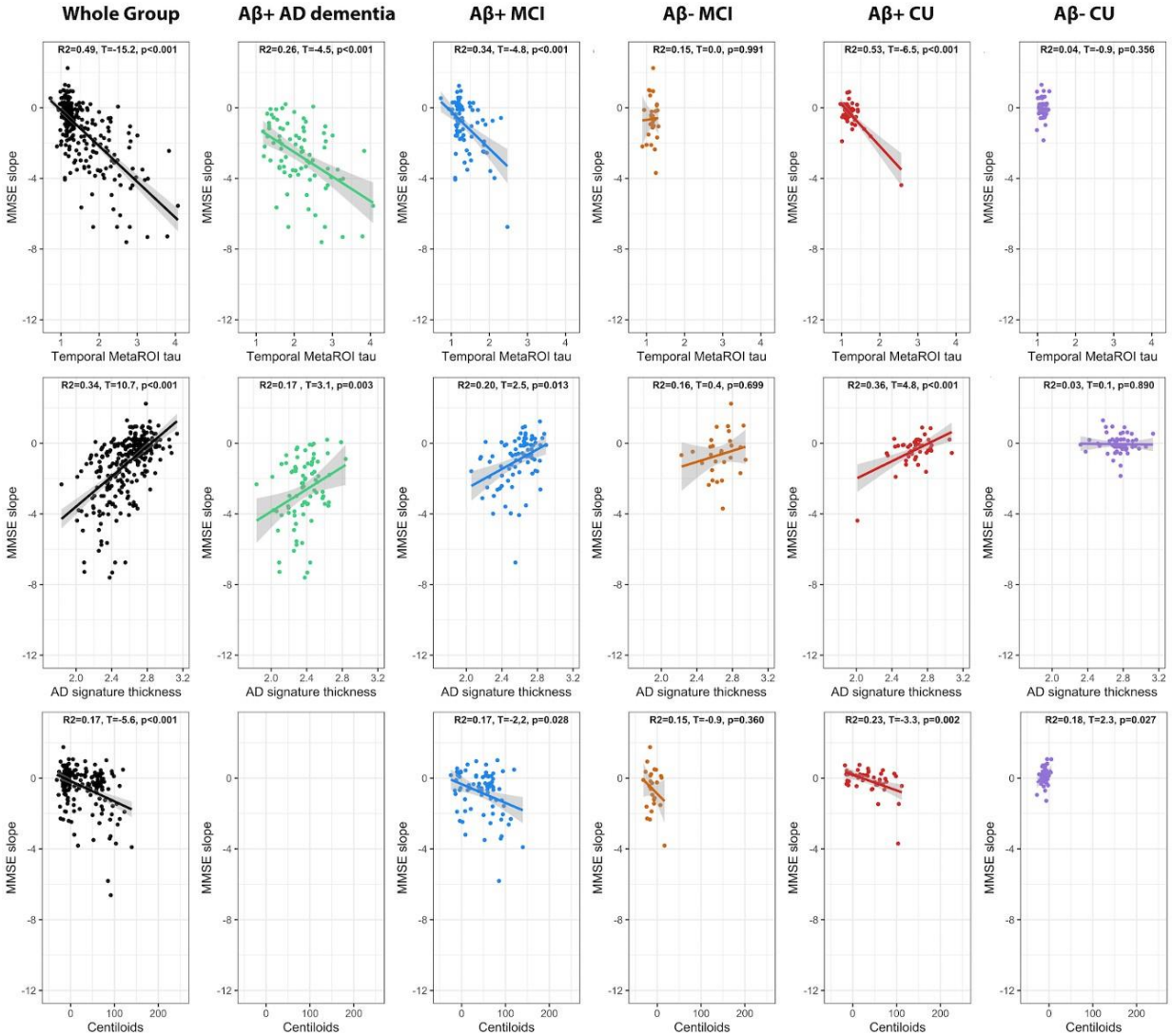
Supplementary Online Content

Ossenkoppele R, Smith R, Mattsson-Carlgren N, et al. Accuracy of tau positron emission tomography as a prognostic marker in preclinical and prodromal Alzheimer disease: a head-to-head comparison against amyloid positron emission tomography and magnetic resonance imaging. *JAMA Neurol*. Published online June 28, 2021. doi:10.1001/jamaneurol.2021.1858

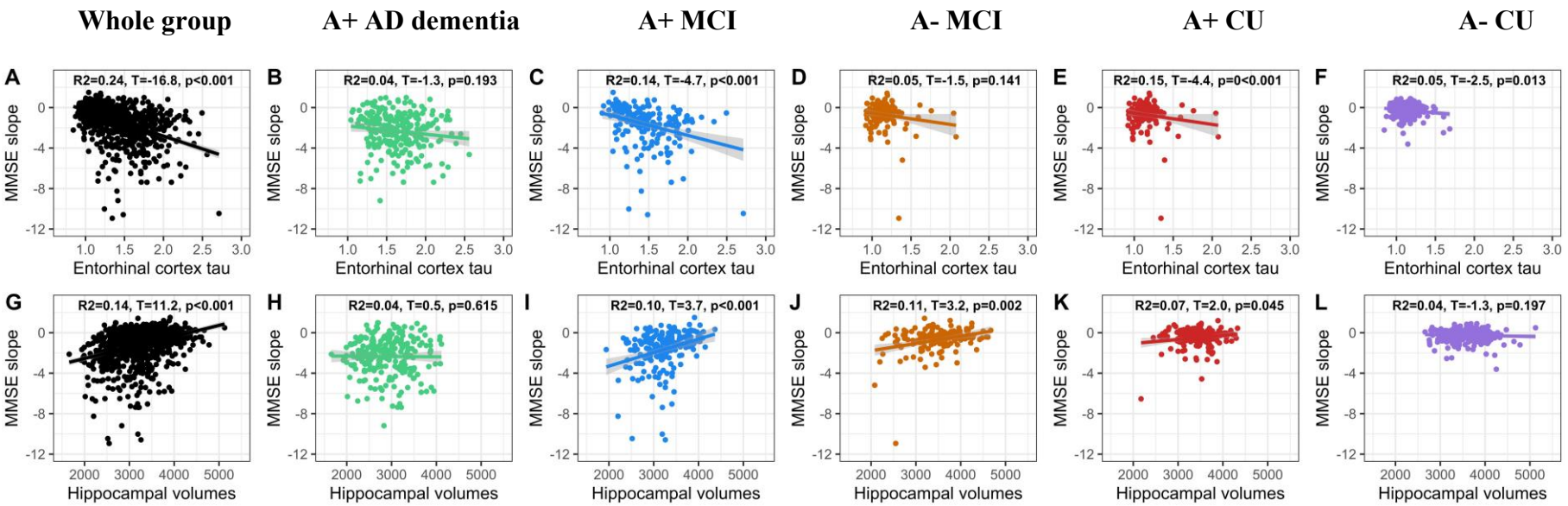
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Replication of Figure 1 (PET vs MRI Comparison) Using [^{18}F]RO948 PET in an Independent Dataset

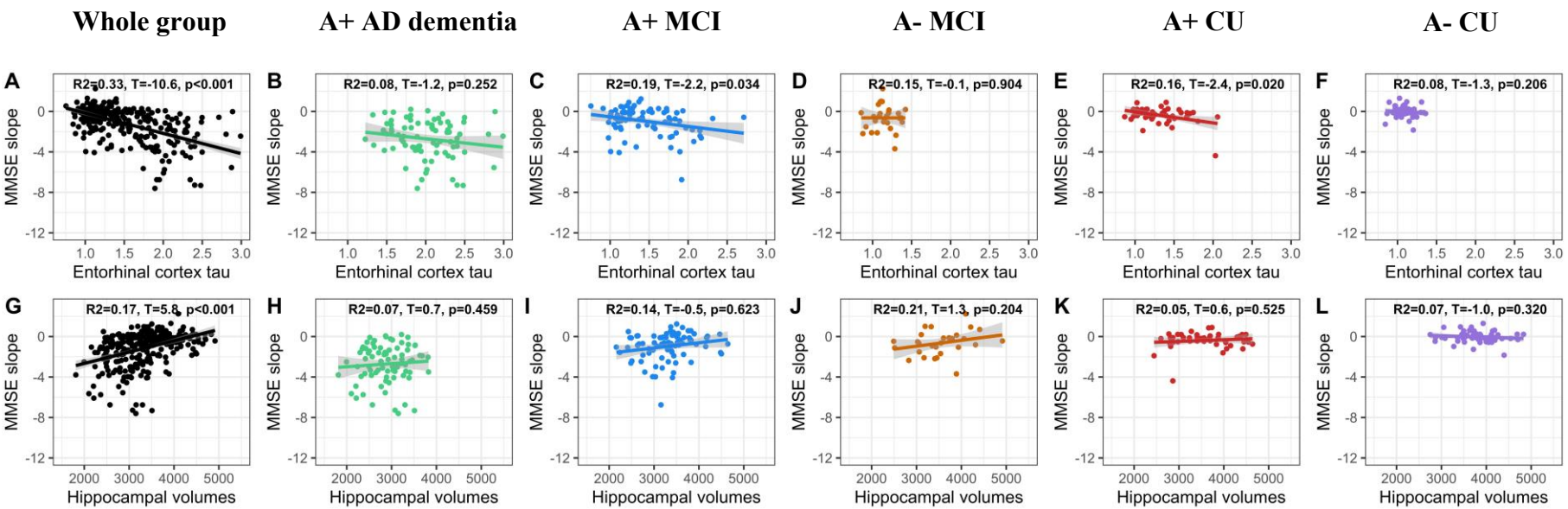


Graphs represent associations between baseline [^{18}F]RO948 (tau) PET uptake in a temporal region-of-interest (upper panel), cortical thickness in an Alzheimer's disease signature region defined on MRI (middle panel) and Amyloid PET (bottom panel) with annual slopes of Mini-Mental State Examination scores across all participants (in black), Aβ+ Alzheimer's disease dementia (in green), Aβ+ mild cognitive impairment (in blue), Aβ- mild cognitive impairment (in orange), Aβ+ cognitively unimpaired individuals (in red) and Aβ- cognitively unimpaired individuals (in purple). Model outputs are derived from a linear regression model between baseline tau PET/MRI/amyloid PET and MMSE slopes, adjusted for age, sex, education and cohort. R^2 values are provided for the full model (including covariates), and T and p-values represent the interaction between the imaging modality and time. Note that amyloid-PET was only available in 5 participants with AD dementia of the Swedish BioFINDER-2 study and therefore now scatterplot was included for this group.

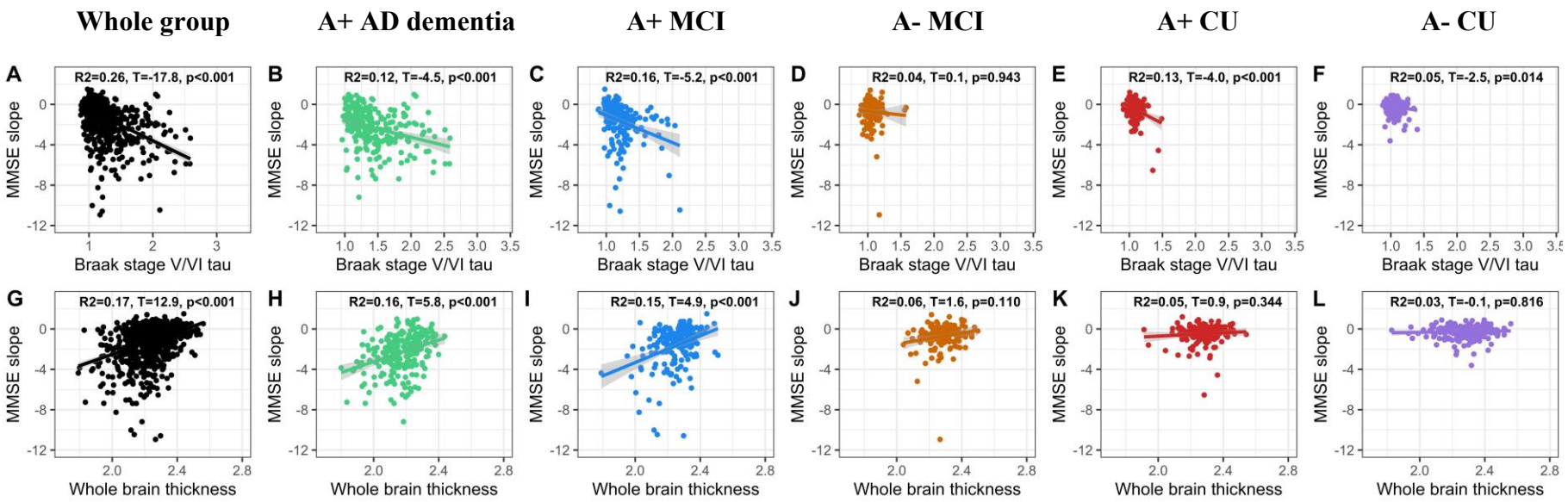
eFigure 2. [^{18}F]Flortaucipir SUVR in Entorhinal Cortex and Hippocampal Volumes as Predictors of Change in MMSE



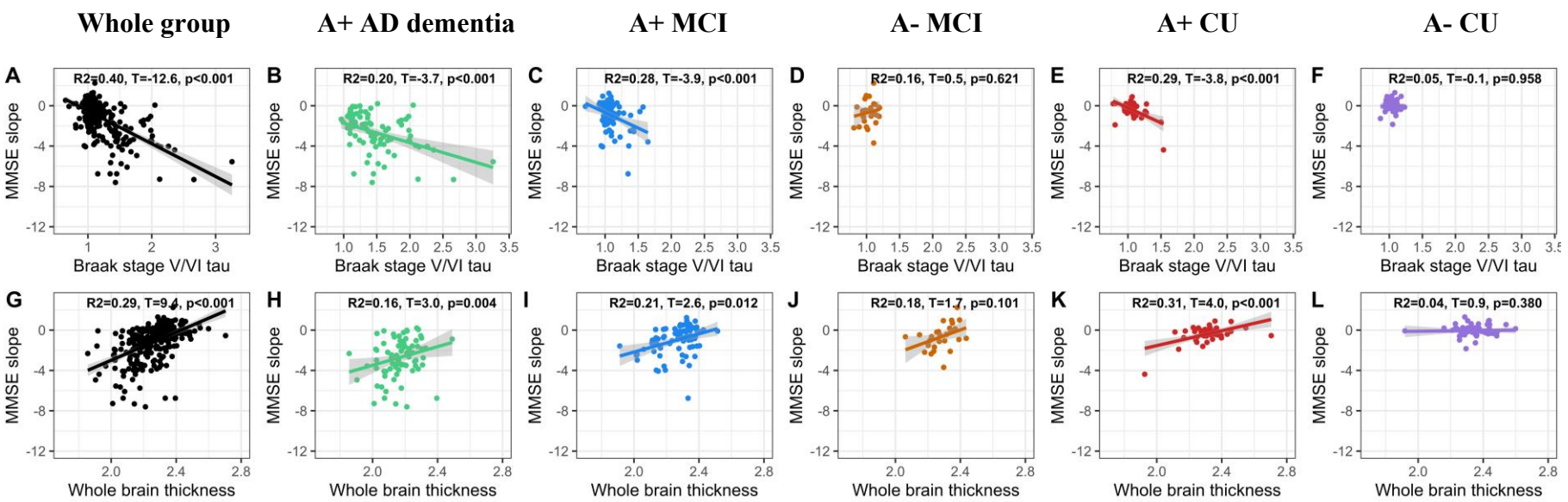
eFigure 3. Replication of eFigure 2 With [^{18}F]RO948 PET in an Independent Dataset



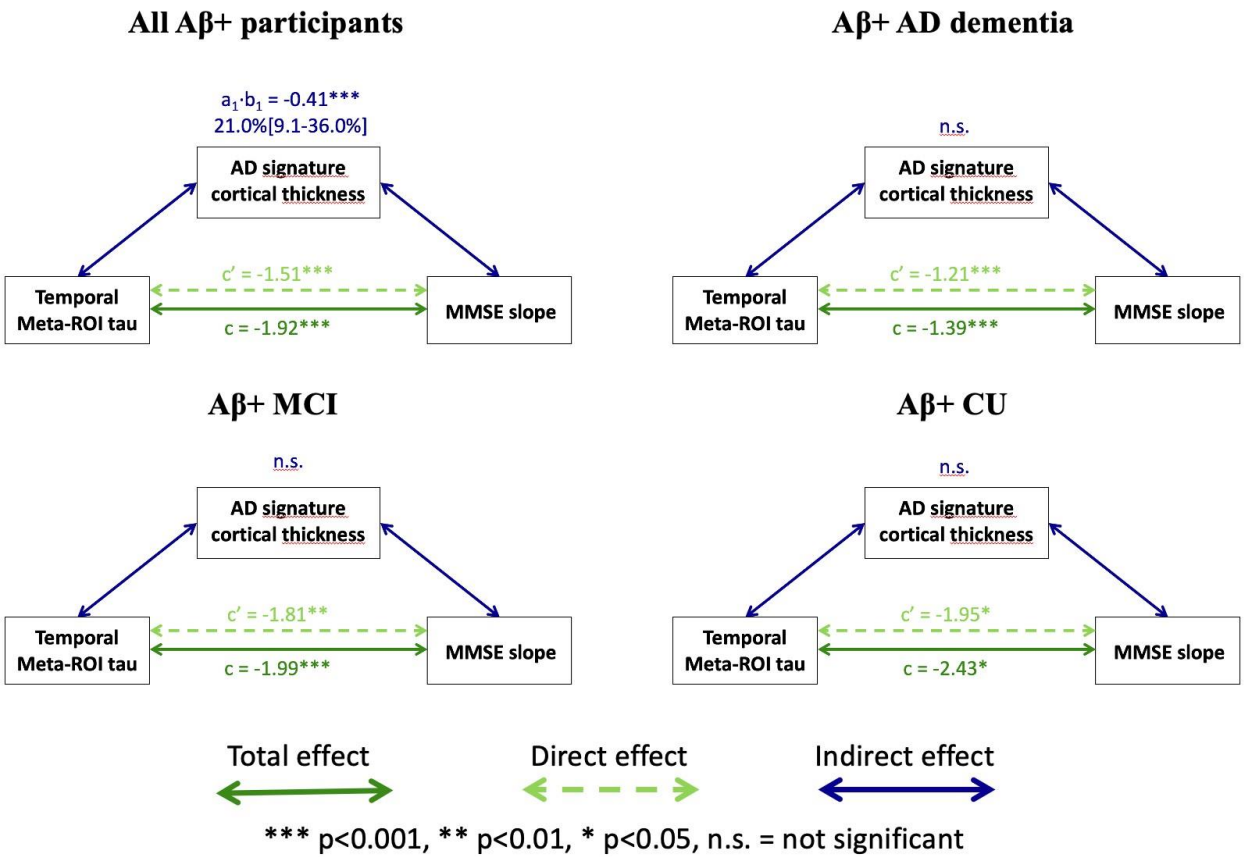
eFigure 4. [^{18}F]Flortaucipir SUVR in Braak V/VI ROIs and Whole Brain Cortical Thickness as Predictors of Change in MMSE



eFigure 5. Replication of eFigure 4 With [18F]RO948 PET in an Independent Dataset



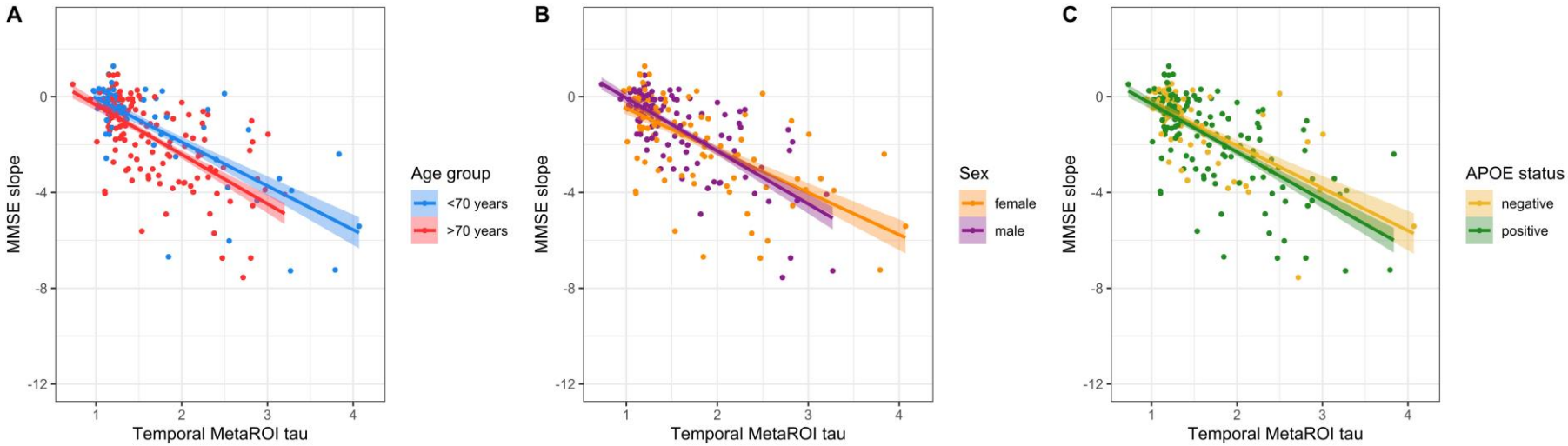
eFigure 6. Replication of Figure 2 (Mediation Analysis) Using [^{18}F]RO948 PET in an Independent Dataset



Path diagrams indicate whether AD-signature cortical thickness mediates the associations between baseline [^{18}F]RO948 SUVR in the temporal meta-ROI and MMSE slopes, adjusting for age, sex, education and *APOE* ε4 status. The direct effect (i.e., coefficient: c') reflects the extent to which MMSE slopes change when baseline tau PET increases by one unit while baseline cortical thickness remains unaltered. The indirect effect (i.e., coefficient: $a_1 \cdot b_1$) reflects the extent to which MMSE slopes changes when baseline tau PET is held constant and baseline cortical thickness changes by the amount it would have changed had baseline tau PET increased by one unit.The coefficient "c" represents the total effect (i.e., direct

+ indirect effects).

eFigure 7. Replication of Figure 3 (Associations With Age, Sex, and *APOE*) Using [^{18}F]RO948 PET in an Independent Dataset



Linear mixed effects models with random intercepts and fixed slopes were performed to examine whether age (A), sex (B) and *APOE* ε4 status (C) moderate the association between baseline [^{18}F]RO948 uptake in a temporal region-of-interest and change over time in Mini-Mental State Examination (MMSE) scores, while adjusting for age, sex, education, cohort and diagnostic group when appropriate. The T- and p-value represent the 3-way interaction Age/Sex/*APOE* ε4 status * time * tau PET. Age was entered as continuous variable in the linear mixed effects models, but was dichotomized at age 70 for visualization purposes.

eTable 1. Participant Characteristics for the Discovery Cohort (A) vs the Replication Cohort (B)

A. [^{18}F]Flortaucipir

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	1135	235	190	144	208	358
Age, years	71.6 (8.3)	71.7 (8.9)	71.5 (8.2)	70.4 (8.5)	74.3 (6.3)	70.5 (8.5)
Sex (% male)	52.2	62.1	48.4	42.4	50.5	52.8
Education, years	13.7 (6.4)	12.6 (5.1)	12.1 (5.4)	12.7 (5.9)	16.1 (9.4)	14.2 (5.2)
APOE ε4, % positive	41.1%	67.3%	60.2%	20.3%	52.5%	17.3%
MMSE, baseline score	26.7 (3.7)	21.6 (5.1)	27.0 (2.6)	28.1 (1.8)	28.9 (1.2)	29.0 (1.2)

B. [^{18}F]RO948

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	296	80	81	28	45	62
Age, years	69.6 (10.3)	74.0 (6.5)	72.1 (7.1)	68.9 (6.8)	70.2 (9.8)	60.9 (13.6)
Sex (% male)	53.4	47.5	55.6	64.3	44.4	59.7
Education, years	12.6 (4.2)	12.1 (4.7)	12.5 (4.4)	11.8 (2.7)	13.1 (4.1)	13.3 (3.5)
APOE ε4, % positive	56.8%	68.4%	66.2%	21.4%	68.9%	37.1%
MMSE, baseline score	25.9 (4.6)	19.9 (4.4)	27.1 (1.9)	27.3 (2.3)	28.8 (1.2)	29.1 (1.1)

Data are presented as mean (standard deviation), unless otherwise stated.
Aβ = amyloid-β, AD = Alzheimer's disease, *APOE* = Apolipoprotein E, CU = Cognitively unimpaired, MCI = Mild cognitive impairment, MMSE = Mini-mental state examination.

eTable 2. Participant Characteristics for the Different Cohorts

BioFINDER-1:

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	136	44	27	1	32	32
Age, years	72.3 (10.3)	71.0 (7.5)	71.6 (9.5)	66	74.1 (8.0)	73.0 (7.1)
Sex (% male)	54.4	56.8	66.7	100	37.5	56.2
Education, years	12.4 (3.7)	12.3 (3.8)	12.4 (3.7)	13.9	11.9 (3.7)	12.8 (3.8)
APOE ε4, % positive	59.2%	64.9%	80.8%	0%	80.0%	16.1%
MMSE, baseline score	25.7 (4.7)	20.8 (4.9)	25.8 (2.9)	30.0	28.9 (1.1)	28.8 (1.1)

Seoul:

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	161	42	37	16	8	58
Age, years	69.4 (9.6)	72.7 (9.5)	71.8 (8.6)	69.8 (9.9)	71.0 (4.4)	65.2 (9.4)
Sex (% male)	64.0	76.2	54.1	68.1	62.5	60.3
Education, years	11.5 (4.9)	10.2 (5.8)	11.8 (4.6)	10.6 (4.4)	12.5 (4.1)	12.4 (4.4)
APOE ε4, % positive	35.0%	58.5%	48.6%	12.5%	37.5%	15.5%
MMSE, baseline score	25.0 (5.0)	19.0 (5.3)	25.4 (3.2)	26.5 (2.3)	27.9 (2.1)	28.3 (1.7)

UCSF:

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	44	28	8	6	1	2
Age, years	63.9 (10.1)	64.6 (10.4)	61.8 (10.0)	67.3 (7.2)	70	60.9 (13.6)
Sex (% male)	61.4	70.4	62.5	33.3	100	0
Education, years	16.9 (2.7)	22.5 (3.9)	17.9 (3.1)	16.8 (1.3)	20.0	18.5 (2.1)
APOE ε4, % positive	45.7%	52.5%	40.0%	0%	0%	100%
MMSE, baseline score	24.6 (4.2)	6.4 (2.7)	17.9 (3.1)	16.8 (1.3)	27.0	30.0 (0)

ADNI:

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	445	17	77	83	116	152
Age, years	71.6 (6.7)	72.1 (10.1)	72.0 (6.9)	70.8 (7.8)	73.5 (6.3)	70.4 (5.5)
Sex (% male)	49.0	35.3	39.0	33.7	57.8	57.2
Education, years	16.5 (2.6)	16.4 (2.6)	15.8 (2.6)	16.5 (2.7)	16.6 (2.4)	16.7 (2.6)
APOE ε4, % positive	36.2%	76.9%	62.7%	17.5%	47.4%	20.1%
MMSE, baseline score	28.5 (1.9)	22.6 (2.6)	27.7 (2.0)	28.5 (1.4)	29.0 (1.2)	29.2 (1.0)

AO5:

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	160	26	41	38	5	50
Age, years	71.3 (9.6)	76.5 (8.2)	72.2 (8.2)	70.3 (9.7)	77.8 (7.0)	67.9 (10.3)
Sex (% male)	48.1	57.5	46.3	50.0	40.0	44.0
Education, years	13.7 (6.4)	12.6 (2.6)	12.6 (2.4)	13.7 (6.7)	13.2 (3.4)	15.2 (9.3)
APOE ε4, % positive	41.4%	73.1%	55.3%	33.3%	40.0%	19.1%
MMSE, baseline score	27.4 (3.4)	21.5 (4.1)	27.5 (1.9)	28.2 (1.8)	29.6 (0.6)	29.5(0.5)

EXPEDITION-3:

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	79	79	NA	NA	NA	NA
Age, years	72.4 (7.5)	72.4 (7.5)	NA	NA	NA	NA
Sex (% male)	62.0	62.0	NA	NA	NA	NA
Education, years	14.7 (2.9)	14.7 (2.9)	NA	NA	NA	NA
APOE ε4, % positive	74.0%	74.0%	NA	NA	NA	NA
MMSE, baseline score	22.9 (2.0)	22.9 (2.0)	NA	NA	NA	NA

BACS:

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	110	NA	NA	NA	46	64
Age, years	77.1 (6.1)	NA	NA	NA	77.0 (7.2)	77.3 (7.2)
Sex (% male)	40.9	NA	NA	NA	39.1	42.2
Education, years	18.2 (12.1)	NA	NA	NA	19.4 (18.4)	17.4 (2.8)
APOE ε4, % positive	26.6%	NA	NA	NA	51.1%	9.4%
MMSE, baseline score	28.7 (1.2)	NA	NA	NA	28.6 (1.4)	28.8 (1.1)

BioFINDER-2:

	Whole group	Aβ+ AD dementia	Aβ+ MCI	Aβ- MCI	Aβ+ CU	Aβ- CU
N	296	80	81	28	45	62
Age, years	69.6 (10.3)	74.0 (6.5)	72.1 (7.1)	68.9 (6.8)	70.2 (9.8)	60.9 (13.6)
Sex (% male)	53.4	47.5	55.6	64.3	44.4	59.7
Education, years	12.6 (4.2)	12.1 (4.7)	12.5 (4.4)	11.8 (2.7)	13.1 (4.1)	13.3 (3.5)
APOE ε4, % positive	56.8%	68.4%	66.2%	21.4%	68.9%	37.1%
MMSE, baseline score	25.9 (4.6)	19.9 (4.4)	27.1 (1.9)	27.3 (2.3)	28.8 (1.2)	29.1 (1.1)

Data are presented as mean (standard deviation), unless otherwise stated.
Aβ = amyloid-β, AD = Alzheimer's disease, *APOE* = Apolipoprotein E, CU = Cognitively unimpaired, MCI = Mild cognitive impairment, MMSE = Mini-mental state examination.

eTable 3. Bootstrapping of R^2 Values From Tau PET vs MRI Models Predicting MMSE Change

	DISCOVERY COHORT ([^{18}F]flortaucipir)				REPLICATION COHORT ([^{18}F]RO948)			
	R^2 difference PET - MRI	**95% CI**	**T**	**P**	**R^2 difference PET - MRI**	**95% CI**	**T**	**P**
Total group	0.099	0.970-0.101	80.3	**<0.001**	0.137	0.136-0.139	147.9	**<0.001**
Aβ+ AD dementia	-0.041	-[0.045-0.036]	-17.2	**<0.001**	0.134	0.129-1.140	50.6	**<0.001**
Aβ+ MCI	0.104	0.097-0.110	30.8	**<0.001**	0.086	0.079-0.094	23.1	**<0.001**
Aβ+ CU	0.098	0.093-0.103	38.6	**<0.001**	0.184	0.163-0.206	16.7	**<0.001**
Aβ- MCI	-0.092	-[0.094-0.091]	-114.0	**<0.001**	-0.047	-[0.048-0.045]	-61.4	**<0.001**
Aβ- CU	0.022	0.018-0.025	13.6	**<0.001**	0.010	0.008-0.011	15.4	**<0.001**

eTable 4. Linear Mixed Models With [^{18}F]RO948 PET and MRI as Predictors of Change in MMSE

	β (SE)	P	R^2	AIC	X^2 for difference	P for difference
ALL Aβ+ PARTICIPANTS						
Model 1: Age, sex, education, cohort			0.066	3070		
Model 2: Model 1 + Tau PET	-0.22 (0.02)	**<0.001**	0.596	2775	307.3	**<0.001**
Model 3: Model 1 + Tau PET + MRI	-0.22 (0.02)	**<0.001**	0.729	2633	107.8	**<0.001**
Model 2: Model 1 + MRI	0.49 (0.05)	**<0.001**	0.409	2868	176.2	**<0.001**
Model 3: Model 1 + MRI + Tau PET	0.48 (0.05)	**<0.001**	0.723	2666	205.5	**<0.001**
Aβ+ AD DEMENTIA						
Model 1: Age, sex, education, cohort			0.152	1187		
Model 2: Model 1 + Tau PET	-0.15 (0.04)	**<0.001**	0.384	1142	46.8	**<0.001**
Model 3: Model 1 + Tau PET + MRI	-0.15 (0.04)	**<0.001**	0.419	1137	6.6	**<0.001**
Model 2: Model 1 + MRI	0.42 (0.14)	**0.002**	0.282	2265	24.0	**<0.001**
Model 3: Model 1 + MRI + Tau PET	0.42 (0.14)	**0.002**	0.413	1144	22.9	**<0.001**
Aβ+ MILD COGNITIVE IMPAIRMENT						
Model 1: Age, sex, education, cohort			0.125	1017		
Model 2: Model 1 + Tau PET	-0.27 (0.05)	**<0.001**	0.300	973	48.4	**<0.001**
Model 3: Model 1 + Tau PET + MRI	-0.27 (0.05	**<0.001**	0.308	971	1.6	**<0.001**
Model 2: Model 1 + MRI	0.35 (0.09)	**<0.001**	0.210	999	22.9	**<0.001**
Model 3: Model 1 + MRI + Tau PET	0.35 (0.09)	**<0.001**	0.274	988	11.2	**<0.001**
Aβ+ COGNITIVELY UNIMPAIRED INDIVIDUALS						
Model 1: Age, sex, education, cohort			0.096	418		
Model 2: Model 1 + Tau PET	-0.25 (0.06)	**<0.001**	0.382	381	40.3	**<0.001**
Model 3: Model 1 + Tau PET + MRI	-0.25 (0.06)	**<0.001**	0.384	381	1.0	0.311
Model 2: Model 1 + MRI	0.13 (0.08)	0.098	0.161	414	7.6	**0.023**
Model 3: Model 1 + MRI + Tau PET	0.16 (0.08)	**0.038**	0.318	395	21.3	**<0.001**

eTable 5. Bootstrapping of R^2 Values From Tau PET vs Amyloid PET Models Predicting MMSE Change

	DISCOVERY COHORT ([^{18}F]flortaucipir)				REPLICATION COHORT ([^{18}F]RO948)			
	R^2 difference TAU – Aβ	**95% CI**	**T**	**P**	**R^2 difference TAU – Aβ**	**95% CI**	**T**	**P**
Total group	0.181	0.178-0.183	147.1	**<0.001**	0.139	0.135-0.143	64.5	**<0.001**
Aβ+ AD dementia	0.149	0.146-0.153	81.1	**<0.001**	NA	NA	NA	**NA**
Aβ+ MCI	0.190	0.184-0.196	63.3	**<0.001**	0.192	0.184-0.199	49.8	**<0.001**
Aβ+ CU	0.102	0.098-0.106	47.0	**<0.001**	0.259	0.240-0.279	26.3	**<0.001**
Aβ- MCI	0.002	0.002-0.003	8.1	**<0.001**	-0.065	-[0.067-0.063]	-61.5	**<0.001**
Aβ- CU	0.034	0.031-0.037	21.7	**<0.001**	-0.096	-[0.099-0.093]	-63.2	**<0.001**

eTable 6. Linear Mixed Models With [^{18}F]Flortaucipir PET and Amyloid PET as Predictors of Change in MMSE

	β (SE)	P	R^2	AIC	X^2 for difference	P for difference
ALL Aβ+ PARTICIPANTS						
Model 1: Age, sex, education, cohort			0.185	8333		
Model 2: Model 1 + Tau PET	-0.21 (0.02)	**<0.001**	0.488	7867	470.0	**<0.001**
Model 3: Model 1 + Tau PET + Amyloid PET	-0.21 (0.02)	**<0.001**	0.492	7862	7.1	**0.008**
Model 2: Model 1 + Amyloid PET	0.001 (0.0002)	**<0.001**	0.254	8254	83.7	**<0.001**
Model 3: Model 1 + Amyloid PET + Tau PET	0.001 (0.0002)	**<0.001**	0.463	8001	254.7	**<0.001**
Aβ+ AD DEMENTIA						
Model 1: Age, sex, education, cohort			0.196	3129		
Model 2: Model 1 + Tau PET	-0.18 (0.03)	**<0.001**	0.329	3050	46.8	**<0.001**
Model 3: Model 1 + Tau PET + Amyloid PET	-0.18 (0.03)	**<0.001**	0.329	3052	0.1	0.822
Model 2: Model 1 + Amyloid PET	-0.0003 (0.0004)	0.386	0.198	3131	1.3	0.522
Model 3: Model 1 + Amyloid PET + Tau PET	-0.0004 (0.0004)	0.328	0.302	3091	41.8	**<0.001**
Aβ+ MILD COGNITIVE IMPAIRMENT						
Model 1: Age, sex, education, cohort			0.225	2855		
Model 2: Model 1 + Tau PET	-0.25 (0.03)	**<0.001**	0.387	2755	104.5	**<0.001**
Model 3: Model 1 + Tau PET + Amyloid PET	-0.25 (0.03)	**<0.001**	0.386	2757	0.0	0.972
Model 2: Model 1 + Amyloid PET	-0.0007 (0.0003)	**0.039**	0.237	2852	7.8	**0.020**
Model 3: Model 1 + Amyloid PET + Tau PET	-0.0007 (0.0003)	**0.032**	0.338	2807	46.3	**<0.001**
Aβ+ COGNITIVELY UNIMPAIRED INDIVIDUALS						
Model 1: Age, sex, education, cohort			0.095	1680		
Model 2: Model 1 + Tau PET	-0.17 (0.06)	**0.004**	0.175	1658	25.9	**<0.001**
Model 3: Model 1 + Tau PET + Amyloid PET	-0.17 (0.06)	**0.004**	0.175	1659	0.2	0.694
Model 2: Model 1 + Amyloid PET	-0.0005 (0.0002)	**0.023**	0.114	1675	8.4	**0.015**
Model 3: Model 1 + Amyloid PET + Tau PET	-0.0005 (0.0002)	**0.023**	0.168	1662	14.7	**<0.001**

eAppendix. ADNI Investigators

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