Supplementary Materials and Methods

Participants

In this study, we recruited 70 elder, naturally right-handed Han Chinese individuals from Zhongda Hospital. The exclusion criteria were as follows: (1) a history of ischemic stroke with a diameter of > 15 mm or a history of cardiogenic cerebral infarction; (2) a history of other neurological disorders, e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, and head trauma; (3) a history of systemic diseases such as severe heart disease, liver disease, kidney failure and tumor; (4) a history of neuropsychological disorders or psychiatric disorders; (5) WM lesions result from other causes (e.g., metabolism, immunity, toxicity, demyelination, infection, etc.); (6) MRI scan contraindications. Notably, ILA patients admitted for acute lacunar stroke were recruited at least 3 months after their last stroke.

Neuropsychological Assessments

To evaluate cognitive performances, neuropsychological assessments were obtained in all participants within a week of their MRI scans. We evaluated their general cognitive function appling the mini-mental state examination (MMSE) and performed a neuropsychological battery to evaluate their multiple cognitive domains, e.g. episodic memory (including auditory verbal learning test-20 min delayed recall[AVLT-DR], Rey-Osterrieth complex figure test delayed recall [CFT-DR] and the logical memory test with a 20 min delayed recall [LMT-DR]), visuospatial function (including clock drawing test [CDT] and Rey-Osterrieth complex figure test [CFT]), information processing speed (including digit symbol substitution test [DSST], trail making tests A [TMT-A], Stroop color-word test A and B [Stroop A and B]), and executive function (including digit span test [DST], trail making tests B [TMT-B], verbal fluency test [VFT], Stroop C and the semantic similarity test [Similarity]). As in our previous studies, composite Z scores were further calculated to represent the performance for each cognitive domain.

A brief description of the various neuropsychological tests is as follows: For the AVLT-DR, participants were

required to recall a previously learned word list after a 20-minute delay; for the CFT-DR, they were asked to reproduce a complex geometric figure from memory after a delay; and for the LMT-DR, they were required to recall the details of a short story after a 20-minute delay. In the CDT, participants were instructed to draw a clock face showing a specified time; in the CFT, they needed to directly copy a complex figure; and in the DSST, they matched symbols to numbers using a key as quickly as possible. For the TMT-A, participants were asked to connect scattered numbers in sequence, and the completion time was recorded. In the Stroop A, they were asked to read the words printed on the card, with the completion time recorded; in the Stroop B, they were asked to name the color of the ink on the card, with the completion time recorded; and in the Stroop C, they were asked to name the incongruent ink color of color words (e.g., the word "RED" printed in blue) while suppressing semantic interference, with the completion time recorded. The DST included forward span (repeating digits in the presented order) and backward span (repeating digits in reverse order); this study primarily involved the backward span. In the TMT-B, participants were required to alternately connect numbers in squares and circles in sequence. The VFT involved recording the number of animals spoken within one minute. In the Similarity, participants were required to explain the conceptual similarities between two words.

MRI Data Acquisition

All participants underwent multimodal MRI scans by a clinical 3.0 Tesla scanner (Siemens Healthcare, Germany) using a 12-channel standard head coil. A high-resolution 3D T1-weighted magnetization prepared rapid gradient echo sagittal sequence covering the whole brain shown as follows: repetition time (TR) = 1,900 ms, echo time (TE) = 2.48 ms, flip angle (FA) = 9°, matrix = 256 × 256, field of view (FOV) = 250 × 250 mm^2, slice thickness = 1 mm, gap = 0 mm, and slices = 176. Diffusion-weight images were acquired using a spin-echo single-shot echo-planar imaging (EPI) sequence: TR/TE = 10,000 ms/90 ms, 30 nonlinear diffusion directions with b = 1000 s/mm^2 and an additional volume with b = 0 s/mm^2, flip angle = 90°, 70 slices, sclice thickness = 2 mm, gap = 0 mm, FOV = 256 × 256 mm^2, matrix = 128 × 128. R-fMRI images were acquired using a gradient-recalled echo-planar imaging sequence: TR/TE = 2,000/25 ms, FA

= 90°, matrix = 64 × 64, FOV = 240 × 240 mm^2, slice thickness = 4.0 mm, gap = 0 mm, and number of slices = 36. Additionally,

axial T2-weighted FLAIR, diffusion-weighted images and susceptibility-weighted images were acquired to detect acute or subacute infarctions, perivascular spaces and cerebral microbleeds.

Image Preprocessing

The FSL (http://www.fmrib.ox.ac.uk/fsl/) was used to preprocess and analyze the DTI data. Briefly, the data preprocessing stages were as follows: correction of eddy current and motion artifacts in DTI data, estimation of the diffusion tensor, fractional anisotropy FA and mean diffusivity computation. Finally, for whole-brain fiber tractography, we employed fiber assignment via a deterministic fiber tracking technique. In line with previous research, we established FA 0.2 or a turning angle more than 45° as the termination criterion of continuous fiber.

The R-fMRI data preprocessing was carried out by using the SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and DPARSFA (http://www. restfmri.net/forum/dparsf) software. Briefly, the first ten functional volumes were removed for scanner stability and participant acclimatization; and the remaining R-fMRI images were further adjusted for timing differences and motion effects. Next, a linear transformation was used to co-register the individual 3D T1-weighted image to the mean functional image. Using a unified segmentation technique, the transformed structural images were then segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid. The structural were then applying a uniform segmentation method. The motion-corrected functioning volumes were further geographically standardized to the Montreal Neurological Institute (MNI) space and reconstructed to 3 mm isotropic voxels utilizing the normalizing variables determined during uniform segmentation. Then, band-pass filtering (0.01 - 0.1 Hz) was performed on the time series of each voxel, and linear trends were eliminated using linear regression approach. Finally, multiple linear regression analysis was performed to eliminate the nuisance signals (6 head motion parameters, mean global signal,

cerebrospinal fluid signal, and WM signal). Remarkably, inadequate image coverage or significant motion artifacts (i.e., translational motion greater than 3 mm or rotational motion greater than 3°) resulted in the exclusion of four ILA patients.

Whole-Brain Network Construction

Using the Automated Anatomically Labeling atlas, the nodes of the structural and functional networks were automatically divided into 90 anatomical regions of interest (ROIs; 45 ROIs for each hemisphere).

Construction of structural connectivity networks.

The skull-stripped T1-weight pictures were initial in a linear manner jointly registered to respective b0 images in the native diffusion space using the FSL linear registration tool in order to produce structural connection networks for each participant. After co-registration, these images were converted to MNI space. The AAL-90 atlas was then translated from MNI space to the native diffusion tensor space by inverting the altered values. To account for the varying surface sizes of regions, the density of streamlines (amount of streamlines per unit surface) was specified as an edge connecting two regions for each participant.

Construction of functional connectivity networks.

To create a whole-brain functional network, as mentioned above, the 90 regions that were divided up according to the AAL-90 atlas represented the nodes in the functional connection network architecture, while the edges were defined as the Pearson correlation coefficient between the mean time series of each node. Considering the ambiguous biological explanation of negative correlation, we restricted our analysis to positive correlation connections and set the negative correlation coefficients as zero.