

## **Supplementary materials**

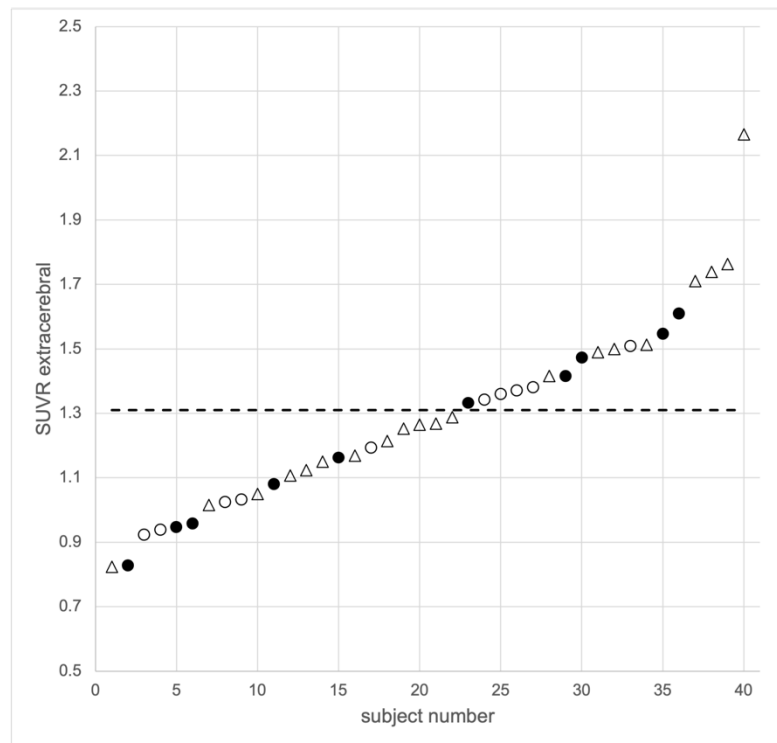
### **Supplementary Material and Methods**

#### *Extended RBV PVC extended*

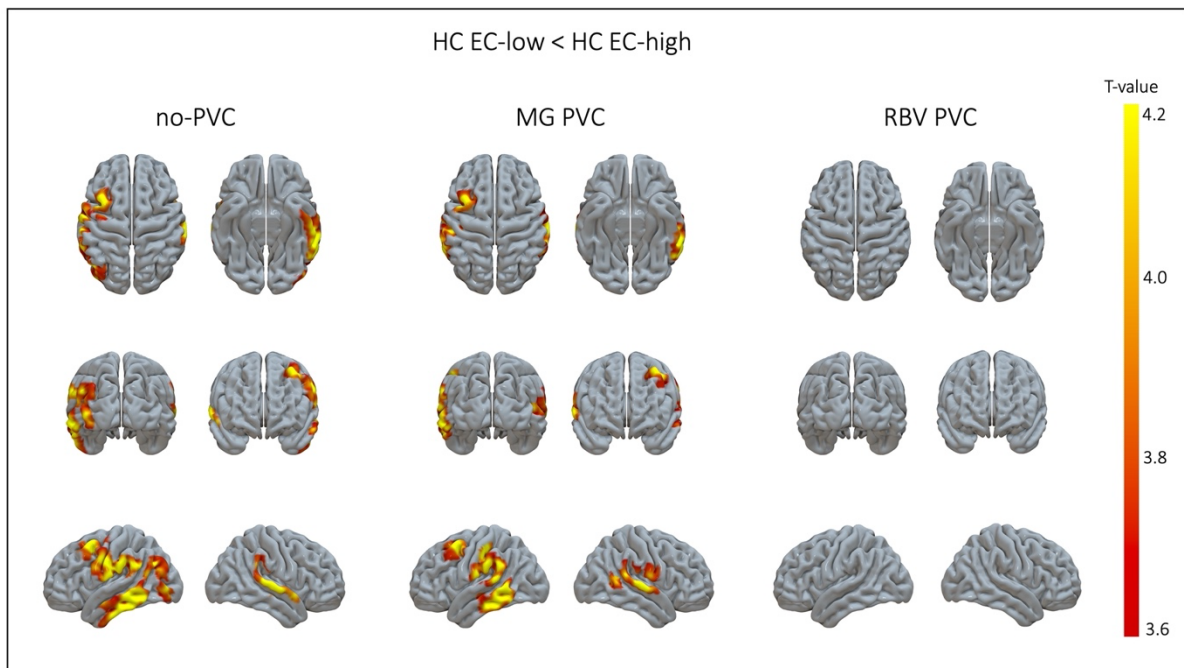
For the extended RBV PVC algorithm, the skull compartment was subdivided into smaller regions by labeling each skull voxel based on the nearest cortical region. First, the distance between each skull voxel and the neighboring cortical voxels were calculated. Next, the label of nearest cortical voxel was used to label each skull voxel. Finally, all skull voxels with the same label were considered as a subregion of the skull compartment. This approach was implemented in Python3.8 and used to apply an extended RBV PVC approach which also takes into account regional effects of meningeal uptake.

## Supplementary Figures

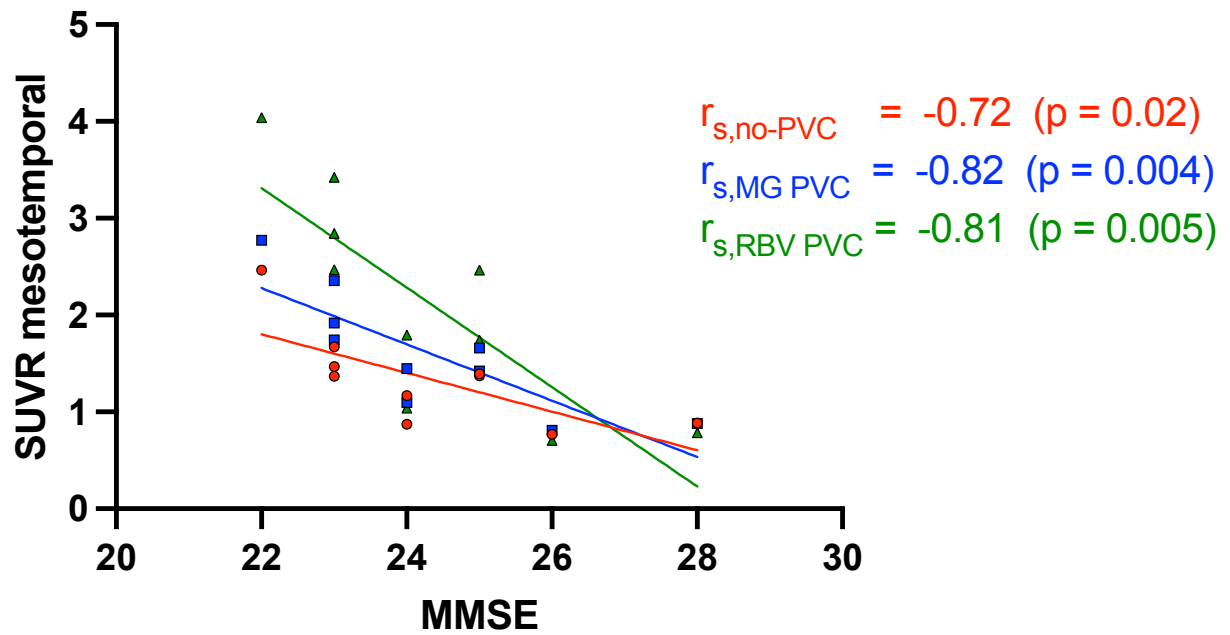
Supplementary Figure 1: Extracerebral [ $^{18}\text{F}$ ]MK-6240 SUVR values of 40 HC with low (n=22) and high (n=18) extracerebral tracer uptake respectively. The dichotomization threshold of 1.31 is indicated by the dashed line. Subjects included in the analysis (HC EC-low and HC EC-high) are presented by circles. Subjects included in the group with mixed extracerebral tracer uptake (HC EC-mixed) are presented by filled symbols. Subject which are not included in the age-matched analysis (but used to determine the dichotomization threshold) are presented by triangles. SUVR = standardized uptake value ratio, HC = healthy controls, EC = extracerebral.



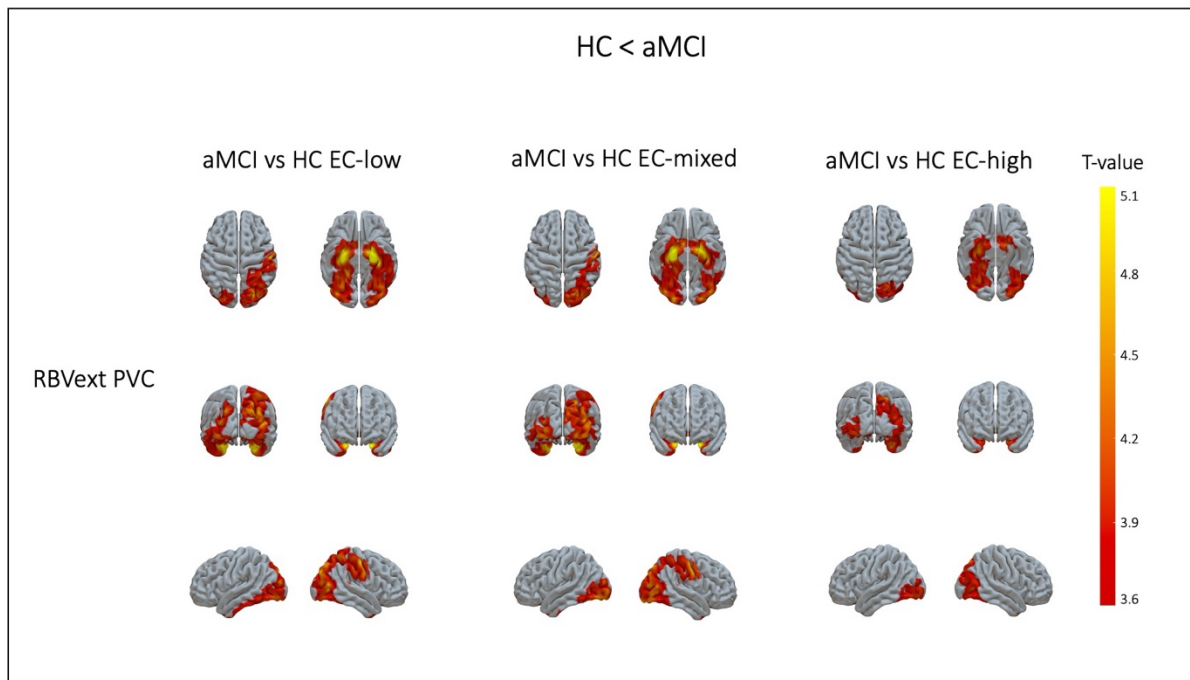
Supplementary Figure 2: T-statistical maps of significant clusters in the voxel-based comparison between [<sup>18</sup>F]MK-6240 SUVR maps of HC with low and high extracerebral tracer uptake using uncorrected SUVR maps (no-PVC), PVC corrected SUVR maps using a MG PVC method which does not correct for PVE of extracerebral tracer uptake and PVC corrected SUVR maps using an RBV PVC method which also corrects for PVE of extracerebral tracer uptake. SUVR = standardized uptake value ratio, HC = healthy controls, EC = extracerebral, MG = Müller-Gartner, PVC = partial volume correction, RBV = region-based voxelwise.



Supplementary Figure 3: Spearman correlation with corresponding correlation coefficients ( $r_p$ ) and p-values between MMSE scores and mesotemporal [ $^{18}\text{F}$ ]MK-6240 SUVR values for data without PVC (no-PVC, red dots), MG PVC (blue squares) and RBV PVC (green triangles). MMSE = Mini-Mental State Examination, SUVR = standardized uptake value ratio, PVC = partial volume correction, MG = Müller-Gartner, RBV = region-based voxelwise.



Supplementary Figure 4: T-statistical maps of significant clusters in the voxel-based comparison between  $[^{18}\text{F}]\text{MK-6240}$  SUVR maps of aMCI patients with HC with low, mixed and high extracerebral tracer uptake respectively using PVC corrected SUVR maps using an extended RBV PVC method (RBVext-PVC) which also corrects for PVE of inhomogeneous extracerebral tracer uptake. SUVR = standardized uptake value ratio, aMCI = amnesic mild cognitive impairment, HC = healthy controls, EC = extracerebral, PVC = partial volume correction, RBVext = extended region-based voxelwise.



## Supplementary Tables

Supplementary Table 1: Merged FreeSurfer segments used in the region-based voxelwise partial volume correction.

1	ctx-lh-caudalanteriorcingulate	7	ctx-rh-caudalanteriorcingulate	13	left-cerebral-white matter
	ctx-lh-isthmuscingulate		ctx-rh-isthmuscingulate	14	right-cerebral-white matter
	ctx-lh-posteriorcingulate		ctx-rh-posteriorcingulate	15	left-cerebellum-white-matter
	ctx-lh-rostralanteriorcingulate		ctx-rh-rostralanteriorcingulate	16	right-cerebellum-white-matter
2	ctx-lh-caudalmiddlefrontal	8	ctx-rh-caudalmiddlefrontal	17	left-cerebellum-cortex
	ctx-lh-lateralorbitofrontal		ctx-rh-lateralorbitofrontal	18	right-cerebellum-cortex
	ctx-lh-medialorbitofrontal		ctx-rh-medialorbitofrontal	19	left-thalamus
	ctx-lh-parsopercularis		ctx-rh-parsopercularis	20	right-thalamus
	ctx-lh-parsorbitalis		ctx-rh-parsorbitalis	21	left-caudate
	ctx-lh-parstriangularis		ctx-rh-parstriangularis	22	right-caudate
	ctx-lh-precentral		ctx-rh-precentral	23	left-putamen
	ctx-lh-rostralmiddlefrontal		ctx-rh-rostralmiddlefrontal	24	right-putamen
	ctx-lh-superiorfrontal		ctx-rh-superiorfrontal	25	left-pallidum
	ctx-lh-frontalpole		ctx-rh-frontalpole	26	right-pallidum
3	left-hippocampus	9	right-hippocampus	27	brain-stem
	left-amygdala		right-amygdala	28	CSF
	ctx-lh-entorhinal		ctx-rh-entorhinal	29	left-accumbens-area
	ctx-lh-parahippocampal		ctx-rh-parahippocampal	30	right-accumbens-area
4	ctx-lh-cuneus	10	ctx-rh-cuneus	31	left-ventalDC
	ctx-lh-lateraloccipital		ctx-rh-lateraloccipital	32	right-ventalDC
	ctx-lh-lingual		ctx-rh-lingual	33	left-choroid-plexus
	ctx-lh-pericalcarine		ctx-rh-pericalcarine	34	right-choroid-plexus
5	ctx-lh-inferiorparietal	11	ctx-rh-inferiorparietal	35	air-cavity
	ctx-lh-postcentral		ctx-rh-postcentral	36	skull
	ctx-lh-precuneus		ctx-rh-precuneus	37	vermis
	ctx-lh-superiorparietal		ctx-rh-superiorparietal	38	pons
	ctx-lh-supramarginal		ctx-rh-supramarginal	39	CSF-extracerebral
6	ctx-lh-bankssts	12	ctx-rh-bankssts	40	head-extracerebral
	ctx-lh-fusiform		ctx-rh-fusiform	41	ctx-lh-paracentral
	ctx-lh-inferiortemporal		ctx-rh-inferiortemporal	42	ctx-rh-paracentral
	ctx-lh-middletemporal		ctx-rh-middletemporal		
	ctx-lh-superiortemporal		ctx-rh-superiortemporal		
	ctx-lh-temporalpole		ctx-rh-temporalpole		
	ctx-lh-transversetemporal		ctx-rh-transversetemporal		
ctx-lh-insula	ctx-lh-insula				

Supplementary Table 2: Regional mean  $\pm$  standard deviation [ $^{18}\text{F}$ ]MK-6240 SUVR values of 10 aMCI patients and three groups of 10 HC with low, mixed and high extracerebral tracer uptake respectively. PVC SUVR values are presented using an extended RBV PVC method (RBVext-PVC) taking into account heterogeneous spill-in of extracerebral tracer uptake within a subject. P-values from VOI-based group comparisons are also reported, with significant p-values in bold. SUVR = standardized uptake value ratio, aMCI = amnesic mild cognitive impairment, HC = healthy controls, EC = extracerebral, PVC = partial volume correction.

	SUVR RBVext PVC				p-value			
	aMCI	HC EC-low	HC EC-mixed	HC EC-high	HC EC-low vs HC EC-high	aMCI vs HC EC-low	aMCI vs HC EC-mixed	aMCI vs HC EC-high
Temporal cortex	2.20 $\pm$ 1.58	1.00 $\pm$ 0.10	1.04 $\pm$ 0.08	1.07 $\pm$ 0.06	0.06	<b>0.0011</b>	<b>0.0021</b>	<b>0.0052</b>
Frontal cortex	1.31 $\pm$ 1.10	0.80 $\pm$ 0.08	0.82 $\pm$ 0.09	0.77 $\pm$ 0.11	0.43	<b>0.0089</b>	<b>0.015</b>	<b>0.0039</b>
Occipital cortex	2.04 $\pm$ 0.73	1.24 $\pm$ 0.13	1.21 $\pm$ 0.09	1.27 $\pm$ 0.08	0.49	<b>0.0066</b>	<b>0.0068</b>	<b>0.0083</b>
Parietal cortex	1.98 $\pm$ 1.32	0.89 $\pm$ 0.09	0.91 $\pm$ 0.10	0.93 $\pm$ 0.12	0.43	<b>0.00049</b>	<b>0.00073</b>	<b>0.0029</b>
Cingulate cortex	1.17 $\pm$ 1.00	0.61 $\pm$ 0.08	0.55 $\pm$ 0.15	0.52 $\pm$ 0.15	0.12	<b>0.011</b>	<b>0.0029</b>	<b>0.0011</b>
Mesotemporal cortex	2.16 $\pm$ 1.19	0.78 $\pm$ 0.09	0.81 $\pm$ 0.11	0.92 $\pm$ 0.37	0.44	<b>0.0030</b>	<b>0.0035</b>	<b>0.015</b>
Caudate nucleus	0.67 $\pm$ 0.19	0.62 $\pm$ 0.12	0.62 $\pm$ 0.12	0.60 $\pm$ 0.18	0.53	0.40	0.40	0.31
Putamen	0.90 $\pm$ 0.17	0.71 $\pm$ 0.15	0.74 $\pm$ 0.16	0.79 $\pm$ 0.20	0.34	0.89	0.86	0.50
Thalamus	0.62 $\pm$ 0.11	0.57 $\pm$ 0.08	0.55 $\pm$ 0.08	0.57 $\pm$ 0.08	0.44	0.29	0.17	0.25
Gray matter	1.67 $\pm$ 1.03	0.88 $\pm$ 0.07	0.90 $\pm$ 0.07	0.90 $\pm$ 0.07	0.62	<b>0.0015</b>	<b>0.0021</b>	<b>0.0021</b>

Supplementary Table 3: Regional effect sizes between 10 aMCI and 10 HC with low, mixed and high extracerebral [<sup>18</sup>F]MK-6240 uptake respectively. Effect sizes were calculated by using SUVR data with an extended RBV PVC method (RBVext-PVC) taking into account heterogeneous spill-in of extracerebral tracer uptake within a subject. aMCI = amnesic mild cognitive impairment, HC = healthy controls, EC = extracerebral, SUVR = standardized uptake value ratio, PVC = partial volume correction.

<b>Effect size</b>	<b>aMCI vs HC EC-low</b>	<b>aMCI vs HC EC-mixed</b>	<b>aMCI vs HC EC-high</b>
Temporal cortex	2.20	2.11	2.06
Frontal cortex	1.63	1.58	1.70
Occipital cortex	1.65	1.68	1.60
Parietal cortex	2.21	2.17	2.12
Cingulate cortex	1.92	2.14	2.27
Mesotemporal cortex	2.78	2.67	2.34
Caudate nucleus	1.09	1.09	1.13
Putamen	1.27	1.22	1.14
Thalamus	1.09	1.12	1.10
Gray matter	1.89	1.85	1.85