Supplementary Materials

Amyloid PET imaging

All subjects also underwent [^{11}C]Pittsburgh Compound B (PiB) PET imaging over 60 min, as previously described [29,30]. An average measure of global amyloid-β burden was estimated in a large neocortical aggregate of frontal, lateral temporoparietal and retrosplenial (FLR) regions, based on distribution volume ratios (DVR) computed using the reference Logan graphical method, with the CerGM as reference region (t* = 40 min). Subjects with PiB DVR values in the FLR region greater than 1.13 were considered as PiB-positive. The 1.13 threshold was determined by applying gaussian mixture model to all available [^{11}C]PiB DVR data (n = 268) collected on the same scanner as this study.

Spectral analysis

Spectral analysis is a data-driven method for evaluating tracer kinetics without assumptions on kinetic compartment configuration. In spectral analysis, tracer activity ($C_T(t)$) in the tissue at time t is described as the convolution of the tracer activity in the plasma ($C_P(t)$) and the impulse response function (IRF(t)):

$$C_T(t) = C_P(t) \otimes IRF(t) \quad (1)$$

$IRF(t)$ contains information about the kinetics of the tissue in response to tracer delivery and can be solved as an analytical sum of distinct exponential terms:

$$IRF(t) = \sum_{j=0}^{M} \alpha_j \, e^{-\beta_j t} \quad (2)$$

Where β_j ($\beta_0 = 0, \beta_j \geq 0$, unit min^{-1}) are the frequency of the spectral components and α_j (unit mL cm^{-3} min^{-1}) are the corresponding amplitudes. M + 1 is the maximum number of terms in the model. The values of β_j are predefined to cover a range of spectral frequencies from:

- Very large β_j: high frequency spectral components, which correspond to blood volume fraction
- Very small β_j: low frequency spectral components, which often correspond to irreversible trapping in the tissue compartments
- Intermediate β_j: spectral components in equilibrium, which indicate the number of identifiable reversible tissue compartments

After fixing the values of β_j to cover an appropriate spectral range, the α_j values were estimated from $C_T(t)$ and $C_P(t)$ by using non-negative least square (NNLS) algorithm. Several macro-parameters can then be derived from the kinetic spectrum:

- Influx rate constant: $K_{1\_SA} = \sum_{j=0}^{M} \alpha_j$, unit: mL cm^{-3} min^{-1} (3)
- Volume of distribution $V_{T\_SA} = \sum_{j=0}^{M} \alpha_j / \beta_j$, unit: mL cm^{-3} (4)

In this study, spectral analysis was implemented using a pre-defined grid of 100 components for β_j, ranging from 10^{-5} to 1 min^{-1} on a logarithmic scale.

Effect size calculation (Hedge's g coefficients)

Due to the small sample size, effect sizes were estimated using Hedge's g coefficients using the formula:

$$g = J(df) \times \frac{(\bar{x} - \bar{y})}{s}$$

where df is the degree of freedom, $\bar{x}$ and $\bar{y}$ are the mean values for each group or time point, s is the pooled standard deviation and J(df) is the bias correction term. The pooled standard deviation and the bias correction term are defined as follows:

$$s = \sqrt{\frac{(n_1 - 1){S_1}^2 + (n_2 - 1){S_2}^2}{n_{1+}n_2 - 2}}$$

where n_1 and n_2 are the sample size of each group or time point.

$$J(df) = \frac{(\Gamma(\frac{df}{2}))}{\sqrt{df/2\Gamma(\frac{df-1}{2})}}$$

where Γ is the gamma function.

The 95% confidence interval for the g coefficients was estimated using bootstrapping (1000 iterations).

Supplementary Table 1. Published [^{18}F]MK-6240 human PET imaging studies: Imaging parameters and reference regions.

Author, year	Journal †	Tomograph	FWHM *	Acquisition duration	SUVR ** interval	Reference region
Pascoal 2018	Alzheimer's Research and Therapy	Siemens HRRT	8mm after smoothing	Up to 180 min	Varied, 90-110 min chosen	Cerebellar gray matter
Betthauser 2019, 2020	J Nucl Med	Siemens ECAT Exact HR+	5 mm	Up to 120 min	70-90 min	Inferior cerebellar gray matter
Lohith 2019	J Nucl Med	Siemens Hirez Biograph	5 mm	0-90 min, break, 120-150 min	60-90 min	Cerebellar gray matter
Guehl 2019	EJNMMI	1. Siemens ECAT Exact HR+ 2. GE Discovery MI	1. 5mm 2. 5mm	Up to 135 min	1. 70-90 min 2. 90-120 min	Cerebellar gray matter
Salinas 2020 ^	JCBFM	Siemens ECAT Exact HR+	5 mm	Up to 150 min	90-120 min	Inferior cerebellar gray matter
Pascoal 2020	Brain	Siemens HRRT	8mm after smoothing	90-110 min	90-110 min	Inferior cerebellum
Pascoal 2021	Nature Medicine	Siemens HRRT	8 mm after smoothing	90-110 min	90-110 min	Cerebellar Crus I gray matter
Therriault 2021 ^^	Neurology	Siemens HRRT	8 mm after smoothing	90-110 min	90-110 min	Inferior cerebellar gray matter
Gogola 2021	J Nucl Med	Siemens ECAT Exact HR+	5 mm	70-90 min	70-90 min	Cerebellar gray matter
Smith 2021	NeuroImage: Clinical	Siemens ECAT Exact HR+	5 mm	70-90 min	70-90 min	Inferior cerebellar gray matter
Mertens 2022 ^^	JCBFM	GE Signa PET/MR	4 mm	90-120 min	90-120 min	Cerebellar gray matter

† J Nucl Med: Journal of Nuclear Medicine; EJNMMI: European Journal of Nuclear Medicine and Molecular Imaging; JCBFM: Journal of Cerebral Blood Flow and Metabolism. * FWHM = full width at half maximum. **SUVR = standardized uptake value ratio. ^ Salinas et.al., 2020: Only example here to apply a 5 mm cerebellar erosion from the outermost voxels. ^^ Examples here to apply region- and voxel- level partial volume correction on the PET data.

Supplementary Table 2. Comparative size (in voxels) of the candidate reference regions and extracerebral masks in the PET space, for a representative subject.

	CerGM	**$CerGM_{3mm}$**	**InfCer**	**WM**	**WM_{4mm}**	**Pons**	**Extracerebral**
ROI size (number of voxels)	22566	6556	10174	88295	15310	3014	121544

Supplementary Table 3. Baseline $SUV_{90\text{-}110}$, longitudinal changes of $SUV_{90\text{-}110}$ in candidate reference regions and extracerebral signal at 6-month and 1-year follow-ups.

		Baseline $SUV_{90\text{-}110}$ (g/mL) (n=32: 24 CN, 8 AD/MCI)	$\triangle SUV_{90\text{-}110}$ at 6-month (n=25: 20 CN, 5 AD/MCI)	$\triangle SUV_{90\text{-}110}$ at 1-year (n=16: 11 CN, 5 AD/MCI)
CerGM	**CN**	0.62±0.12	0.04±0.07 (-0.09, 0.18)	0.04±0.13 (-0.15, 0.26)
	AD/MCI	0.59±0.17		
$CerGM_{3mm}$	**CN**	0.53±0.13	0.05±0.06 (-0.10, 0.16)	0.04±0.11 (-0.10, 0.26)
	AD/MCI	0.51±0.17		
PVC CerGM	**CN**	0.54±0.20	0.03±0.14 (-0.32, 025)	-0.002±0.17 (-0.22, 0.36)
	AD/MCI	0.62±0.26		
Inferior CerGM	**CN**	0.67±0.13	0.04±0.08 (-0.12, 0.22)	0.04±0.13 (-0.10, 0.24)
	AD/MCI	0.59±0.17		
WM	**CN**	0.44±0.09*	0.05±0.06 (-0.05, 0.16)	0.02±0.11 (-0.24, 0.21)
	AD/MCI	0.75±0.20*		
WM_{4mm}	**CN**	0.42±0.11	0.05±0.05 (-0.04, 0.17)	0.02±0.10 (-0.25, 0.20)
	AD/MCI	0.51±0.15		
PVC WM	**CN**	0.34±0.14	0.02±0.09 (-0.22, 0.20)	-0.01±0.12 (-0.28, 0.19)
	AD/MCI	0.56±0.10		
Pons	**CN**	0.29±0.07	0.02±0.05 (-0.06, 0.08)	-0.002±0.07 (-0.16, 0.13)
	AD/MCI	0.32±0.09		
PVC Pons	**CN**	0.18±0.09	0.02±0.06 (-0.11, 0.13)	-0.01±0.09 (-0.19, 0.16)
	AD/MCI	0.27±0.09		
Extracerebral	**CN**	0.79±0.15	0.01±0.12 (-0.22, 0.39)	0.0002±0.16 (-0.20, 0.38)
	AD/MCI	0.74±0.17		

* = significantly different between the CN and AD/MCI groups. Baseline $SUV_{90\text{-}110}$ are reported as mean±std and longitudinal changes are reported as mean±std (min, max).

Supplementary Table 4. Target region distribution volume ratio (DVR) and $SUVR_{90\text{-}110}$ values (entorhinal, amygdala, inferior temporal and precuneus) for each candidate reference region in the CN and AD/MCI groups. Target region DVR were calculated using two-tissue compartmental model (2TCM), Logan graphical analysis, reference tissue methods (multilinear reference tissue modeling (MRTM2) and reference Logan graphical analysis) and SUVR using the 90-110 min of dynamic data.

	CerGM		**CerGM3mm**		**InfCer**		**WM**		**WM_{4mm}**		**Pons**	
	CN	**AD/MCI**	**CN**	**AD/MCI**	**CN**	**AD/MCI**	**CN**	**AD/MCI**	**CN**	**AD/MCI**	**CN**	**AD/MCI**
	2TCM DVR											
Entorhinal	1.1±0.21	1.57±0.44	1.25±0.33	1.74±0.52	1.01±0.15	1.55±0.42	1.56±0.4	1.76±0.35	1.86±0.61	2.32±0.7	2±0.52	2.5±0.89
Amygdala	0.79±0.22	1.35±0.57	0.89±0.25	1.49±0.63	0.74±0.24	1.33±0.57	1.1±0.23	1.51±0.6	1.31±0.4	1.99±0.9	1.4±0.31	2.17±1.11
Inferior Temporal	1.27±0.28	2.06±1.08	1.45±0.43	2.29±1.28	1.16±0.21	2.02±1.04	1.81±0.51	2.26±0.99	2.15±0.77	3.05±1.71	2.31±0.68	3.32±1.99
Precuneus	0.92±0.1	1.56±0.97	1.04±0.13	1.75±1.15	0.86±0.13	1.53±0.93	1.3±0.16	1.71±0.91	1.54±0.26	2.34±1.54	1.67±0.25	2.54±1.76
	Logan DVR											
Entorhinal	1.02±0.08	1.53±0.44	1.18±0.15	1.67±0.66	0.91±0.11	1.51±0.41	1.61±0.33	1.69±0.4	1.84±0.44	2.31±0.93	2.03±0.42	2.51±1.04
Amygdala	0.75±0.21	1.27±0.5	0.87±0.25	1.37±0.6	0.68±0.21	1.26±0.53	1.16±0.3	1.38±0.44	1.33±0.37	1.89±0.85	1.46±0.39	2.07±0.98
Inferior Temporal	1.3±0.28	1.93±0.94	1.53±0.49	2.13±1.28	1.14±0.16	1.9±0.9	2.08±0.69	2.1±0.89	2.38±0.85	2.96±1.81	2.63±0.91	3.23±2
Precuneus	0.89±0.11	1.47±0.84	1.02±0.13	1.64±1.14	0.79±0.16	1.45±0.79	1.38±0.19	1.61±0.82	1.58±0.29	2.28±1.61	1.75±0.29	2.48±1.77
	MRTM2 DVR											
Entorhinal	1.04±0.12	1.75±0.63	1.13±0.18	1.93±0.82	0.99±0.1	1.77±0.64	1.41±0.23	1.48±0.22	1.58±0.32	2.44±0.84	1.83±0.49	2.75±1.06
Amygdala	0.81±0.11	1.39±0.49	0.86±0.12	1.52±0.65	0.78±0.12	1.41±0.5	1.07±0.13	1.18±0.2	1.19±0.16	1.87±0.64	1.31±0.22	2.16±0.79
Inferior Temporal	1.16±0.15	2.3±1.08	1.28±0.25	2.58±1.41	1.1±0.11	2.33±1.1	1.6±0.32	1.87±0.47	1.8±0.44	3.12±1.4	2.12±0.69	3.74±1.89
Precuneus	0.93±0.08	2.2±1.45	0.99±0.1	2.52±1.86	0.9±0.08	2.24±1.48	1.23±0.11	1.71±0.65	1.38±0.17	2.86±1.78	1.52±0.24	3.63±2.5
	Reference Logan DVR											
Entorhinal	1.04±0.12	1.7±0.57	1.13±0.17	1.84±0.71	0.99±0.1	1.73±0.58	1.34±0.21	1.43±0.21	1.46±0.28	2.17±0.65	1.75±0.42	2.5±0.85
Amygdala	0.82±0.12	1.38±0.47	0.87±0.13	1.49±0.6	0.79±0.12	1.4±0.49	1.05±0.12	1.16±0.18	1.15±0.15	1.72±0.47	1.3±0.2	2.02±0.67
Inferior Temporal	1.15±0.15	2.22±1	1.28±0.25	2.44±1.24	1.1±0.12	2.25±1.02	1.5±0.28	1.79±0.44	1.63±0.37	2.83±1.18	2.04±0.62	3.31±1.52
Precuneus	0.93±0.08	2.1±1.3	0.99±0.1	2.33±1.58	0.9±0.08	2.14±1.33	1.2±0.11	1.64±0.6	1.32±0.17	2.67±1.48	1.5±0.24	3.17±1.97
	$SUVR_{90\text{-}110}$											
Entorhinal	1.14±0.16	2.12±0.9	1.34±0.25	2.57±1.4	1.06±0.14	2.17±0.95	1.58±0.28	1.6±0.26	1.73±0.38	2.44±0.84	2.41±0.58	3.84±1.52
Amygdala	0.8±0.21	1.64±0.72	0.94±0.23	1.98±1.1	0.75±0.22	1.68±0.77	1.1±0.19	1.23±0.25	1.19±0.23	1.87±0.64	1.66±0.31	2.97±1.21
Inferior Temporal	1.25±0.18	2.71±1.43	1.47±0.29	3.31±2.11	1.16±0.15	2.78±1.49	1.74±0.37	1.98±0.5	1.92±0.5	3.11±1.4	2.66±0.71	4.94±2.46
Precuneus	0.89±0.14	2.51±1.87	1.04±0.17	3.13±2.68	0.83±0.15	2.58±1.95	1.23±0.14	1.75±0.74	1.34±0.23	2.86±1.77	1.87±0.36	4.58±3.18

Supplementary Table 5. Cross-sectional effect size (Hedge's g coefficients) for differentiating target region $SUVR_{90\text{-}110}$ between diagnostic and Aβ status groups using the candidate reference regions. Values are expressed as mean (95% confidence interval estimated using bootstrap).

	AD/MCI (n=8) and CN (n=24)					
	CerGM	**$CerGM_{3mm}$**	**InfCer**	**WM**	**WM_{4mm}**	**Pons**
Entorhinal	1.37 (0.24,2.45)	1.47 (0.3,2.58)	1.1 (0.04,2.09)	-0.04 (-0.82,0.74)	1 (0.02,1.93)	1.1 (0.08,2.07)
Amygdala	1.48 (0.32,2.59)	1.55 (0.36,2.67)	1.21 (0.13,2.25)	0.58 (-0.26,1.41)	1.29 (0.22,2.31)	1.33 (0.23,2.38)
Inferior Temporal	1.29 (0.17,2.35)	1.36 (0.22,2.45)	1.09 (0.04,2.09)	0.45 (-0.4,1.28)	1.04 (0.04,2)	1.11 (0.07,2.1)
Precuneus	1.1 (0.04,2.12)	1.14 (0.06,2.16)	0.99 (-0.05,1.97)	0.86 (-0.13,1.81)	1.06 (0.02,2.06)	1.06 (0.01,2.06)
	Aβ+ (n=18) and Aβ- (n=14)					
	CerGM	**$CerGM_{3mm}$**	**InfCer**	**WM**	**WM_{4mm}**	**Pons**
Entorhinal	0.89 (0.17,1.59)	0.78 (0.08,1.47)	0.97 (0.24,1.68)	0.18 (-0.52,0.87)	0.48 (-0.2,1.14)	0.37 (-0.3,1.04)
Amygdala	1.17 (0.4,1.91)	1.19 (0.42,1.94)	1.03 (0.29,1.75)	1.3 (0.53,2.05)	1.11 (0.38,1.82)	0.81 (0.1,1.5)
Inferior Temporal	0.78 (0.07,1.46)	0.84 (0.13,1.53)	0.71 (0.01,1.39)	0.19 (-0.5,0.88)	0.44 (-0.22,1.1)	0.4 (-0.27,1.06)
Precuneus	0.68 (-0.01,1.35)	0.72 (0.02,1.39)	0.64 (-0.05,1.31)	0.45 (-0.22,1.11)	0.55 (-0.11,1.2)	0.5 (-0.17,1.15)

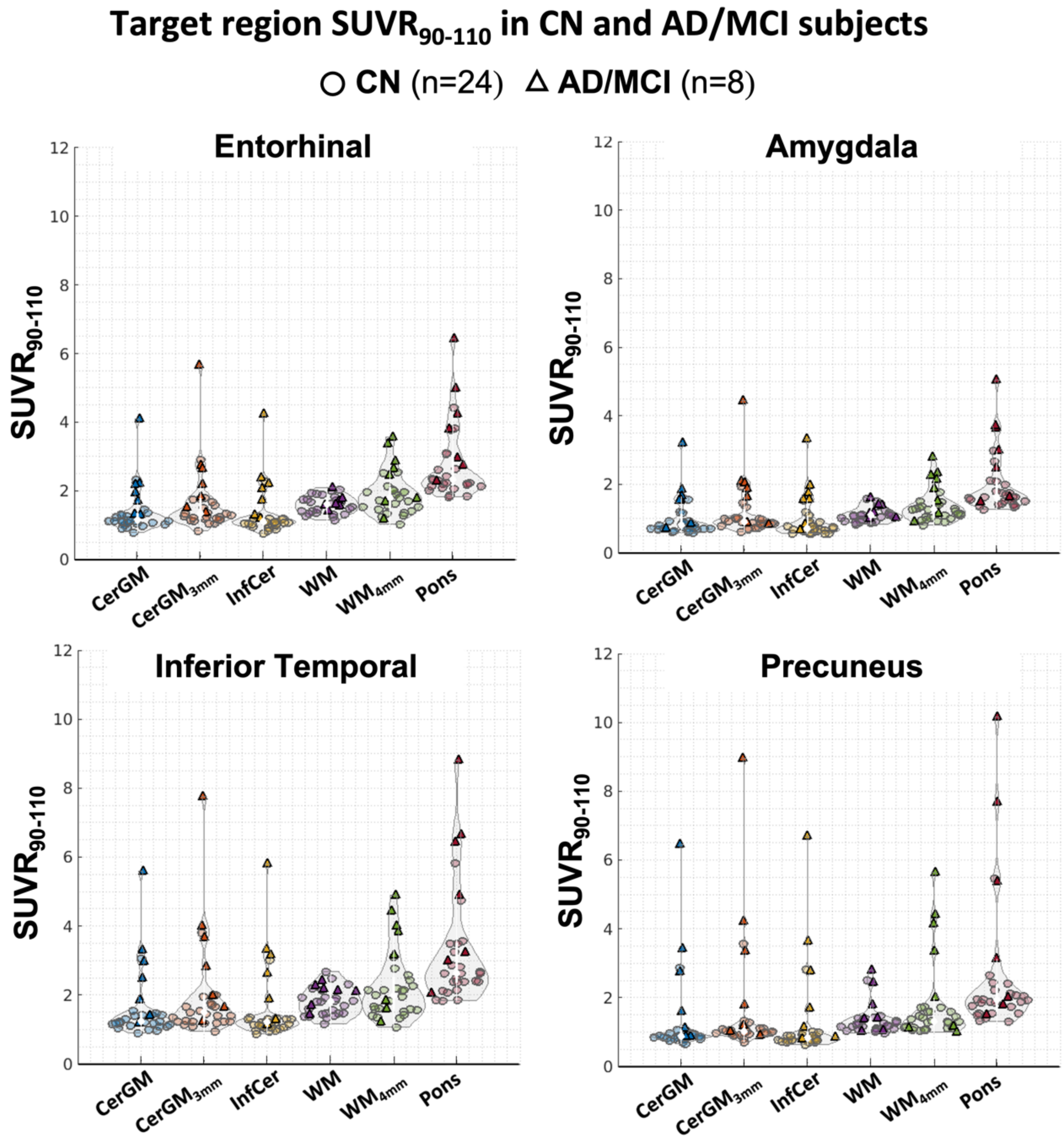
Supplementary Table 6. Longitudinal effect size (Hedge's g coefficients) for detecting changes over a one-year period in target region $SUVR_{90-110}$ in AD/MCI and in Aβ+ individuals using the candidate reference regions. Values are expressed as mean (95% confidence interval estimated using bootstrap).

	AD/MCI (n=5)					
	CerGM	**$CerGM_{3mm}$**	**InfCer**	**WM**	**WM_{4mm}**	**Pons**
Entorhinal	-0.12 (-0.35,0.18)	-0.11 (-0.41,0.2)	-0.13 (-0.57,0.11)	-0.28 (-2.01,0.37)	0.01 (-1.36,0.55)	0.12 (-0.99,0.66)
Amygdala	-0.03 (-0.22,0.17)	-0.05 (-0.44,0.39)	-0.06 (-0.68,0.14)	0.03 (-0.18,0.14)	0.12 (-0.06,0.82)	0.2 (-0.06,1.12)
Inferior Temporal	0 (-0.19,0.56)	-0.02 (-0.26,0.42)	-0.02 (-0.23,1.13)	0.14 (-1.01,0.64)	0.14 (-0.28,0.71)	0.2 (-0.18,0.85)
Precuneus	-0.05 (-0.16,0.17)	-0.07 (-0.28,0.07)	-0.06 (-0.2,0.17)	-0.05 (-0.34,0.26)	-0.02 (-0.44,0.26)	0.03 (-0.27,0.29)
	Aβ+ (n=8)					
	CerGM	**$CerGM_{3mm}$**	**InfCer**	**WM**	**WM_{4mm}**	**Pons**
Entorhinal	-0.08 (-0.31,0.11)	-0.09 (-0.37,0.15)	-0.09 (-0.35,0.13)	-0.1 (-0.77,0.51)	0.06 (-0.32,0.47)	0.12 (-0.23,0.53)
Amygdala	0 (-0.11,0.12)	-0.02 (-0.15,0.09)	-0.02 (-0.17,0.13)	0.12 (-0.17,0.47)	0.16 (-0.16,0.56)	0.19 (-0.05,0.51)
Inferior Temporal	-0.02 (-0.28,0.23)	-0.04 (-0.36,0.26)	-0.03 (-0.32,0.25)	-0.01 (-0.55,0.52)	0.08 (-0.26,0.47)	0.13 (-0.25,0.57)
Precuneus	-0.04 (-0.16,0.07)	-0.06 (-0.25,0.11)	-0.04 (-0.19,0.09)	-0.05 (-0.28,0.17)	-0.01 (-0.19,0.18)	0.04 (-0.18,0.29)

Supplementary Table 6. Extracerebral [18F]MK-6240 uptake ($SUVR_{90-110}$) at baseline and follow-ups for the high and low extracerebral uptake groups. The $SUVR_{90-110}$ values are expressed as mean ± standard deviation.

	High extracerebral (SUVR >1.39)		**Low extracerebral (SUVR ≤1.39)**	
	n	$SUVR_{90-110}$	**n**	$SUVR_{90-110}$
Baseline (32)	16 (12 CN, 4 AD/MCI)	2.01±0.70	16 (12 CN, 4 AD/MCI)	1.14±0.14
6 months (26)	12 (8 CN, 4 AD/MCI)	2.04±0.47	13 (12 CN, 1 AD/MCI)	1.07±0.20
1 year (16)	7 (3 CN, 4 AD/MCI)	2.04±0.62	9 (8 CN, 1 AD/MCI)	1.09±0.15

Supplementary Figure 1. Target region $SUVR_{90-110}$ obtained using different reference regions for the CN and AD/MCI subjects.



Supplementary Figure 2. Extracerebral $SUVR_{90\text{-}110}$ threshold. **a)** Histogram of extracerebral $SUVR_{90\text{-}110}$ identified a binary threshold of 1.39, **b**) which separated all subjects into high-extracerebral-signal and low-extracerebral-signal groups. Eroded CerGM by 3mm was used as the reference region.