Supplemental Material S1. Supplemental methods.

MRI Acquisition

The patient underwent MRI scanning at UCSF on a 3T Siemens Prisma Fit scanner. T1-weighted magnetization prepared rapid gradient echo (MPRAGE) MRI sequence was used for the VBM and PET analysis (sagittal slice orientation, slices per slab = 160, resolution = 1 mm isotropic, matrix = 240 × 256, repetition time = 2,300 ms, inversion time = 900 ms, flip angle = 9°; echo time = 2.9 ms). For the PET data processing, the MRI was segmented using Freesurfer 5.3 (http://surfer.nmr.mgh.harvard) and Statistical Parametric Mapping (SPM12; Wellcome Trust Center for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm). For VBM analysis, the MRI was preprocessed using SPM12.

MRI Preprocessing and VBM Analysis

Structural T1-weighted images were visually inspected for artifacts, and underwent bias-correction, segmentation into tissue compartments, and spatial normalization using a single generative model with the standard SPM12 parameters. The default tissue probability maps for grey matter, white matter, cerebrospinal fluid, and all other voxels from SPM12 (TPM.nii) were used. To optimize intersubject registration, each participant's image was warped to a template derived from 300 confirmed neurologically healthy older adults (ages 44–86, $M \pm SD$: 67.2 ±7.3; 113 males, 186 females) scanned with one of three magnet strengths (1.5T, 3T, 4T), using affine and nonlinear transformations with the help of the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) method, with standard implementation in SPM12. In all preprocessing steps, default parameters of the SPM12 toolbox were used. Total volume of each tissue compartment was calculated by applying the modulated, warped and segmented masks for gray matter, white matter, and CSF to the corresponding MWS probability map for that individual, and the total intracranial volume (TIV) was derived by summing the three volumes. The spatially normalized, segmented, and modulated gray matter images were smoothed with an 8-mm FWHM isotropic Gaussian kernel for use in VBM analysis.

Tau-PET Acquisition, Preprocessing, and Analyses

^{18}F-Flortaucipir (FTP)-PET imaging was acquired on a Siemens Biograph PET/CT scanner at the Lawrence Berkeley National Laboratory (LBNL) with the patient and control participants. FTP was synthesized and radiolabeled at LBNL's Biomedical Isotope Facility. We analyzed PET data that was acquired 80–100 min after the injection of ~10 mCi of FTP (four 5-min frames). A low-dose CT scan was performed for attenuation correction prior to PET acquisition, and data were reconstructed using an ordered subset expectation maximization algorithm with weighted attenuation and smoothed with a 4 mm Gaussian kernel with scatter correction (final image resolution: 6.5 × 6.5 × 7.25 mm based on Hoffman phantom). PET frames were realigned, averaged and co-registered onto their corresponding MRI. Standardized Uptake Value Ratio (SUVR) image was created in native space using MRI-defined inferior cerebellum gray matter as a reference region (Maass et al., 2017).

Aβ-PET Acquisition, Preprocessing, and Analyses

Aβ-PET was available using ^{11}C-Pittsburg Compound B (PIB, injected dose: ~15 mCi). PET was acquired from the patient and control participants at LBNL on the same Siemens Biograph PET-CT scanner used for FTP-PET. The same reconstruction parameters for FTP-PET

were applied. We created 50-70 min native-space SUVR maps with cerebellar grey matter used as a reference region and defined using MRI and Freesurfer (Villeneuve et al., 2015). Aβ-PET positivity was assessed visually (Rabinovici et al., 2007), as validated against autopsy (La Joie et al., 2019).

FDG-PET Acquisition, Preprocessing, and Analyses

A dynamic FDG-PET scan was acquired from the patient and control participants for 30 minutes (6 × 5 min frames) after 30 minutes of eyes-open quiet rest following intravenous injection of ^{18}F-FDG on the same Siemens Biograph PET-CT scanner at LBNL used for FTP-PET. The same reconstruction parameters for FTP-PET were applied. SUVR image was calculated in native-space using data acquired 30- to 60-minutes post-injection and pons (manually cleaned from FreeSurfer-derived brainstem) as the reference region.

PET Scans Visualization

All the native-space FTP-, PIB-, and FDG-PET SUVR images were warped to Montreal Neurological Institute (MNI) template using the deformation parameters derived from the MRI-based unified segmentation (Ashburner & Friston, 2005) procedure using SPM12, for the sake of visualization.

References

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage*, *26*(3), 839–851.

Baker, S. L., Harrison, T. M., Maaß, A., La Joie, R., & Jagust, W. (2019). Effect of off-target binding on 18F-Flortaucipir variability in healthy controls across the lifespan. *Journal of Nuclear Medicine*. Advance online publication. https://doi.org/10.2967/jnumed.118.224113

Choi, J. Y., Cho, H., Ahn, S. J., Lee, J. H., Ryu, Y. H., Lee, M. S., & Lyoo, C. H. (2018). Off-target 18F-AV-1451 binding in the basal ganglia correlates with age-related iron accumulation. *Journal of Nuclear Medicine*, *59*(1), 117–120.

Jack, C. R., Petersen, R. C., Xu, Y. C., Waring, S. C., O'Brien, P. C., Tangalos, E. G., ... & Kokmen, E. (1997). Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology*, *49*(3), 786–794.

Klunk, W. E., Koeppe, R. A., Price, J. C., Benzinger, T. L., Devous Sr, M. D., Jagust, W. J., ... & Rowe, C. C. (2015). The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET. *Alzheimer's & Dementia*, *11*(1), 1–15.

La Joie, R., Ayakta, N., Seeley, W. W., Borys, E., Boxer, A. L., DeCarli, C., ... & Ikonomovic, M. D. (2019). Multisite study of the relationships between antemortem [11C] PIB-PET Centiloid values and postmortem measures of Alzheimer's disease neuropathology. *Alzheimer's & Dementia*, *15*(2), 205-216.

La Joie, R., Bejanin, A., Fagan, A. M., Ayakta, N., Baker, S. L., Bourakova, V., ... & Maass, A. (2018). Associations between [18F] AV1451 tau PET and CSF measures of tau pathology in a clinical sample. *Neurology*, *90*(4), e282–e290.

La Joie, R., Perrotin, A., Barré, L., Hommet, C., Mézenge, F., Ibazizene, M., ... & de La Sayette, V. (2012). Region-specific hierarchy between atrophy, hypometabolism, and β-amyloid (Aβ) load in Alzheimer's disease dementia. *Journal of Neuroscience*, *32*(46), 16265–16273.

Maass, A., Landau, S., Baker, S. L., Horng, A., Lockhart, S. N., La Joie, R., ... & Alzheimer's Disease Neuroimaging Initiative. (2017). Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. *NeuroImage*, *157*, 448–463.

O'Brien, P. C., & Dyck, P. J. (1995). Procedures for setting normal values. *Neurology*, *45*(1), 17–23.

Rabinovici, G. D., Furst, A. J., O'Neil, J. P., Racine, C. A., Mormino, E. C., Baker, S. L., ... & Mathis, C. A. (2007). 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology*, *68*(15), 1205–1212.

Villeneuve, S., Rabinovici, G. D., Cohn-Sheehy, B. I., Madison, C., Ayakta, N., Ghosh, P. M., ... & Lehmann, M. (2015). Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: Statistical and pathological evaluation. *Brain*, *138*(7), 2020–2033.