Supplementary Methods

Neuropsychological testing

A neuropsychological test battery was performed in all subjects, covering the following domains:

- Verbal memory: assessed with the Dutch equivalent of the California Verbal Learning Test (Verbale Leer- en Geheugen Taak);[1]
- Visuospatial memory: assessed with the Location Learning Test;[2]
- Information processing speed: assessed with the Letter Digit Substitution Test, which is an equivalent of the Symbol Digit Modalities Test;[3]
- Short-term and working memory: short-term memory was assessed with the Digit Span forward condition, whereas working memory was assessed with the Digit Span backward condition and Letter-Number Sequencing. These tests are part of the Wechsler Adult Intelligence Scale;[4]
- Verbal fluency: assessed with the Word List Generation, including three categories: animals, professions and m-words (one minute per subtest).[5]

MRI acquisition parameters

The protocol included a three dimensional T1-weighted (3DT1) magnetization prepared rapid acquisition gradient-echo images (repetition time (TR): 2700 ms; echo time (TE): 5.07 ms; inversion time: 950 ms; flip angle: 8°; 176 sagittal slices with 1.3 mm thickness; field of view (FOV): 248 x 330 mm^2; 1.3 mm in-plane resolution) for brain volume measurements and axial turbo spin-echo proton density (PD)/T2-weighted images (TR: 3160 ms; TE: 25/86 ms; 46 axial slices with 3 mm thickness; FOV: 188 x 250 mm^2; 1.0 mm in-plane resolution) for WM lesion detection. In addition, diffusion-weighted echo-planar images (TR: 6800ms; TE: 90 ms; 59 axial

slices with an isotropic 2 mm resolution) were obtained with 60 volumes with noncollinear diffusion gradients (b-value: 700 s/mm^2) and 10 volumes without directional weighting. For FC analysis, resting-state (RS) fMRI was performed (200 volumes of echo-planar images, TR: 2850 ms; TE: 60 ms; 36 slices with 3.0 mm thickness; FOV: 211 x 211 mm^2; 3.3 mm in-plane resolution).

Resting-state functional connectivity analysis

The fMRI data were preprocessed in Melodic, consisting of: 1) discarding the first five volumes; 2) motion correction; 3) spatial smoothing (6 mm full-width-at-half-maximum), and; 4) high-pass filtering (1 s). Next, the functional image was registered to the 3DT1 image using boundary-based registration, and subsequently non-linearly registered to MNI152 standard space. The inverse of the aforementioned registration steps was calculated in order to register the cortical areas of the Automated Anatomical Labeling atlas[6] in standard space to native 3DT1. Subsequently, this atlas in native 3DT1 space was masked for grey matter by using the segmentation obtained by SIENAx. The subcortical structures derived by FIRST were added to the atlas, resulting in an atlas of 92 cortical and subcortical brain regions. This novel brain atlas was then registered to the participant's fMRI space and subsequently voxels prone to fMRI artefacts were excluded for each subject (i.e., voxels with a signal intensity in the lowest quartile of the robust intensity range). For each atlas region, the mean timeseries was obtained and imported into Matlab R2012a. Pearson correlation coefficients were used to correlate activity between all regions during the entire resting-state scan (absolute values), resulting in a matrix of 92 by 92 connections for each participant. Subsequently, in order to investigate relative changes in functional connectivity (FC) for each participant, and to filter out between-

subject global increases or decreases in FC, for each participant each correlation coefficient was normalized for the person's average correlation strength and standard deviation of the entire correlation matrix, resulting in Z-scores of FC. From this matrix, the ipsilateral and contralateral functional connections between limbic (bilateral amygdala, hippocampus, and thalamus) and frontal structures (bilateral anterior cingulate cortex, medial prefrontal cortex, dorsolateral prefrontal cortex, and ventral prefrontal cortex) were selected (see figure 1). Next, for each limbic region separately we calculated the average FC with the frontal areas.

Supplementary references

1 Mulder JL, Dekker, P.H., Dekker, R. Verbale Leer- en Geheugentest. Lisse, The Netherlands: Swets and Zeitlinger, 1996.

2 Bucks RS, Willison JR. Development and validation of the location learning test (LLT): A test of visuo-spatial learning designed for use with older adults and in dementia. Clin Neuropsychol 1997;11:273-286.

3 Jolles J, Houx PJ, van Boxtel MPJ, Ponds RWHM. Maastricht Aging Study: Determinants of Cognitive Aging. Maastricht, The Netherlands: Neuropsychological Publishers, 1995.

4 Wechsler D. Wechsler Adult Intelligence Scale - administration and scoring manual, 3rd ed. San Antonio, TX: The Psychological Corporation, 1997.

5 Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment, 4th ed. New York: Oxford University Press, 2004.

6 Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273-289.