Supplementary table 1. Previous PET studies using specific TSPO ligands and comparing individuals with Alzheimer's disease or mild cognitive impairment to healthy controls

Reference	Study population	TSPO tracer	Study design	Methodology	TSPO tracer binding in AD dementia vs healthy controls	TSPO tracer binding in MCI vs healthy controls	Correlation between TSPO tracer binding and cognition or disease severity	Correlation between TSPO tracer binding and amyloid or tau load	Correlation between TSPO tracer binding and atrophy or glucose metabolism
Kreisl et al. Brain 2013	19 AD dementia, 10 prodromal AD, 13 HC	[11C]PBR28	Cross-sectional	2-tissue-compartment model with arterial input (outcome: total distribution volume/free fraction of radioligand (V_T/f_P)	Higher binding in cortical areas including middle and inferior temporal cortex, inferior parietal cortex and entorhinal cortex: ~30% higher without partial volume correction, ~45% after partial volume correction.	No difference in any brain region	Higher regional TSPO binding correlated with worse performance on MMSE, CDR-SB, Logical Memory Immediate, Block Design, and Trail Making part B tasks in multiple regions including inferior parietal, temporal cortices and precuneus in AD (dementia and prodromal combined).	After partial volume correction, positive regional correlation with PIB in inferior parietal lobule, superior temporal cortex, precuneus, hippocampus and parahippocampal gyrus in AD (dementia and prodromal combined). Without partial volume correction, there was no correlation with PIB in any brain region.	Negative correlation with grey matter volume in inferior parietal lobule, superior temporal cortex, middle and inferior temporal cortex, entorhinal cortex, posterior cingulate cortex, parahippocampal gyrus, occipital cortex, precuneus and cerebellum in AD without partial volume correction. After partial volume correction, negative correlation only in inferior parietal lobule and entorhinal cortex.
Lyoo et al. J Nucl Med 2015	25 AD dementia, 11 prodromal AD, 21 HC. Some individuals were included in Kreisl 2013.	[11C]PBR28	Cross-sectional	2-tissue-compartment model with arterial input (outcome: V_T/f_P) and SUVR method with cerebellar grey as the pseudo-reference region	Higher binding (~24% V_T/f_P, 6-9% SUVR and ~10% DVR) in temporoparietal regions in AD than in HC or MCI. No statistically signifficant differences in V_T values were observed between the groups. No difference between cerebellar SUV or V_T/f_P.	No difference in any brain region	Both higher VT/fP values and SUVRs in the combined middle and inferior temporal cortex were correlated with worse CDR-SB in AD (dementia and prodromal combined).		
Kreisl et al. Neurobiol Aging 2016	14 AD (dementia and prodromal combined), 11 HC	[11C]PBR28	Longitudinal (32 mo)	SUVR method with cerebellar grey as the pseudo-reference region	Higher increase in binding in AD patients (annual increases of 2.5-7.7%) vs controls (-2.2-0.4%) in inferior parietal, occipital, entorhinal, temporal cortices, precuneus and hippocampus.		Worsening in CDR-SB correlated with increased TSPO binding in prefrontal, superior and inferior parietal cortices and precuneus in AD (dementia and prodromal combined).	No regional correlation between change of PBR28 and change of PIB binding in AD or controls.	Negative regional correlation between change in TSPO binding and in voxel count in prefrontal, inferior parietal, occipital, temporal cortices and precuneus in AD. No correlation in controls.
Kreisl et al. Neurobiol Aging 2017	11 amnestic AD (dementia and prodromal combined), 15 HC, 11 PCA	[11C]PBR28	Cross-sectional	2-tissue compartmental model (outcome: VT/fP) and SUVR method with cerebellar grey as pseudo-reference region	VT/f_P were 15-70% higher in inferior parietal, precuneus and occipital cortex in PCA vs controls and in middle and inferior temporal and entorhinal cortices in amnestic AD vs controls. SUVR were 15-40% higher in parietal, occipital, temporal cortices, precuneus and hippocampus in PCA vs controls and in prefrontal, inferior parietal, temporal, entorhinal cortices, hippocampus and precuneus in amnestic AD vs controls.		Negative regional correlation with visuospatial performance in superior and inferior parietal, occipital cortices and precuneus in the combined group of amnestic AD and PCA; no correlation between TSPO binding and performance on the delayed word list recall.		Negative regional correlation with voxel count in superior parietal lobule, occipital cortex, precuneus, and entorhinal cortex. Correlations were primarily seen in PCA but for entorhinal cortex in amnestic AD.
Fan et al. Eur J Nucl Med Mol Imaging 2018	13 MCI (7 amyloid-positive), 9 HC	[11C]PBR28	Cross-sectional	Three methods: spectral analysis (outcome: impulse response function parametric map), 2-tissue compartmental model with and without a vascular component, and Logan graphical analysis (outcomes: V_T)		IRF parametric mapping showed 19-27% higher TSPO binding in amyloid-positive MCI in temporal, cingulate, medial temporal lobe, thalamus, hippocampus, amygdala, cerebellum and in whole brain. The single-subject analysis detected 7 MCI patients (5 amyloid-positive and 2 amyloid-negative) with significant clusters of higher binding compared to the healthy controls. Compartmental analysis showed 31-32% higher binding in thalamus and left medial temporal cortex. Individually, 4/7 of amyloid-positive MCI showed higher uptake compared to the controls, while one amyloid-negative MCI subject showed higher binding. Logan parametric maps did not find any significant difference at the group level.			

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Dani et al. Brain 2018	16 AD dementia, 9 amyloid positive MCI, 7 amyloid-negative MCI, 19 amyloid-negative HC	[11C]PBR28	Cross-sectional	Logan graphical analysis (outcome: V_T)	No statistically significant voxel-level group differences	No statistically significant voxel-level group differences		Positive voxel-wise correlations with flutemetamol throughout the cortex in AD, especially in parietal cortex. Correlation with flutemetamol was higher and more extensive in MCI, especially in frontal and temporal cortex. In amyloid-positive MCI, there were positive voxel-wise correlations with tau tracer AV1451 in frontal, temporal, parietal and cingulate cortex. In AD dementia, there were positive correlations with tau load in the frontal, temporal, parietal, occipital and insular cortex.	
Schain et al. Neuroimage 2018	21 AD dementia, 15 HC	[11C]PBR28	Cross-sectional	2-tissue compartmental model (outcome: V_T/f_P) and simultaneous estimation with arterial input or template input function (outcome: BP)	Not statistically significantly higher (16%) VT/f_P in inferior temporal cortex but statistically significantly higher (30%) BP. No difference in TSPO binding in cerebellum. (Differences only in inferior temporal cortex and cerebellum were tested.)				
Femminella et al. Neurology 2019	37 early MCI (19 amyloid-positive, 16 amyloid-negative), 18 HC	[11C]PBR28	Cross-sectional	Logan graphical analysis (outcome: V_T)		13 of 37 patients with MCI (35%) were classified as having increased [11C]PBR28 V_T compared to controls on single-subject analysis. No difference in group means was found.		Positive voxel-wise correlations with flutemetamol in amyloid-positive MCI in the posterior cingulate and middle frontal gyrus.	Positive voxel-wise correlations with gray matter volume in both amyloid-positive and negative MCI, mainly in frontal, temporal and parietal regions in amyloid-positive MCI and frontal and parietal regions in amyloid-negative MCI. Higher hippocampal volume correlated with higher cortical PBR28 in MCI. No correlation between PBR28 and gray matter or hippocampal volume at the ROI level.
Hamelin et al. Brain 2016	24 AD dementia, 34 prodromal AD, 20 amyloid-negative HC, 6 amyloid-positive HC	[18F]DPA-714	Cross-sectional and clinical follow-up (24 mo) for 18 prodromal AD and 12 AD dementia	SUVR method with cerebellar grey matter as the pseudo-reference region	Higher (16%, 0.2 SUVR units) binding in posterior cingulate, precuneus, parietal and temporal cortex in AD dementia compared to amyloid-negative HCs.	Higher (16%, 0.2 SUVR units) binding in global cortical grey matter, frontal, anterior cingulate, medium cingulate, posterior cingulate, precuneus, parietal, temporal and occipital cortex in prodromal AD compared to amyloid-negative HCs. Higher binding was detected at regional and voxel level. Binding was higher in prodromal AD compared to AD dementia but there was no statistically significant difference.	Positive regional correlation between MMSE and binding in global cortical grey matter in AD (dementia and MCI combined). There was higher global gray matter binding in slow decliners (n=10) than in fast decliners (n=20).	Positive correlation between global cortical grey matter DPA-714 and PIB in AD (dementia and prodromal AD combined)	Positive correlation between binding in global cortical gray matter and grey matter volume in the combined AD group. Correlation was even stronger when the analysis was restricted to the prodromal AD.
Hamelin et al. Brain 2018	19 AD dementia, 33 prodromal AD, 17 amyloid-negative HC, 4 amyloid-positive HC	[18F]DPA-714	Longitudinal (24 mo): functional and cognitive follow-up for 52 AD and 21 amyloid-negative controls; PET and MRI follow-up for 21 AD and 13 amyloid-negative HC	SUVR method with cerebellar grey matter as the pseudo-reference region	At baseline, higher (~16 %, 0.2 SUVR units) binding in cortical grey matter, especially in the temporal and parietal regions in AD (dementia and prodromal combined). No significant difference between prodromal and dementia. Cortical binding increased compared to amyloid-negative controls over time (8.3% per year vs 4.2%); subjects with the highest binding at baseline tended to have the lowest increase over two years.	Cortical binding increased over time (15.1% per year vs 4.2% in controls); subjects with the highest binding at baseline tended to have the lowest increase over two years.	At baseline, positive correlation between cortical grey matter binding and MMSE score in AD (dementia and prodromal combined). Baseline binding in cortical regions had a negative correlation with the worsening of CDR-SB, decrease in MMSE, decrease in long-term memory composite score in AD. Binding in cortical regions was higher in functional slow decliners and cognitive slow decliners compared to fast decliners. Longitudinal increase in cortical binding correlated with worsening of CDR-SB and MMSE decrease.	At baseline, positive correlation with cortical PIB binding.	At baseline, positive correlation between cortical grey matter binding and left hippocampal volume and cortical volume in AD (dementia and prodromal combined). Baseline binding had a negative correlation with the percentage of decrease of hippocampal volume. Longitudinal increase in binding was associated with volume decrease in left hippocampal and in frontal and parieto-temporal cortex.

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Varrone et al. Eur J Nucl Med Mol Imaging 2015	9 AD dementia, 7 HC	[18F]FEMPA	Cross-sectional	Logan graphical analysis (outcome V_T)	If only HABs (4 HC, 5 AD) were included, higher (20%) binding was found in the medial and lateral temporal cortex, posterior cingulate, caudate, putamen, thalamus and cerebellum.		Weak nonsignificant negative correlation between binding in cortical (frontal, temporal, parietal and occipital), limbic (medial temporal cortex and posterior cingulate) and subcortical regions (caudate, putamen and thalamus) and MMSE score in the whole study population (controls and AD combined).		
Suridjan et al. Mol Psychiatry 2015	18 AD dementia, 21 HC	[18F]FEPPA	Cross-sectional	2-tissue compartmental model and Logan graphical parametric map (outcomes: V_T)	After partial volume correction, higher (46-56%) binding in hippocampus, temporal, prefrontal, parietal and occipital cortex. Without partial volume correction, higher (26-30%) binding in temporal, prefrontal, parietal and occipital cortices. In white matter, higher (23-37%) binding in the cingulum bundle, posterior limb of the internal capsule, and superior longitudinal fasciculus.		No correlation between grey matter or white matter binding and severity or length of disease. Higher binding in parietal cortex was associated with greater impairment in visuospatial ability and higher binding in posterior limb of the internal capsule was associated with poorer visuospatial, language, and memory function in AD.		
Knezevic et al. J Cereb Blood Flow Metab 2018	11 aMCI (8 amyloid-positive), 14 HC (3 amyloid-positive)	[18F]FEPPA	Cross-sectional	2-tissue compartmental model with arterial input (outcome: V_T), SUVR method with cerebellum as pseudo-reference		No statistically significant differences in V_T or SUVR in any of the ROIs (prefrontal, temporal, inferior parietal, and occipital cortices, and hippocampus) between aMCI and HC or between amyloid-positive aMCI and amyloid-negative HCs (4-6% higher binding in temporal cortex, prefrontal cortex, inferior parietal, and occipital cortex and 23% higher binding in hippocampus in amyloid-positive aMCI vs amyloid-negative HC).	No correlation between binding and performance in general cognition, memory, language, attention, visuospatial or executive functions in aMCI.	Positive correlation with PIB in the hippocampus in aMCI	
Cagnin et al. Lancet 2001	8 AD dementia, 1 MCI, 15 HC	[11C]*(R)* PK11 195	Cross-sectional, longitudinal MRI (12-24 mo)	SRTM; reference tissue extracted with cluster analysis (outcome: BP)	Higher binding (~100%; 0.1 BP unit) in inferior and middle temporal gyri, fusiform gyri, left parahippocampal gyrus, left amygdala, left posterior cingulate, inferior parietal lobules.	Increase in fusiform gyri, inferior temporal gyri, and left parahippocampus (only 1 individual)			Areas with high uptake showed subsequently highest rates of atrophy
Edison et al. Neurobiol Dis 2008	13 AD dementia, 10 HC	[11C]*(R)* PK11 195	Cross-sectional	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)	Higher binding (20-35%; 0.1 BP unit) in whole cortex, frontal, temporal, parietal, occipital, anterior and posterior cingulate cortices, striatum and cerebellum. No difference in the hippocampus.		Negative regional correlation between MMSE scores and tracer binding in whole cortex, posterior cingulate gyrus, parietal and frontal cortical regions in AD	No regional correlation with PIB	
Wiley et al. Arch Neurol 2009	6 AD dementia, 6 MCI, 5 HC	[11C]*(R)* PK11 195	Cross-sectional	SRTM with cerebellum as reference tissue (outcome BP) and SUVR with subcortical white matter as reference (outcome: ROI to subcortical white matter reference region ratio)	No difference in any brain region	No difference in any brain region		No difference in uptake between amyloid-positive (n=12) and amyloid-negative individuals (n=5) and no regional correlation with PIB	

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Okello et al. Neurology 2009	13 MCI (7 amyloid-positive), 10 HC, 15 AD dementia	[11C]*(R)* PK11195	Cross-sectional	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)	Binding in AD was not statistically compared to controls (~16%, 0.06 BP units) higher binding in whole cortex, anterior cingulate, posterior cingulate, frontal cortex, temporal cortex)	Amyloid-positive MCI had higher binding (29-37%; 0.1 BP unit) in the anterior cingulate, posterior cingulate and frontal cortex; after correction for multiple comparisons, only frontal cortex uptake remained statistically significant. Amyloid-negative MCI had no difference in binding. Individually, TSPO binding was increased in 5 of 13 (38%) subjects with MCI, three with AD-range and two with normal-range PIB binding.	No regional correlation between MMSE scores or disease duration in amyloid-positive MCI. Negative regional correlation between MMSE scores and tracer uptake in the anterior cingulate and temporal cortex in the amyloid-negative MCI.	No regional correlation with PIB in MCI	
Yokokura et al. Eur J Nucl Med Mol Imaging 2011	11 AD dementia, 10 HC	[11C]*(R)* PK11195	Cross-sectional	SRTM; reference tissue extracted with cluster analysis (outcome: BP)	Several fold higher (0.2-0.3 BP units) binding in medial frontal, parietal, temporal, anterior cingulate, posterior cingulate, parahippocampal cortices and precuneus. No difference in the hippocampus.		Negative regional correlation between MMSE scores and binding in left anterior cingulate cortex, left precuneus, left hippocampus and left middle frontal cortex in AD	Negative regional correlation with PIB uptake in posterior cingulate cortex in AD	No regional correlations between tracer binding and glucose metabolism were found in AD
Schuitemaker et al. Neurobiol Aging 2013	19 AD dementia and 10 prodromal AD, 21 HC	[11C]*(R)* PK11195	Cross-sectional, clinical status follow-up	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)	No difference except small clusters of increased binding in occipital cortex.	No difference in prodromal AD compared to HC. No difference between progressive-MCI (n=7) and non-progressive MCI (n=3).	No regional correlation with cognitive function (MMSE, NYU, RAVLT, Trail making test A and B; Digit forward and backward) in MCI or AD.		
Fan et al. Alzheimer's Dement 2015	10 AD dementia, 10 MCI, 16 HC, (11 PDD)	[11C]*(R)* PK11195	Cross-sectional	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)	AD patient group had 36-52% increases of [11C](R)PK11195 BP in cortical regions	MCI subjects showed 28-36% increase in cortical regions.	Negative voxel-wise correlation with MMSE in temporoparietal, occipital, and frontal cortices in AD	Positive voxel-wise correlations with PIB in frontal, temporal, parietal and occipital cortices, parahippocampus, insula, and the thalamus in AD. Also positive correlations in MCI, but the number of voxels was much lower.	Negative correlations with glucose metabolism in frontal, temporoparietal, and occipital cortical regions both in AD and MCI. Additionally, negative correlations were seen in posterior cingulate, hippocampus, parahippocampus, putamen, and insula in AD and in parahippocampus, and insula in MCI.
Femminella et al. J Alzheimer's Dis 2016	8 AD dementia, 8 HC, (9 PDD)	[11C]*(R)* PK11195	Cross-sectional	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)	Higher binding (~50%; 0.15-0.2 BP units) in whole cortex, frontal, parietal, temporal, medial temporal and occipital cortex, hippocampus, anterior cingulate, posterior cingulate, thalamus and striatum.		Negative regional correlation between MMSE and binding in hippocampus, medial temporal lobe and whole cortex in the whole study population.		Negative voxel-wise correlations (but not regional) with hippocampal volume in the temporal, frontal, parietal and occipital cortex, hippocampus and parahippocampus in AD. Negative voxelvise correlations with hippocampal glucose metabolism in frontal, temporal and parietal cortex in AD.
Parbo et al. Brain 2017	42 MCI (26 amyloid-positive), 10 HC	[11C]*(R)* PK11195	Cross-sectional	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)		Higher binding mainly in lateral temporal and frontal and parietal cortex in the amyloid-positive MCI group versus controls. Twenty-two (85%) of amyloid-positive MCI cases had PK11195 binding above the range of controls whereas only four (25%) of amyloid-negative MCI had raised PK11195 binding within the same voxels and this was borderline.		Positive voxel-wise correlations with PIB in frontal, temporal and parietal cortices in amyloid-positive MCI	
Parbo et al. Neurobiol Dis 2018	6 AD dementia (5 amyloid-positive), 20 MCI (11 amyloid-positive), 10 HC (2 amyloid-positive)	[11C]*(R)* PK11195	Cross-sectional	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)	Amyloid-positive AD (dementia and MCI combined) had higher binding in cortical regions compared to controls. There was no significant difference between AD dementia (n=5) and controls.		No regional or voxel-wise correlation with MMSE in amyloid-positive AD (dementia and MCI combined)	No voxel-wise or regional correlation with tau load in amyloid-positive AD (dementia and MCI combined). Positive voxel-wise correlation with amyloid load in parietal, lateral temporal and frontal areas in amyloid-positive AD (dementia and MCI combined).	
Passamonti et al. Neurology 2018	9 AD dementia, 7 prodromal AD, 13 HC, (16 PSP)	[11C]*(R)* PK11195	Cross-sectional	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)	Higher binding in the temporal, parietal and occipital cortex, hippocampus, amygdala and medial temporal lobe in AD (dementia and prodromal AD combined)		Negative regional correlation between the RAVLT delayed recall scores and binding in the precuneus in AD (dementia and prodromal combined)		

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Fan et al. Brain 2015	8 AD dementia, 14 HC	[11C]*(R)* PK11 195	Longitudinal (16 mo)	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)	At baseline, 30% higher binding in frontal, temporal, parietal, occipital cortex, hippocampus and striatum. At follow-up, the mean global tracer binding increased from 30% to 46%: 6/8 AD patients showed increased binding and 2/8 showed reduced binding.			Positive voxel-wise correlations with PIB in temporal, frontal, and parietal lobe in AD at baseline	Negative voxel-wise correlations with glucose metabolism in AD at baseline
Fan et al. Brain 2017	8 MCI (4 amyloid-positive), 14 HC	[11C]*(R)* PK11 195	Longitudinal (14 mo)	SRTM; reference tissue extracted with supervised cluster analysis (outcome: BP)		At baseline, ~40% higher binding in MCI vs HC in medial temporal lobe, hippocampus, anterior temporal lobe, posterior temporal lobe, parietal and frontal gyri at baseline. Longitudinal reduction of ~20% in frontal, temporal, parietal, and occipital cortices, anterior cingulate, posterior cingulate and hippocampus in MCI, especially in amyloid-positive MCI.		Positive voxel-wise correlations with PIB in cortical regions in MCI; amyloid-positive MCI showed stronger correlations.	

Note: Studies using second-generation TSPO ligands without genotype information have been excluded.

Abbreviations: AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; BP, binding potential; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; HAB; high affinity binder; HC, healthy control; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NYU, New York University paragraph recall test; PCA, posterior cortical atrophy; PDD, Parkinson's disease dementia; PIB, Pitsburgh compund B; PSP, progressive supranuclear palsy; RAVLT, Rey's Auditory Verbal Learning Test; SRTM, simplified reference-tissue model; SUVR, simplified standardized uptake value ratio; TSPO, translocator protein.