# Supplementary Material

**Low Ankle-Brachial Index Relates to Alzheimer-Signature Cerebral Glucose Metabolism in Cognitively Impaired Older Adults**

## SUPPLEMENTARY METHODS

*[$^{11}$C] Pittsburgh compound B (PiB)–positron emission tomography (PET) image acquisition and preprocessing*

Participants underwent simultaneous three-dimensional (3D) PiB-PET and 3D T1-weighted magnetic resonance imaging (MRI) using a 3.0T Biograph mMR scanner (PET-MR scanner; Siemens, Washington, DC, USA) according to the manufacturer's approved guidelines. After intravenous administration of 555 MBq of [$^{11}$C] PiB (range, 450-610 MBq), a 30-min emission scan was obtained 40 min after the injection. The PiB-PET data were collected in list mode and processed for routine corrections, such as uniformity, ultrashort echo time (UTE)-based attenuation, and decay corrections, and were reconstructed into a 256 × 256 image matrix using iterative methods (6 iterations with 21 subsets).

The following image preprocessing steps were performed using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 2014a (Mathworks, Natick, MA, USA). Static PiB-PET images were co-registered to individual T1 structural images and transformation parameters were calculated for spatial normalization of individual T1 images to the standard Montreal Neurological Institute (MNI) template. Using IBASPM software, we used the inverse transformation parameters to transform coordinates from the automatic anatomic labeling (AAL) 116 atlas [1] into an individual space for each subject (resampling voxel size = 1 × 0.98 × 0.98 mm), and the non-gray matter portions of the atlas were individually masked using the cerebral gray matter segment image from each subject.

Mean regional $^{11}$C-PiB uptake values from cerebral regions were extracted using the individual AAL116 atlas from the T1-coregistered PiB-PET images. Cerebellar gray matter was used as the reference region for quantitative normalization of cerebral PiB uptake values due to its relatively low amyloid-β (Aβ) deposition [2]. To measure PiB uptake in cerebellar gray matter regions, a probabilistic cerebellar atlas (Institute of Cognitive Neuroscience, UCL; Cognitive Neuroscience Laboratory, Royal Holloway) was transformed into individual space in the same manner as

described above. Of the 28 anatomical structural regions in the cerebellar atlas, all cerebellar lobular regions except the vermis were included to extract the mean cerebellar uptake values.

*[$^{18}$F] Fludeoxyglucose (FDG)-PET image acquisition and preprocessing*

The participants fasted for at least 6 h and rested in a waiting room for 40 min prior to the scans after intravenous administration of 0.1 mCi/Kg of [$^{18}$F] FDG radioligand. The PET data collected in list mode (5 min × 4 frames) were processed for routine corrections such as attenuation, scatter, random coincidences, and radioactive decay. MR-based attenuation correction was done using an ultrashort echo time sequence. After inspecting the data for any significant head movements, we reconstructed them into a 20-min summed image using iterative methods (5 iterations with 21 subsets).

The following image processing steps were performed using SPM12 implemented in Matlab 2014a. First, static FDG-PET images were co-registered to individual T1 structural images, and transformation parameters were calculated for the spatial normalization of individual T1 images to a standard MNI template and used to spatially normalize the PET images to the MNI template. Intensity was normalized using the pons as the reference region after smoothing the spatially normalized FDG-PET images with a 12-mm Gaussian filter.

*Magnetic resonance image (MRI) acquisition and preprocessing*

MRI acquisition

All T1-weighted images and fluid attenuated inversion recovery (FLAIR) images were acquired in the sagittal orientation using the abovementioned 3.0T PET-MR machine. T1-weight MRI acquisition parameters were as follows: repetition time (TR) = 1,670 ms, echo time (TE) = 1.89 ms, field of view (FOV) 250 mm, and 256 × 256 matrix with a 1.0-mm slice thickness. The parameters for acquiring FLAIR images were TR = 5,000 ms, TE = 173 ms, echo spacing = 3.46 ms, FOV = 250 mm, averages = 1.0, matrix size = 256 × 256, and slice thickness = 1.0 mm.

Image preprocessing for measurement of AD-signature cortical thickness

All MRIs were automatically segmented using FreeSurfer ver. 5.3 (http://surfer.nmr.mgh.harvard.edu/) and the minor segmentation errors were corrected manually. Based on the Desikan–Killiany atlas [3], mean cortical thickness values were obtained from the

AD-signature regions, including the entorhinal, inferior temporal, middle temporal, and fusiform gyrus according to a previous study [4].

Volume measurement of white matter hyperintensities (WMH)

We followed a validated automatic procedure published previously [5]. Briefly, the procedure consisted of 11 steps, including spatial coregistration of T1 and FLAIR images, fusing of T1 and FLAIR images, segmentation of T1, attainment of transformation parameters, deformation and obtainment of the white matter mask, obtainment of FLAIR within the white matter mask, intensity normalization of the masked FLAIR, nomination of candidate WMH with a designated threshold, creation of a junction map, and elimination of the junction. There were two modifications in the current processing procedure compared to the original study: (a) an optimal threshold of 70 was applied, as it was more suitable for our data compared to the threshold of 65 used in the original study; and, (b) given that individuals with acute cerebral infarcts were not enrolled in our sample, we did not use diffusion weighted imaging in the current automated procedure.

## REFERENCES


[1] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2012) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**, 273-289.

[2] Lopresti BJ, Klunk WE, Mathis CA, Hoge JA, Ziolko SK, Lu X, Meltzer CC, Schimmel K, Tsopelas ND, DeKosky ST, Price JC (2005) Simplified quantification of Pittsburgh Compound B amyloid imaging PET studies: a comparative analysis. *J Nucl Med* **46**, 1959-1972.

[3] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968-980.

[4] Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995) Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* **33**, 636-647.

[5] Jack CR Jr, Wiste HJ, Weigand SD, Rocca WA, Knopman DS, Mielke MM, Lowe VJ, Senjem ML, Gunter JL, Preboske GM, Pankratz VS, Vemuri P, Petersen RC (2014) Age-specific population frequencies of cerebral beta-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *Lancet Neurol* **13**, 997-1005.

[6] Tsai JZ, Peng SJ, Chen YW, Wang KW, Li CH, Wang JY, Chen CJ, Lin HJ, Smith EE, Wu HK, Sung SF, Yeh PS, Hsin Y (2014) Automated segmentation and quantification of white matter hyperintensities in acute ischemic stroke patients with cerebral infarction. *PLoS One* **9**, e104011.