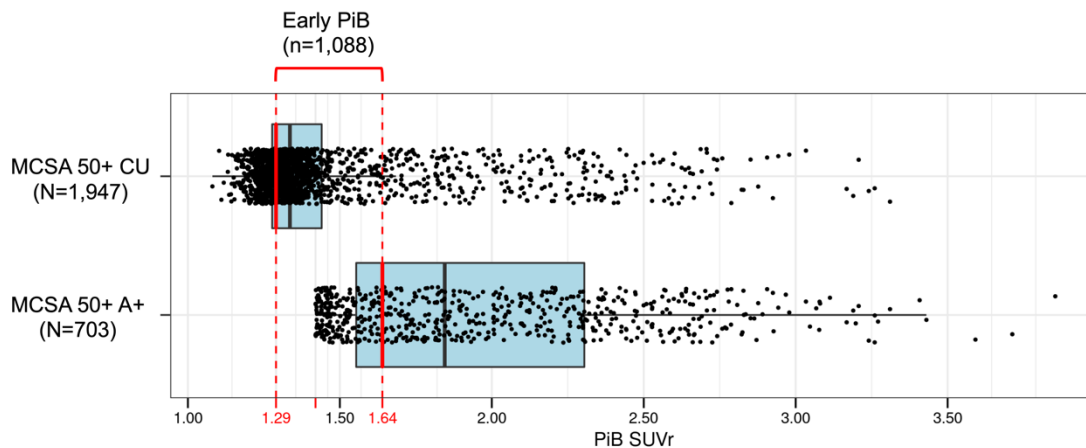


Supplemental Data

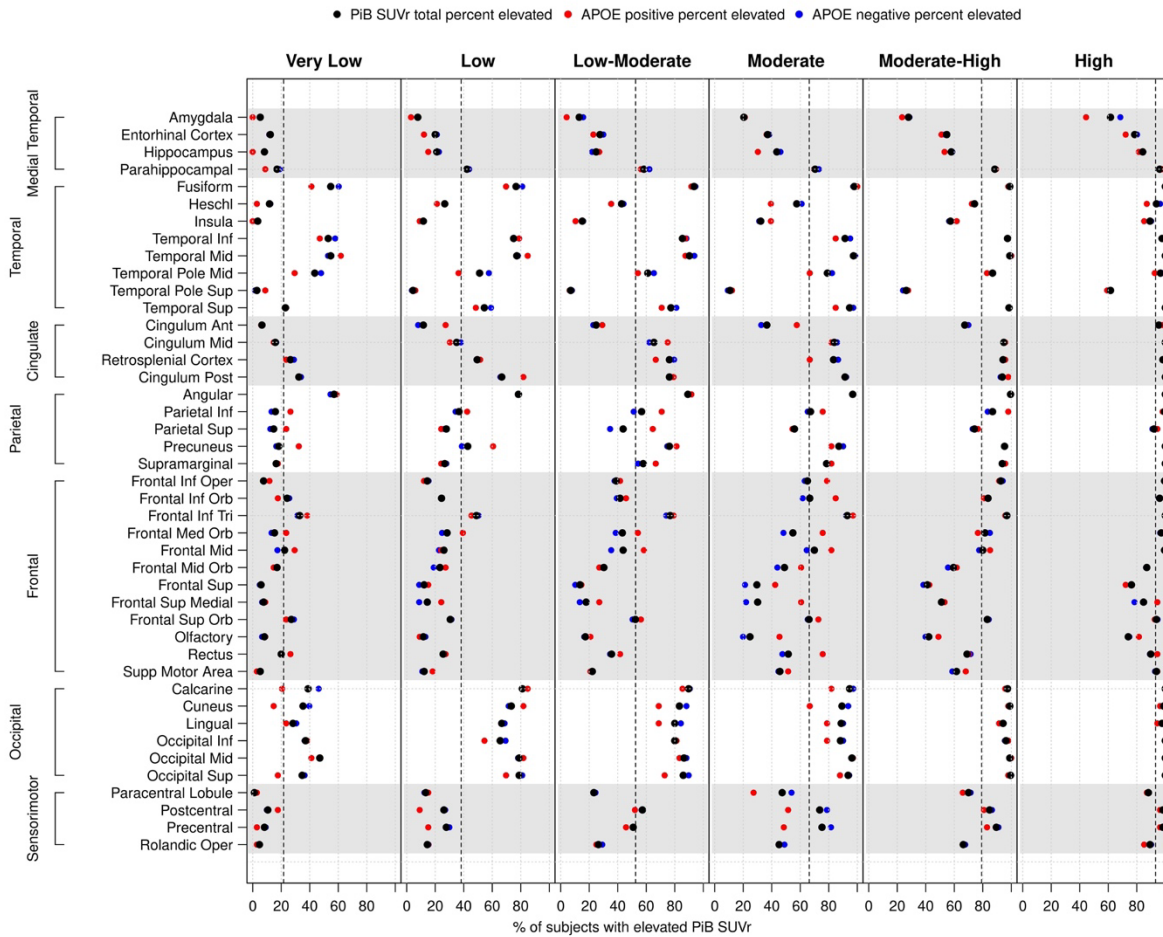
Statistical test

The difference of demographic variables (i.e., age, education, global PiB-SUVr, APOE ϵ 4, and diagnosis) between subgroups were assessed by the ANOVA and Pearson's Chi-squared test. The pair-wise comparison of regional PiB-SUVr between clusters was tested by a Student's two-sample t-test. The annual % SUVr change was calculated as $(\text{follow-up SUVr} - \text{baseline SUVr}) / (\text{baseline SUVr} \times \text{time difference in years})$. The pair-wise comparison of annual % SUVr change between clusters was assessed by a Student's two-sample t-test. Throughout the analysis, the p-value was not corrected for multiple comparison (two-tailed, $\alpha=0.05$). Analyses were performed using R Statistical Software (version 3.6.2).

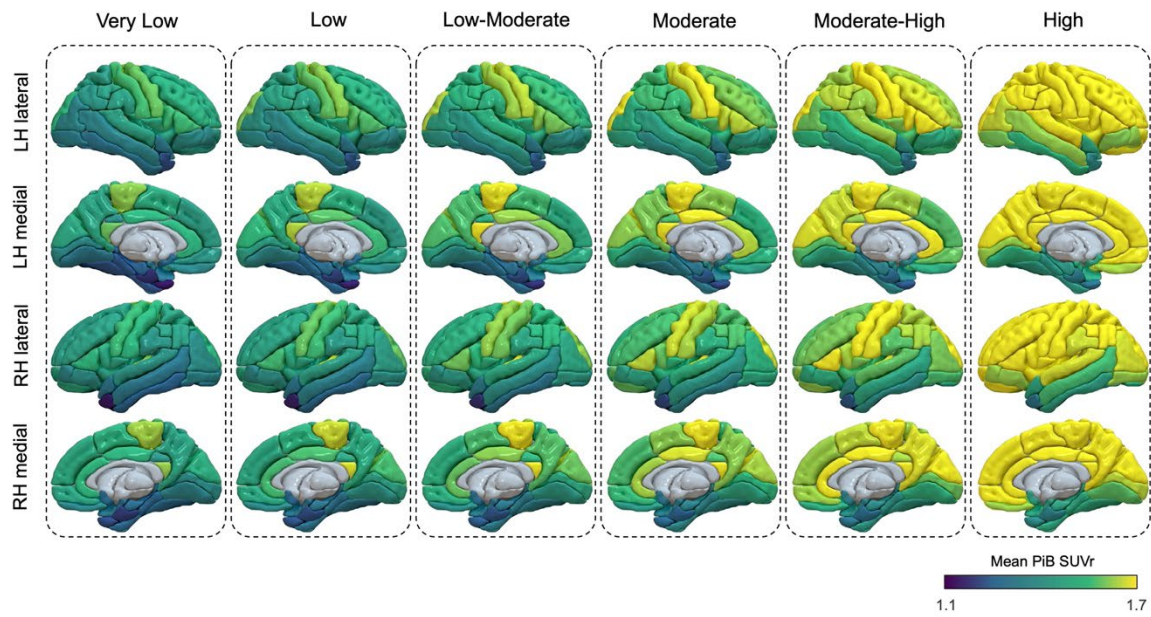
Supplemental Figure



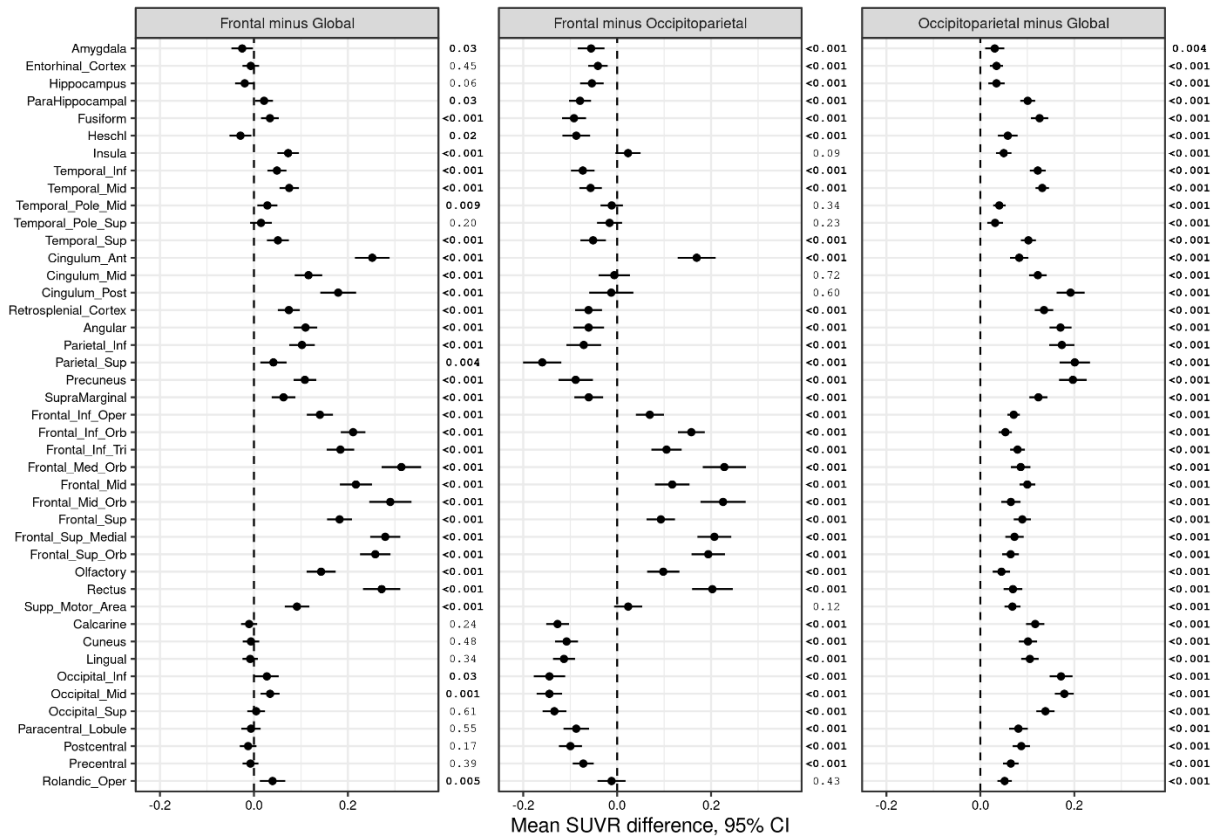
Supplemental Figure 1. A graphic representing population selection criteria and specific groupings chosen for analysis.



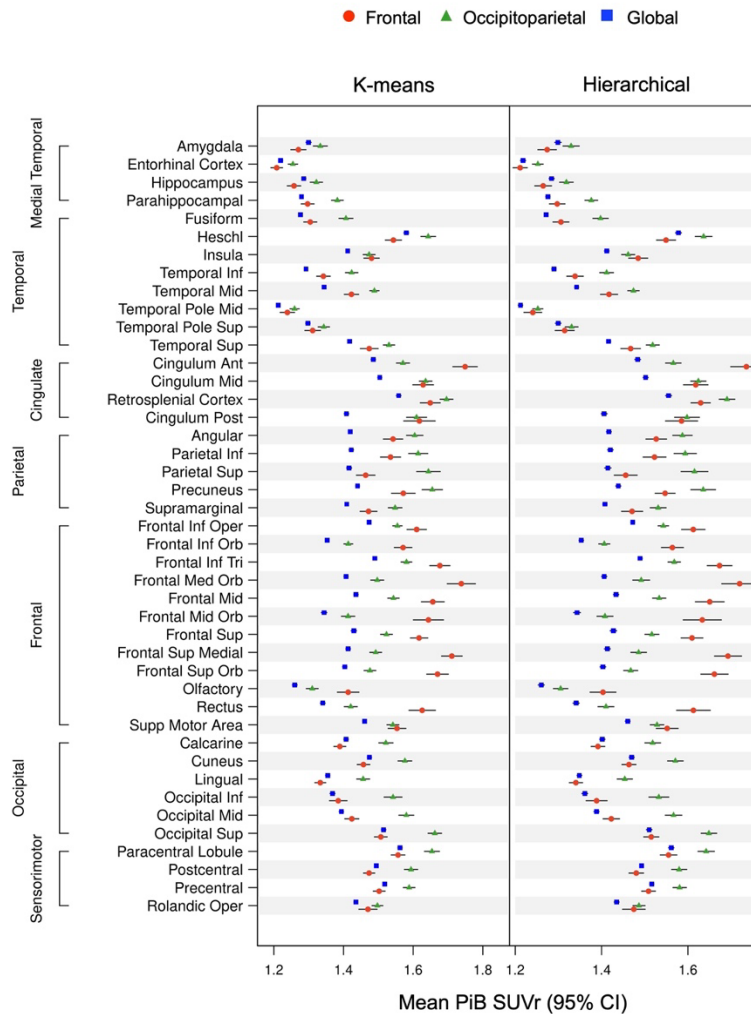
Supplemental Figure 2. The percentage of participants in each subgroup with elevated PiB signal by brain region. The percentage of participants with elevated PiB for each brain region is shown (black dot) for each subgroup (very low, low, low-moderate, moderate, moderate-high, and high). Brain regions are grouped by lobe as indicated on the y-axis. The mean percentage of the number of regions with elevated global PiB for each subgroup is represented by a black dashed line and shows an increasing trend across subgroups as 20.26%, 37.66%, 53.11%, 66.31%, 80.06%, 93.41% from ‘very low’ to ‘high’. The red dot illustrates APOE carriers and the blue dot for APOE non-carriers.



Supplemental Figure 3. SUVr map of PiB displayed by brain regions in each subgroup.



Supplemental Figure 4. Pair-wise comparison of regional SUVR between clusters. The pair-wise comparisons of mean SUVR (i.e., frontal minus global, frontal minus occipitoparietal, and occipitoparietal minus global) were performed using a Student's two-sample t-test. Error bars indicate 95% confidence intervals.

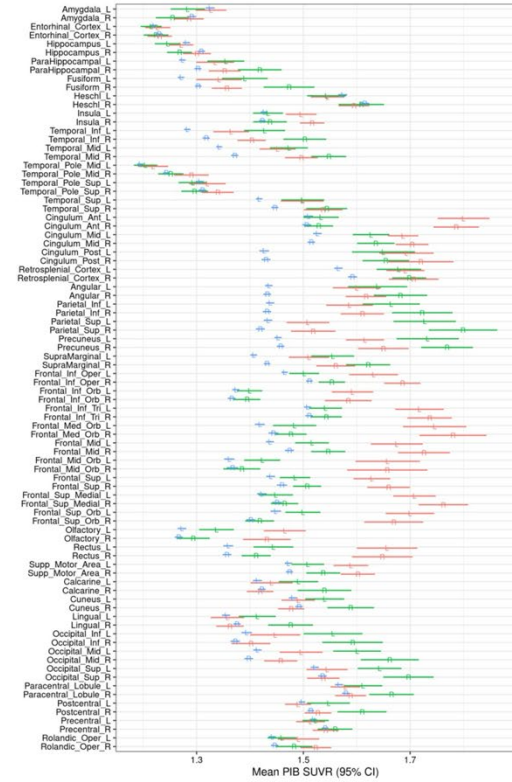


Supplemental Figure 5. The comparison of two different clustering methods.

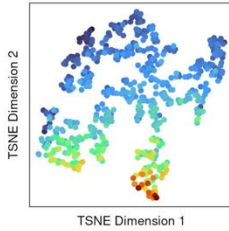
K-mean clustering and hierarchical clustering, in the three highest subgroups of the Early PiB group (moderate, moderate-high, high) were compared. The number of clusters was restricted as 3 (K=3) for both K-mean (frontal; n=49, occipitoparietal; n=65, global; n=369) and hierarchical (frontal; n=60, occipitoparietal; n=131, global; n=362). Both algorithms showed similar results. Error bars indicate 95% confidence intervals.

Supplemental Figure 6. Clustering leaving regions separated by hemispheres. A. Mean PiB-SUVr by clusters. (B-E) TSNE projection result.

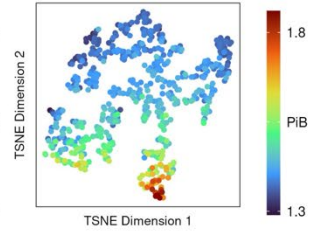
A. Regional PiB-SUVr



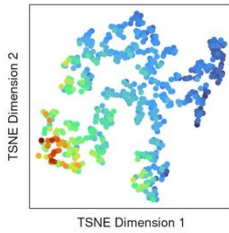
B. Left frontal



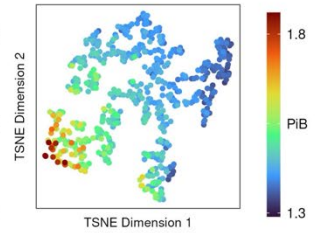
C. Left frontal

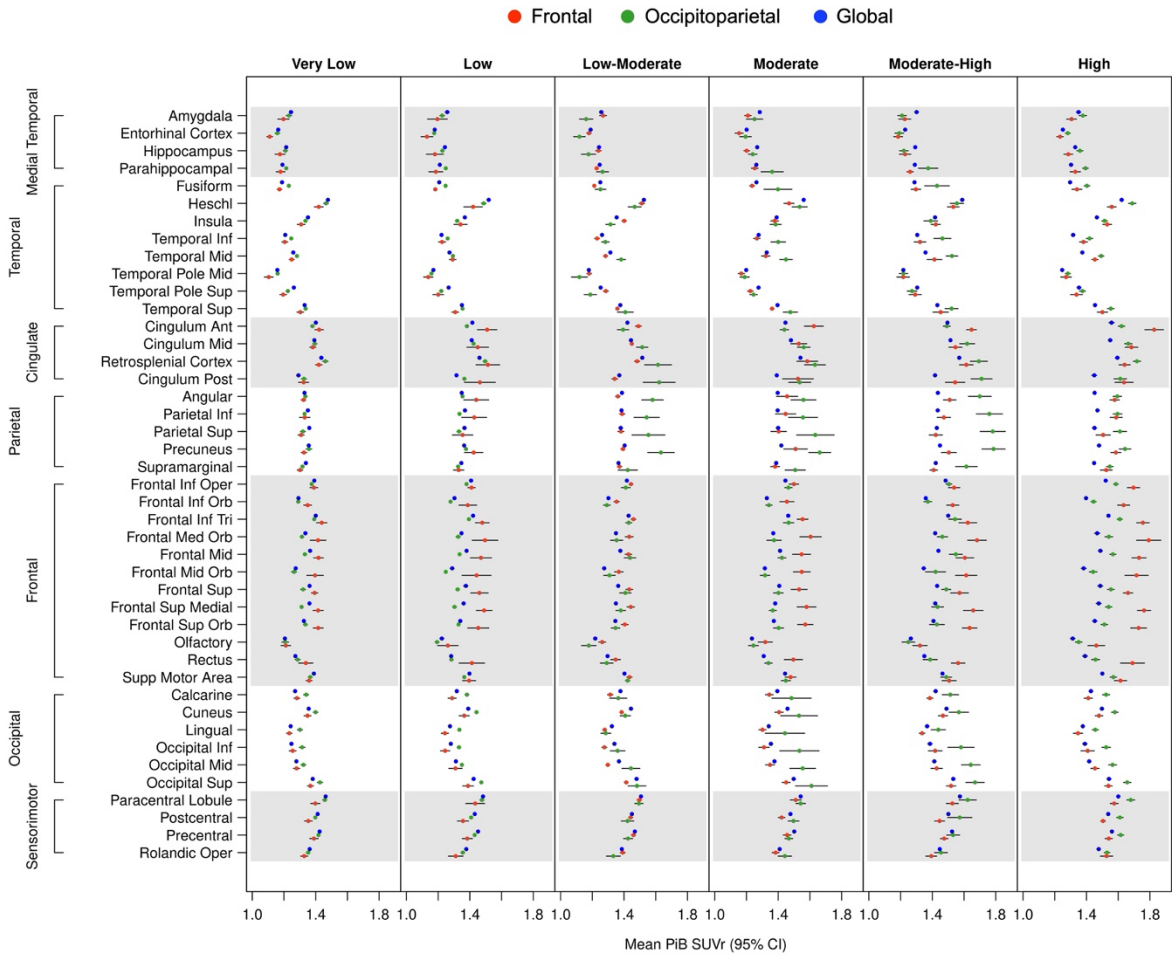


D. Left occipitoparietal

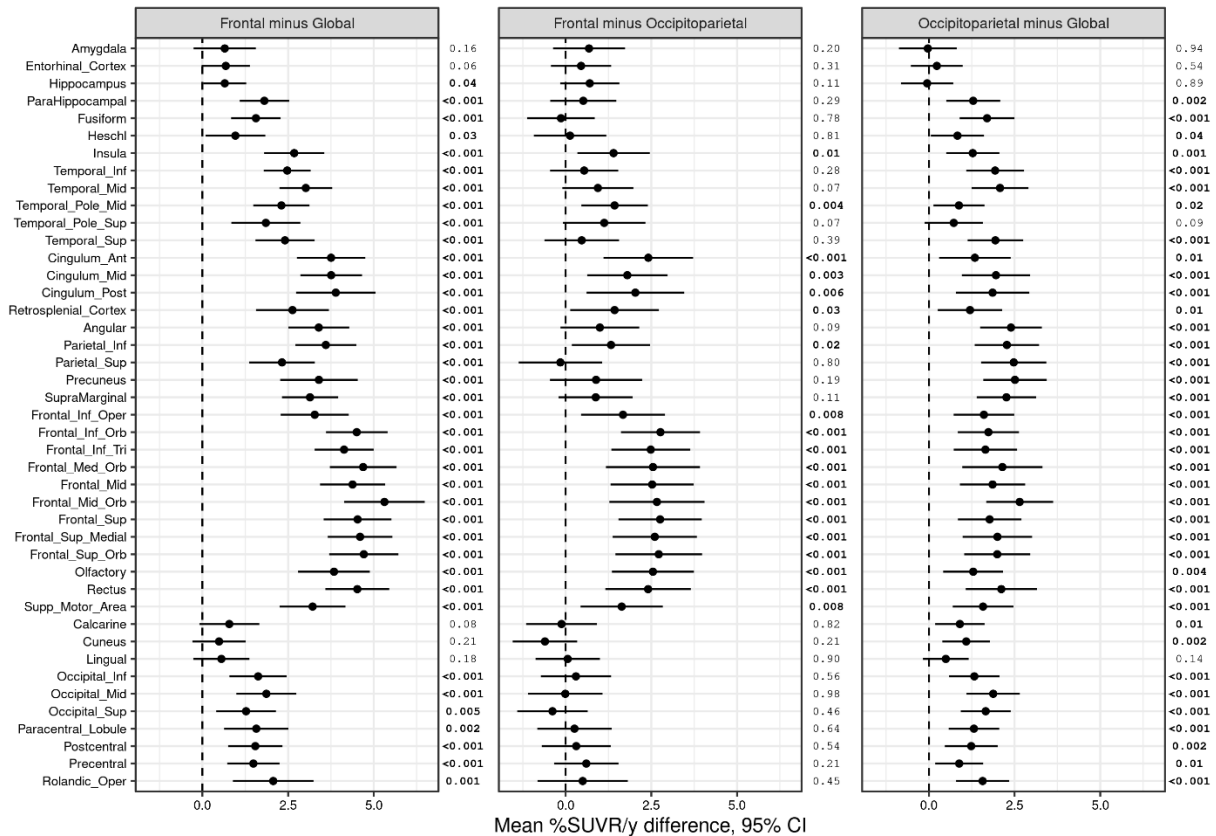


E. Right occipitoparietal





Supplemental Figure 7. Regional PiB deposition in each subgroup by hierarchical cluster. Each column shows the clusters obtained with hierarchical cluster-ing (K=3) using each subgroup. Clusters were analyzed by mean PiB SUVR over brain regions. Starting from low-moderate and moderate subgroup, a similar pat-tern showing differences in cingulate, frontal lobe and occipital lobe is observed.



Supplemental Figure 8. Pair-wise comparison of annual % SUVr change between clusters. The pair-wise comparisons of annual % SUVr change (i.e., frontal minus global, frontal minus occipitoparietal, and occipitoparietal minus global) were performed using a Student's two-sample t-test.

Supplemental Table 1. Demographics for overall MCSA 50+ population, populations to compute selection criteria tertiles (MCSA 50+ CU, MCSA 50+ A+), and overall Early PiB population.

	MCSA 50+ (N=2255)	MCSA 50+ CU (N=1947)	MCSA 50+ A+ (N=703)	Early PiB (N=1088)
Age, years				
Mean (SD)	72 (10)	70 (10)	78 (8)	72 (9)
Range	50 - 95	50 - 95	53 - 95	50 - 94
Sex, N (%)				
Female	1062 (47.1%)	933 (47.9%)	336 (47.8%)	528 (48.5%)
Male	1193 (52.9%)	1014 (52.1%)	367 (52.2%)	560 (51.5%)
Education, years				
N-Miss	1	0	0	1
Mean (SD)	14.77 (2.66)	14.95 (2.54)	14.54 (2.72)	14.60 (2.66)
Range	0.00 - 20.00	6.00 - 20.00	6.00 - 20.00	0.00 - 20.00
Diagnosis, N (%)				
N-Miss	7	0	2	6
CU	1947 (86.6%)	1947 (100.0%)	530 (75.6%)	969 (89.6%)
MCI	265 (11.8%)	0 (0.0%)	141 (20.1%)	107 (9.9%)
DEM	32 (1.4%)	0 (0.0%)	28 (4.0%)	6 (0.6%)
OTHER	4 (0.2%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
APOE ε4, N (%)				
N-Miss	134	118	40	69
Non-carrier	1505 (71.0%)	1327 (72.6%)	356 (53.7%)	770 (75.6%)
Carrier	616 (29.0%)	502 (27.4%)	307 (46.3%)	249 (24.4%)
GM PVC PiB SUVr				
Mean (SD)	1.51 (0.42)	1.46 (0.35)	1.97 (0.49)	1.38 (0.07)
Range	1.08 - 3.85	1.08 - 3.36	1.42 - 3.85	1.30 - 1.62

Supplemental Table 2. Ethnic distribution of the early PiB cohort

Asian	Black/African-american	White	More than one	Unknown/not-reported
3	3	1071	9	2

Supplemental Table 3. ROI specific SUVR cut points derived from younger cognitively unimpaired individuals in the MCSA (30-49 years, n=164). Each regional cut point value is from the 95th percentile per ROI of the younger cognitively unimpaired individuals. The cut points for the left hemisphere, right hemisphere, and bilateral brain were separately calculated for each brain region.

Lobe	Region	PiB SUVR left	PiB SUVR right	PiB SUVR total
Medial Temporal	Amygdala	1.38	1.33	1.33
	Entorhinal Cortex	1.23	1.21	1.21
	Hippocampus	1.28	1.28	1.27
	Parahippocampal	1.25	1.24	1.23
Temporal	Fusiform	1.18	1.21	1.19
	Heschl	1.52	1.56	1.53
	Insula	1.41	1.43	1.41
	Temporal Inf	1.19	1.24	1.22
	Temporal Mid	1.24	1.28	1.26
	Temporal Pole Mid	1.15	1.21	1.16
	Temporal Pole Sup	1.32	1.34	1.33
	Temporal Sup	1.33	1.37	1.35
Cingulate	Cingulum Ant	1.48	1.46	1.47
	Cingulum Mid	1.42	1.44	1.43
	Retrosplenial Cortex	1.44	1.52	1.47
	Cingulum Post	1.31	1.33	1.32
Parietal	Angular	1.34	1.31	1.32
	Parietal Inf	1.40	1.36	1.37
	Parietal Sup	1.40	1.38	1.39
	Precuneus	1.37	1.37	1.38
	Supramarginal	1.35	1.38	1.36

	Frontal Inf Oper	1.40	1.46	1.43
	Frontal Inf Orb	1.33	1.32	1.32
	Frontal Inf Tri	1.42	1.45	1.41
	Frontal Med Orb	1.35	1.41	1.37
	Frontal Mid	1.37	1.42	1.39
Frontal	Frontal Mid Orb	1.32	1.33	1.33
	Frontal Sup	1.43	1.47	1.45
	Frontal Sup Medial	1.42	1.45	1.42
	Frontal Sup Orb	1.41	1.35	1.36
	Olfactory	1.29	1.31	1.28
	Rectus	1.33	1.32	1.33
	Supp Motor Area	1.44	1.45	1.45
	Calcarine	1.30	1.29	1.29
	Cuneus	1.38	1.38	1.38
Occipital	Lingual	1.27	1.27	1.27
	Occipital Inf	1.27	1.27	1.27
	Occipital Mid	1.31	1.27	1.29
	Occipital Sup	1.41	1.40	1.40
	Paracentral Lobule	1.54	1.54	1.54
Sensorimotor	Postcentral	1.43	1.47	1.45
	Precentral	1.46	1.48	1.46
	Rolandic Oper	1.41	1.44	1.42

Supplemental Table 4. Comparisons of annual change of cognitive test scores by clusters. Statistical test: ¹Linear model ANOVA; ²Pearson's Chi-squared test.

Abbreviations: MMSE - mini-mental state examination; CDR - clinical dementia rating scale

Annual change of cognitive test score	Frontal (N=50)	Occipitoparietal (N=109)	Global (N=312)	p value ¹	Pair-wise p value ²		
					Frontal vs. Occipitoparietal	Frontal vs. Global	Occipitoparietal vs. Global
MMSE, mean (SD)	-0.062 (0.312)	-0.044 (0.717)	-0.090 (0.581)	0.77	0.82	0.61	0.55
Memory, mean (SD)	-0.007 (0.201)	-0.043 (0.267)	0.012 (0.198)	0.07	0.35	0.53	0.0503
Visuospatial, mean (SD)	-0.031 (0.160)	-0.033 (0.231)	-0.011 (0.198)	0.55	0.95	0.43	0.37
Attention, mean (SD)	-0.075 (0.104)	-0.117 (0.227)	-0.064 (0.146)	0.02	0.11	0.52	0.02
Language, mean (SD)	-0.029 (0.245)	-0.031 (0.257)	-0.039 (0.198)	0.93	0.96	0.8	0.79
CDR-sum of box, mean (SD)	0.010 (0.250)	0.114 (0.698)	0.044 (0.292)	0.21	0.15	0.35	0.3
CDR global, mean (SD)	0.009 (0.070)	0.027 (0.114)	0.005 (0.062)	0.03	0.21	0.68	0.049

Supplemental Table 5. Comparisons of clusters by change in diagnosis. Statistical test: ¹Pearson’s Chi-squared test. Abbreviations: CU- cognitively unimpaired; MCI – mild cognitively impaired.

Change in diagnosis, baseline to follow-up	Frontal (N=55)	Occipitoparietal (N=116)	Global (N=321)	p value
CU to CU	47 (85.5%)	93 (80.2%)	276 (86.0%)	
CU to MCI	3 (5.5%)	6 (5.2%)	12 (3.7%)	
CU to dementia	0 (0.0%)	1 (0.9%)	1 (0.3%)	
Dementia to MCI	0 (0.0%)	1 (0.9%)	0 (0.0%)	
Dementia to dementia	1 (1.8%)	0 (0.0%)	1 (0.3%)	0.557 ¹
MCI to CU	1 (1.8%)	6 (5.2%)	15 (4.7%)	
MCI to MCI	3 (5.5%)	6 (5.2%)	14 (4.4%)	
MCI to dementia	0 (0.0%)	2 (1.7%)	2 (0.6%)	
Other to CU	0 (0.0%)	1 (0.9%)	0 (0.0%)	