

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 mm³ 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 ($\text{dcCL}_{\text{FBB}} = 151.42 \times \text{dcSUVR}_{\text{FBB}} - 142.24$) and FMM ($\text{dcCL}_{\text{FMM}} = 148.52 \times \text{dcSUVR}_{\text{FMM}} - 137.09$).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 -florbetapir. Three-dimensional PET images were reconstructed in a $128 \times 128 \times 47$ matrix with $2.00 \times 2.00 \times 3.27 \text{ mm}^3$ voxel size at Samsung Medical Center (SMC) and in a $256 \times 256 \times 223$ matrix with $1.591 \times 1.591 \times 1.00 \text{ mm}^3$ 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 A β -cognitively unimpaired (CU) participants in an independent SMC cohort, as in previous

studies.^{4,5} Adjusted HV (HV_a) 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 HV_a of 1,453 participants in an independent SMC imaging registry comprising participants with CU, amnesic 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 10th 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 mm³) 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 evaluated: 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

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