Supplementary Methods

Supplementary Method 1. *Protocols of amyloid PET imaging acquisition*

For amyloid PET imaging acquisition, CT images were acquired using a 16-slice helical CT (140 keV, 80 mA; 3.75mm section width) for attenuation correction. According to the protocols proposed by the ligand manufacturers, a 20-min emission PET scan with dynamic mode (consisting of 4×5 min frames) was performed 90 min after injection of a mean dose of 311.5 MBq of FBB or 185 MBq of FMM. 3D PET images were reconstructed in a 128×128×48 matrix with a voxel size of 2.00×2.00×3.27 mm^3 using the ordered-subsets expectation-maximization (OSEM) algorithm (FBB iterations = 4 and subset = 20; FMM iterations = 4 and subset = 20).

Supplementary Method 2. *Methods of conversion equations to Centiloid units*

In our previous study, we directly converted the standardized uptake value ratio (SUVR) of the FBB or FMM CTX VOI into a direct comparison of Centiloid units (dcCL) using the dcCL conversion equation.[1] Cerebral cortex segmentation was derived from the segmentation method on the SPM8 and automatic anatomical labeling template. The whole-cerebellum mask was downloaded from the Global Alzheimer's Association Interactive Network website (http://www.gaain.org). No corrections were applied to the PET images for brain atrophy or partial-volume effects. FBB-FMM cortical target region volume of interest-derived SUVR was converted to dcCL with transformation equation derived from previous studies of FBB ($dcCL_{FBB} = 151.42 \times dcSUVR_{FBB} - 142.24$) and FMM ($dcCL_{FMM} = 148.52 \times dcSUVR_{FMM} - 137.09$).[1]

Supplementary Method 3. *Protocols of Tau PET imaging acquisition*

FTP PET images were acquired for 20-min at 80 min after intravenous bolus

injections of approximately 280 MBq ^{18}F-flortaucipir. Three-dimensional PET images were reconstructed in a 128×128×47 matrix with 2.00×2.00×3.27 mm^3 voxel size at Samsung Medical Center (SMC) and in a 256×256×223 matrix with 1.591×1.591×1.00mm^3 voxel size at Gangnam Severance Hospital, using the OSEM algorithm (iteration = 6 and subset = 16).

Supplementary Method 4. *Tau PET regional SUVR analysis*

To measure FTP PET regional SUVR, we used FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu) to delineate the region of interest (ROI) masks after coregistration with corresponding MR using SPM12. The cerebellar gray matter was used as the reference region. The region-based voxel-wise correction method was used for partial volume correction and was performed using the PETPVC toolbox for tau PET images.[2] Therefore, we measured the partial volume effect–corrected regional SUVR for the following 25 cortical regions: inferior, middle, and superior frontal; orbitofrontal; paracentral; precentral; inferior and superior parietal; postcentral; precuneus; supramarginal; medial and lateral occipital; lingual; insula; inferior, middle, and superior temporal; fusiform; entorhinal; parahippocampal; anterior and posterior cingulate; amygdala; and hippocampus. Finally, we created bilateral Braak stage ROIs.

Supplementary Method 5. *Measurement of adjusted hippocampal volume*

To measure hippocampal volume (HV), we used an automated hippocampus segmentation method using a graph cut algorithm combined with an atlas-based segmentation and morphological opening as described in an earlier study.[3] We averaged right and left hippocampal volumes and adjusted them for intracranial volume (ICV) by calculating the residual from a linear regression of HV versus intracranial volume among 366 Aβ–cognitively unimpaired (CU) participants in an independent SMC cohort, as in previous

studies.[4, 5] Adjusted HV (HVa) can be interpreted as the deviation in cubic millimeters of a participant's hippocampal volume from what is expected given their ICV.[5] We excluded one patient because of a segmentation error during hippocampal volume measurement. Therefore, the final study sample consisted of 205 participants.

Supplementary Method 6. Development of the cutoff for HV

In order to develop the cutoff for HV, we applied machine learning K-means clustering methods using the HVa of 1,453 participants in an independent SMC imaging registry comprising participants with CU, amnestic mild cognitive impairment, and Alzheimer's disease (AD) dementia. We restricted our analysis to two clusters. Each participant was assigned a probability of belonging to either Cluster A (low hippocampal volume) or Cluster B (high hippocampal volume). The cut-off value corresponds to the 10^{th} percentile of Cluster B (higher hippocampal volume).[6]

Supplementary Method 7. *Measurement of WMH volume and rating of lacunes and microbleeds*

We quantified white matter hyperintensities (WMH) volume (in mm^3) on fluid-attenuated inversion recovery (FLAIR) images using an automated method.[7] Lacunes were defined as small lesions (≤ 15 mm and ≥ 3 mm in diameter) with low signal on T1-weighted images, high signal on T2-weighted images, and a perilesional halo on 80 axial slices of FLAIR images, as proposed by Wardlaw et al.[8] Cerebral microbleeds were defined as lesions ≤ 10 mm in diameter on 20 T2* GRE-MRI axial slides using criteria proposed by Wardlaw et al.[8]

Supplementary Method 8. *A standardized neuropsychological test battery*

The Seoul Neuropsychological Screening Battery 2nd edition is a standardized neuropsychological battery widely used in South Korea.[9] Five cognitive domains were evaluateed: attention (digit span task forward/backward); visuospatial function (Rey-Osterrieth Complex Figure Test (RCFT)); language (the Korean version of the Boston Naming Test); memory (delayed recall scores of the Seoul Verbal Learning Test and RCFT); and frontal/executive function (Controlled oral word association test and Stoop test).

Supplementary References

1 Cho SH, Choe YS, Kim HJ*, et al.* A new Centiloid method for (18)F-florbetaben and (18)F-flutemetamol PET without conversion to PiB. *Eur J Nucl Med Mol Imaging* 2020;47:1938-48.

2 Thomas BA, Erlandsson K, Modat M*, et al.* The importance of appropriate partial volume correction for PET quantification in Alzheimer's disease. *European journal of nuclear medicine and molecular imaging* 2011;38:1104-19.

3 Kwak K, Yoon U, Lee D-K*, et al.* Fully-automated approach to hippocampus segmentation using a graph-cuts algorithm combined with atlas-based segmentation and morphological opening. *Magnetic resonance imaging* 2013;31:1190-6.

4 Jack CR, Jr., Knopman DS, Weigand SD*, et al.* An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol* 2012;71:765-75.

5 Jack CR, Jr., Wiste HJ, Weigand SD*, et al.* Different definitions of neurodegeneration produce similar amyloid/neurodegeneration biomarker group findings. *Brain* 2015;138:3747-59.

6 Villeneuve S, Rabinovici GD, Cohn-Sheehy BI*, et al.* Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation. *Brain* 2015;138:2020-33.

7 Jeon S, Yoon U, Park JS*, et al.* Fully automated pipeline for quantification and localization of white matter hyperintensity in brain magnetic resonance image. *International Journal of Imaging Systems and Technology* 2011;21:193-200.

8 Wardlaw JM, Smith EE, Biessels GJ*, et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurology* 2013;12:822-38.

9 Kang Y, Na DL. *Seoul Neuropsychological Screening Battery*. Seoul: Human Brain Research & Consulting Co, 2003.